Hiroshima Journal of Medical Sciences
Vol.34, No.2, 215~246, June, 1985
HIJM 34-33

Studies with the Total Artificial Heart Using Sheep as an Adult Animal Model

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(Received March 25, 1985)

Key words: Total artificial heart, JARVIK-7 total artificial heart, Long-survival sheep

ABSTRACT

The sheep was developed as an adult animal model for artificial heart research at the University of Utah. A JARVIK-7™ pneumatic total artificial heart, designed for human use (stroke volume 100ml), was implanted in 43 sheep from 1980 through 1983. Experimental results from these implanted sheep indicate excellent hemodynamic performance of the pneumatic heart system, insignificant mineralization of the pumping diaphragm, and stable laboratory values and body weight. The longest survival time was 297 days in 1982. The sheep has proven to be a good experimental model for the long-term testing of a total artificial heart. However, because of several problems, the average survival days of these sheep was not consistently extended; 63 days in 1980 (5 cases), 12 days in 1981 (15 cases), 71 days in 1982 (8 cases), and 30 days in 1983 (15 cases). From the analyses of the experimental data of these sheep, as current problems, postimplantation hemolysis, renal failure, pulmonary dysfunction, infection with vegetative thrombus, mechanical accident, and renal infarctions are identified, and the mechanisms of these problems are discussed. Further study is needed to identify the mechanisms to eliminate postimplantation hemolysis, renal failure, and pulmonary dysfunction, to consistently obtain long-term surviving sheep. For long-term survival, prevention of infection is an important factor.

A cardiac output monitor and diagnostic unit (COMDU™) was used for the cardiac output measurement and evaluation of the hemodynamic performance of the ventricles, which proved to be very useful for animal and human application of the pneumatic total artificial heart.

The artificial heart is a device to replace total cardiac function, or to partially support cardiac function, the device for total cardiac replacement is called a total artificial heart, and the device for supporting partial cardiac function is called a ventricular or heart assist device. Ventricular assist devices have been developed and implanted clinically in several laboratories and hospitals[21,47,58,62].

The total artificial heart was first implanted within an animal's chest by Dr. Akutsu and Dr. Kolff in 1957[1]. Dogs were used in the early experiments, then the dog was replaced with the sheep animal model. The Artificial Heart Research Laboratory at the University of Utah was established by Dr. Willem J. Kolff in 1967. Initially sheep were used for artificial heart studies in the Utah laboratory. However, because of several problems which made it difficult to sustain the sheep, especially coagulopathies[13], researchers began to implant the artificial heart in calves. Since the late 1960's, the calf was the common animal for artificial heart research.

An early goal, obtaining a 100-hr survivor, was achieved in 1970[34]. As a result of advances and improvements in materials and design of the artificial heart, fabrication techniques, heart drivers, surgical procedures, and postoperative animal management, the animal survival records were extended almost yearly in this laboratory: 95 days in 1974[35], 184 days in 1976[36], 221 days in 1978[43], and 268 days in 1980[23].

The number of potential total artificial heart human recipients was estimated by the National Heart, Lung, and Blood Institute Advisory Council Working Group to be between 10,000 and 23,000 per year in the United States, which included patients unweanable after cardiopulmonary bypass for corrective cardiac surgery, intractable myocardial infarction cases, chronic congestive heart failure cases, and cardiomyopathies[54].

The total artificial heart was implanted clinically at the Texas Heart Institute in 1969 and 1981. This heart, placed in two patients, sustained life for 64 hr and 53 hr, respectively, before orthotopic cardiac transplantations were performed[10,11,17].

Based on the data from animal experiments, the University of Utah was given permission from the Food and Drug Administration in 1981 for clinical application of a permanent, pneumatic, total artificial heart. On December 2, 1982, a pneumatic total artificial heart for permanent use was implanted in a patient at the University of Utah Medical Center[28].

Recently specific limitations to long-term experiments, which were considered unique to the calf, were identified. First, the calf continued to grow after implantation, outgrowing the capacity of the artificial heart. Second, mineralization on the flexible diaphragm of the ventricle was severe in the growing calf[6-8]. Because of these limitations, a nongrowing adult sheep was reconsidered.

Many studies were done on sheep to avoid serious coagulopathies during and after surgery[61]. Several adjustments, such as changing from a bubble oxygenator to a membrane oxygenator, restricting use of the cardiotomy sucker[12], and meticulous suturing of all the anastomoses were made to avoid these difficulties. These improvements resulted in longer survival times, the longest of which was 169 days in 1980 and 297 days in 1982.

Experimental results from these implanted sheep indicate excellent hemodynamic performance of the total artificial heart, insignificant mineralization of the pumping diaphragm, absence of fibroblastic proliferation (pannus), and stable laboratory values and body weight.

This report consists of the analysis of the experimental data of one sheep which survived 297 days, and of another sheep implanted with the JARVIK-7 pneumatic total artificial heart, and an attempt to identify the major problems encountered during these experiments.

MATERIALS

A. Total Artificial Heart

The technology in the application of solution-cast polyurethanes for the fabrication of the ventricles was developed in 1973. The materials were cast over stainless-steel molds which had been cleaned ultrasonically in ethanol[30]. The JARVIK-7 artificial heart (stroke volume 100 ml, designed for human use) was made from a segmented polyether polyurethane, Biomer™ (Ethicon, Inc., Somerville, New Jersey, U.S.A.) (Fig. 1). The ventricular housings were cast to proper thickness and had two layers of Dacron reinforcing mesh embedded midway through the multiple pours of Biomer[30]. The housings were 0.135 inch thick. The diaphragm consisted of four separate Biomer membranes, with dry

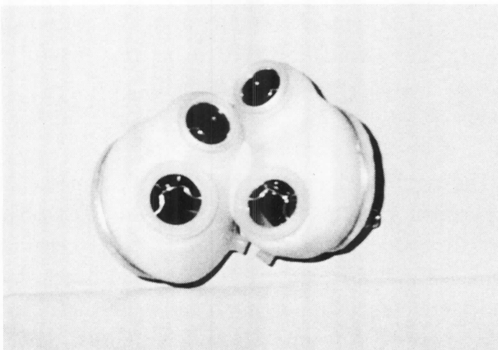


Fig. 1. The JARVIK-7 pneumatic total artificial heart made from Biomer (used with permission from Robert K. Jarvik, M.D., Symbion, Inc., Salt Lake City, Utah, USA).

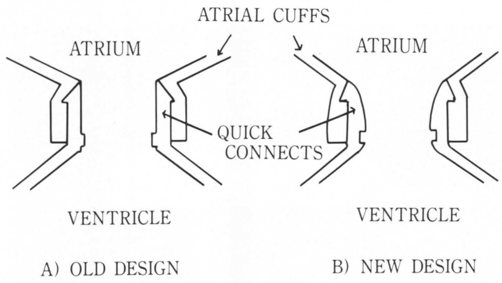


Fig. 2. Comparison of old design and new design of quick connects.

graphite used between the layers as lubricant. Each of the four pumping membranes was 0.006 inch thick. A blood-side membrane and the blood-contacting surface of the housing were formed continuously by solution casting in order to eliminate thrombus formation at the diaphragm-housing junction[26,30]. The bases were made from polycarbonate. Valve-holding quick connect rings were made from polycarbonate and coated with Biomer. Since 1978, a new design of quick connect was used to prevent pannus formation (Fig. 2)[27]. Four Björk-Shiley™ Valves with pyrolytic carbon discs (Shiley Laboratories, Santa Ana, California, U.S.A.) were used in the inflow (29 mm) and outflow (27 mm) positions. The resulting assembly then included: 1) a housing with coated polycarbonate (valve retaining) quick connect rings; 2) a blood-side diaphragm; 3) two intermediate diaphragms; 4) an air-side diaphragm; and 5) a polycarbonate support base. Four pressure monitoring and blood sampling lines were built into the atrial cuffs and the outflow grafts. The atrial sewing cuff consisted of a flexible, Biomer, quick connect and Darcon™ velour (Meadox Medicals, Inc., Oakland, New Jersey, U.S.A.) with smooth, Biomer, blood-contacting surface. The outflow graft was made of Cooley™ low-porosity graft (Meadox Medicals, Inc., Oakland, new Jersey, U.S.A.) 30 mm in diameter, with a Biomer quick connect, which was sewn to a 24 mm diameter Cooley graft in order to match the diameter to the aorta and pulmonary artery of the sheep. The ventricle was attached to the pneumatic control unit via a 30 F USCI™ venous cannula (Division of C.R. Bard, Inc., Billerica, Massachusetts, U.S.A.) and polyvinyl chloride tube (3/8 in ID) coated with Biomer, which tube was a total of 6 ft in length. The subcutaneous portion of the pneumatic tube (venous cannula) was covered with polyester velour to allow tissue ingrowth. The percutaneous lead (skin button) was a strain relief of the drive line with polyester velour, felt flange, and Silastic sleeve (Fig. 3)[23].

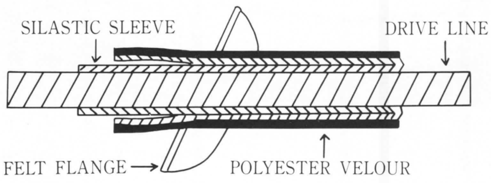


Fig. 3. Strain-relief type of percutaneous lead (skin button) consisting of polyester velour, felt flange and a Silastic sleeve.

B. UTAHDRIVE Heart Driver

The total artificial heart reported here was driven by compressed air. The pneumatic control unit (UTAHDRIVE™) had two electrically controlled solenoid valves which applied compressed air through two air drive lines to the artificial ventricles during systole and exhausted air to atmosphere during diastole. Two valves were used to regulate the rise rate of ventricular pressure (dP/dT).

The driving pressure was adjusted manually by pressure regulators and dials (one for the right ventricle and one for the left ventricle) on the control module. The control module also had thumb switches to set percent systole (duration of systole) and heart rate. Compressed air was supplied from a large compressor by a central tubing system or from portable compressed nitrogen tanks, in the event of an emergency.

Emergency power supplies were incorporated into a control module which took over in case of a power failure, and which also allowed freedom of movement for up to five days. During diastole, negative ventricular pressure (0 to −15 cm H_2O) could be provided if needed by an electrically controlled vacuum system which was portable and had a low noise level (Fig. 4).

C. Cardiac Output Monitor and Diagnostic Unit: the COMDU

A cardiac output monitor and diagnostic unit

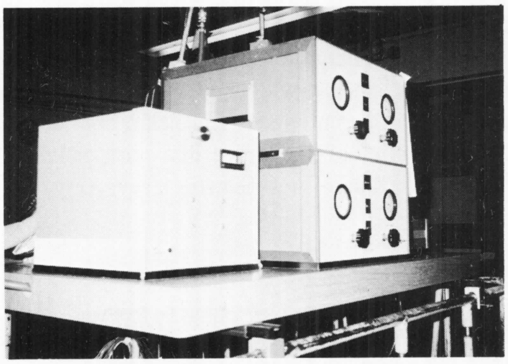


Fig. 4. The UTAHDRIVE pneumatic heart drivers (one is for back-up) with a portable vacuum system. (Used with permission from Robert K. Jarvik, M.D., Symbion, Inc., Salt Lake City, Utah, USA.)

(COMDU) was developed for pneumatically powered blood pumps[46]. The COMDU consisted of an airflow measuring transducer and computer for evaluating and displaying the diastolic air wave form (Fig. 5). The COMDU measured exhausted air flow to determine the amount and rate of blood flowing into each ventricle. The rate of blood entering the ventricle provided diagnostic information.

Correlation of stroke volume, filling rate, and the shape of the filling curve, coupled with air drive line pressures, permitted the diagnosis of several conditions such as hypovolemia, pericardial tamponade, poor fit of the ventricles, malfunctioning valves, pumping diaphragm problems, malfunctioning heart drivers, and improper adjustment of driving parameters.

METHODS

A. Surgical Procedure

A sheep was confined in a cage for two days to get used to its new environment. It was fasted from food for 18 hr and water for 12 hr, and given 2g of Oxytetracycline HCI (Medamycin™, Med-Tech Inc., Elwood, Kansas, U.S.A.) orally. This procedure eliminated the complication of gas accumulation in the gastrointestinal tracts of the animal during anesthesia.

The sheep was weighed and taken into the anesthesia induction room. An Angiocath™ intravenous catheter (The Deseret Company, Sandy, Utah, U.S.A.) was placed percutaneously into

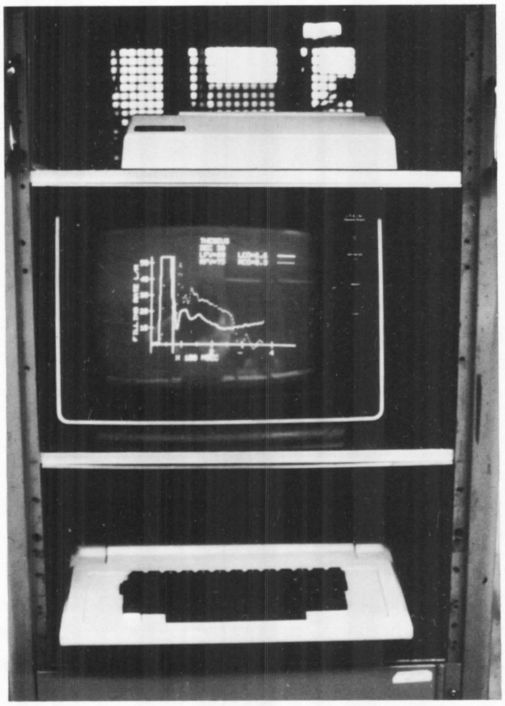


Fig. 5. The COMDU: a computer for evaluating and displaying the diastolic airflow curve (used with permission from Robert K. Jarvik, M.D., Symbion, Inc., Salt Lake City, Utah, USA).

the left external jugular vein, and blood samples were collected for the normal values. Two milligrams atropine sulfate (Elkins-Sinn, Inc., Subsidiary of A.H. Robins Company, Cherry Hill, New Jersey, U.S.A.) and 10 mg/kg of thiopental sodium (Pentothal™, Abbott Laboratories, North Chicago, Illinois, U.S.A.) were given intravenously for anesthesia. The sheep was placed on the surgery table, lying on its left side. The sheep was intubated and connected to a pressure-regulated respirator (Bird Mark 14™, Bird Space Technology, Palm Springs, California, U.S.A.), and Halothane (Fluothane™, Ayerst Laboratories, Inc., New York, New York, U.S.A.) was given to maintain anesthesia (0.25 to 1.50%). Blood gas determinations were repeated during the anesthesia.

After the appropriate presurgical preparation, the sheep was taken into the operating room and draped with double or triple layers of drapes. The left saphenous artery and vein were cannulated with catheters for monitoring arterial pressure and inferior vena caval pressure during cardiopulmonary bypass. The right external jugular vein and carotid artery were exposed, and tapes were placed for later use as tourniquets during cardiopulmonary bypass. Right thoracotomy was adopted as the preferred surgical technique in this laboratory after 1973[50]. Thirty milligrams of succinylcholine chloride (Anectine™, Burroughs Wellcome Company, Research Triangle Park, North Carolina, U.S.A.) was administered intravenously and a skin incision was made over the fifth rib. After the skin incision, the skin was slid anteriorly and the incision continued down onto the lateral aspect of the fourth rib. The fourth rib was removed from its periosteal bed. Prior to entering the chest, the skin and cutaneous muscles were lifted from the deeper tissues for tunneling of the pneumatic drive lines, and the incisions for the orifices were made through the skin. After the chest was opened, tourniquets were placed around the superior vena cava (SVC), the azygous vein, and the inferior vena cava (IVC). The right lateral wall of the pericadium was removed and the pleural sac containing the intermediate lobe of the right lung was also opened. The aorta was tourniqueted with a doubled tape.

The sheep was heparinized with 3 mg/kg of heparin sodium (The Upjohn Company, Kalamazoo, Michigan, U.S.A.). The arterial return line from the cardiopulmonary bypass circuit was placed retrograde into the right carotid artery and venous cannula into the SVC via the jugular vein, and the IVC via the right auricular appendage. partial cardiopulmonary bypass was established for 3 to 5 min at about 0.5 liters/min flow to get an adequate mixture of blood and priming solution. SciMed™ membrane oxygenator (SciMed Life Systems, Inc., Minneapolis, Minnesota, U.S.A.), Sarns™ roller pump (Sarns, Inc., ann Arbor, Michigan, U.S.A.), and Pall Ultipor™ blood filter (Pall Biomedical Products Corporation, Glencove, New York, U.S.A.) were used for the cardiopulmonary bypass. The priming solutions were 3 liters of lactated Ringer's solution, 0.5 liter 10% W/V Dextran 40 in dextrose (Rheomacrodex™, Pharmacia Laboratories, Division of Pharmacia Inc., Piscataway, New Jersey, U.S.A.), 5000 units heparin, penicillin G, and 50 mEq of sodium bicarbonate. During cardiopulmonary bypass the body temperature was cooled to 29° to 30°C, and the average pump flow was 4.5 to 5.5 liters/min.

The apex of the natural heart was reflected out of the pericardial sac and the hemiazygous vein, which drains the anterior, five or six left intercostal veins into the great coronary vein, was ligated.

After total carodiopulmonary bypass was established, the ventricular myocardium was excised at the atrioventricular junction and pulmonary artery, and aortic valve leaflets. All of the leaflets of the mitral and tricuspid valves were trimmed from the atrioventricular rings, all of the ventricular myocardium was removed from the lateral aspects of both right and left sides, and the septum was trimmed to within 2 to 4 mm of the atrioventricular junction. The pulmonary artery was separated from the aorta and each edge was trimmed when resecting the valve leaflets. A 3-0 silk suture was placed, encircling the ostia of the coronary sinus in the posterior aspect of the right atrium. The right outflow graft was trimmed to 5 to 6 cm in length including the quick connect system. It was attached to the pulmonary artery in a continuous, running suture using 4-0 Prolene™ (Ethicon Inc., Somerville, New Jersey, U.S.A.). In the same way, the left outflow graft was trimmed to 2 to 3 cm in length including the quick connect system, and sutured to the aorta with a 4-0 Prolene continuous, running suture. The left atrial cuff was trimmed to approximately 2 cm long on a straight line, to facilitate suturing along the intra-atrial septum. The right cuff was trimmed on a straight line to accommodate the septum, and was much larger than the left. A 2-0 Prolene mattress suture was placed at the cranial end of the septum, and the suture line was run as a continuous mattress along the septum, connecting the right atrial cuff to the left atrial cuff. Then the 3-0 Prolene sutures were placed at the edge of the septum and the atrial cuffs were attached with a continuous, running suture. All of the anastomoses were tested by using quick connect tester plugs and injecting blood under pressure.

Rewarming by cardiopulmonary bypass was begun in order to bring the sheep's temperature back to normal. The four pressure monitoring and blood sampling lines were pulled through the 8th intercostal space and passed off the table to be connected to the pressure transducers. The left artificial ventricle had previously been partially filled with saline, and the air drive-line tube (30 F USCI venous cannula) was pulled through the sixth intercostal space at the costochondral junction, then through the percutaneous lead, and then through the previously formed tunnel, exiting the previously prepared perforation of the skin. This cannula was connected to the polyvinyl chloride tube which was passed off the table and connected to the pneumatic heart driver. The left atrial quick connect was snapped in position, and the aortic quick connect was connected, with strict attention paid to avoid any torsion of the aortic graft.

The ventricle was primed by aspirating air from the chamber as the bronchial blood flowed into the left atrium. After the air was vented, the tourniquet was removed from the aorta, the left ventricle was activated at approximately 40 beats/min, and the driving pressure was set to establish left ventricular emptying. The left ventricle was then elevated out of the chest and all suture lines were inspected and areas of hemorrhage were corrected. The left ventricle was then placed in the chest, positioned by withdrawing the excess length of pneumatic drive line outside the chest. The drive line of the right ventricle was passed through the fifth intercostal space at the costochondral junction. The percutaneous lead was attached to the drive line in the same way as the left one. The right atrial cuff was fastened via the quick connect system, and then the outflow graft was connected without any torsion in the pulmonary artery. The tourniquet was loosened from the inferior vena cava, and the inferior vena caval line was partially occluded to force blood into the right atrium while the air was evacuated through the priming port. The right ventricle was activated by increasing the driving pressure, which was set to obtain proper emptying of the right ventricle, and the tourniquet was loosened from the superior vena cava for partial bypass.

The respirator was turned on at approximately 20 mm Hg air driving pressure, with positive end expiratory pressure (PEEP). During the cardiopulmonary bypass, the lungs were static on about 7 cm of water PEEP.

All of the suture lines were examined for leaks. The inferior vena caval line was completely occluded and the superior vena caval line was partially occluded, then the cardiopulmonary bypass was weaned off. During this period the heart rate was increased to 90 beats/min and the driving pressures were increased to get complete emptying of both right and left ventricles. After the cardiopulmonary bypass was totally weaned, the venous uptake cannulae were removed, and protamine sulfate (Eli Lilly and Company, Indianapolis, Indiana, U.S.A.) was given to neutralize the heparin. Two chest drainage tubes were placed and the chest was close.

The carotid artery and jugular vein were repaired with 6-0 Prolene suture. The catheters in the saphenous vessels were pulled out and the vessels were ligated. The sheep was then placed in the cart in sternal recumbancy (the normal resting posture of sheep). Intermittent vacuum was established on the chest drains.

B. Postsurgical Management

The aortic pressure (AOP), pulmonary arterial pressure (PAP), left atrial pressure (LAP), right atrial pressure (RAP), left driving pressure (LDP), and right driving pressure (RDP) were continuously monitored using a multichannel chart recorder (Hewlett Packard, Palo Alto, California, U.S.A.).

Cardiac output was continuously measured using the COMDU. Blood gas analysis was repeated using a PH-Blood-Gas Analyzer 813™ (Instrumentation Laboratory, Lexington, Massachusetts, U.S.A.), and the activated clotting time (ACT) was measured by a Hemochron 400™ (International Technidyne Corporation, Metuchen, New Jersey, U.S.A.). The sheep's temperature was brought back to normal by the addition of a heating blanket. The chest drains were stripped repeatedly with roller strippers.

Blood transfusions were administered for replacement of fluid loss through the chest drainage tubes. Extubation of the endotracheal tube was performed when the tidal volume became over 10 ml/kg, arterial pO_2 was above 60 mm Hg, and arterial pCO_2 was below 45 mm Hg under the room air. The sheep was removed from the operating room into the animal holding area after the hemodynamic condition became stable.

Pneumatic heart drivers were positioned on a platform suspended on the top of the cage, which gave easy access to the animal, drive lines, and pressure monitoring lines. All pressures were monitored overhead and carried to a central recorder bank. Food and water were given from the first postoperative day in unlimited amounts.

After removal of the chest drainage tubes on the second or third postoperative day, anticoagulant therapy was begun with 5,000 to 20,000 units of heparin placed in one liter of normal saline in the flush bag for the blood pressure lines. A blood gas analysis was taken every two hr after moving the animal to the holding area, and hematocrit and ACT were monitored every 4 hr. These monitoring intervals were extended as the sheep's condition became more stable. Body temperature was taken every four hr, and the animal was weighed each week. Antibiotics were given during and after the surgery for five days, and also when the sheep had high fever spikes with positive blood cultures.

C. Pneumatic Driving Parameters and Blood Pressures

Pneumatic drive parameters were set manually in an attempt to obtain complete emptying of both ventricles during each cardiac cycle. The pressure waveforms of the air drive lines and aortic and atrial pressures were monitored and recorded every hour. Cardiac output (CO) was measured by the COMDU at least once a week throughout the experiment.

Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) in dynes·sec/cm^5 were calculated from the following equations:

$$SVR = \frac{\text{mean AOP} - \text{mean RAP}}{\text{CO (liters/min)}} \times 80$$

AOP: aortic pressure
RAP: right atrial pressure

$$PVR = \frac{\text{mean PAP} - \text{mean LAP}}{\text{CO (liters/min)}} \times 80$$

PAP: pulmonary arterial pressure
LAP: left atrial pressure

The sheep were exercised three times a week throughout the course of the experiment, walking on the treadmill for 30 min at about three to four kilometers per hour. During treadmill exercise the driving parameters were not changed.

D. Hematologic and Chemical Analyses

Hematologic and chemical analyses were performed once weekly. The battery of tests consisted of standard hematologic procedures: red blood cell count, white blood cell count with differential, hematocrit (Hct), whole blood hemoglobin, free plasma hemoglobin; and coagulation assays: prothrombin time (PT), partial thromboplastin time, platelet count, fibrinogen, platelet aggregates, and fibrin degradation products.

The chemical analyses consisted of electrolytes; sodium (Na^+), potassium (K^+), and calcium (Ca^{++}); inorganic phosphorus, total protein (albumin and globulin), total bilirubin, glucose, total cholesterol, enzymatic assays such as serum glutamic oxaloacetic transminase (SGOT), serum glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), and alkaline phosphatase; and renal function tests such as blood urea nitrogen (BUN) and creatinine.

E. Pathophysiological Evaluation

The sheep was autopsied by overhead suspension in the natural standing position. This allowed a very valid evaluation of the position of the artificial heart, and all of the organs within the chest. The prosthetic device was removed from the sheep and evaluated to assess the effect of blood exposure on the polyurethanes. Organs were weighed and examined macroscopically. Histopathological specimens were collected and submitted to the diagnostic laboratory. Bacterial cultures were taken from some parts of the blood-contacting surface of the ventricles and grafts. The ventricles were rinsed with normal saline and the right ventricle was submitted for more extensive device retrieval examination[6]. The left ventricle was placed on durability testing in water[14].

RESULTS

A. Postoperative Course

An adult, 97 kg male sheep (TH82S5) was implanted with a JARVIK-7 heart on June 2, 1982. Cardiopulmonary bypass time was 95 min, the sheep recovered quickly, and the endotracheal tube was removed 3 hr after the operation. the values of arterial blood gas analyses after extubation were: pH 7.39, pCO_2 39.5 mmHg, pO_2 72.0 mmHg, and base excess -0.7 mEq/liter. The sheep stood up unassisted at 4 hr after surgery, and was removed from the operating room into the animal holding area. Food and water were given from the first postoperative day, and the sheep showed a good appetite a few days after the surgery.

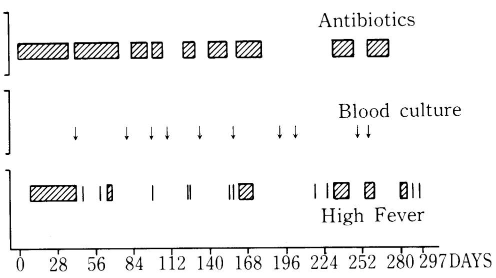


Fig. 6. The postoperative course of the sheep (TH82 S5). Antibiotics were given when the sheep had high fever spikes or the blood culture was positive. The sheep showed no clinical symptoms or signs after a certain period of anitibiotic administration, although the blood culture was still positive.

The animal had a high fever (over 40.0°C), that lasted from the 8th to the 66th postoperative day in spite of large doses of antibiotics. Several combinations of antibiotics were continuously given without effect until all pressure monitoring lines were cut and sealed on the 66th postoperative day. After that, antibiotics were given when the sheep had high fever spikes or the blood culture was positive (Fig. 6). Antibiotics were selected according to the result of the cultured organism's sensitivity test. Repeated blood cultures were consistently positive, but with different organisms isolated (Table 1). Sometimes the sheep showed no clinical symptoms or signs, even though the blood culture was positive. The preoperative body weight was 97 kg and was kept around 100 kg during the experiments (Fig. 7).

B. Pneumatic Drive Parameters and Blood Pressures

Aortic and atrial pressures were monitored

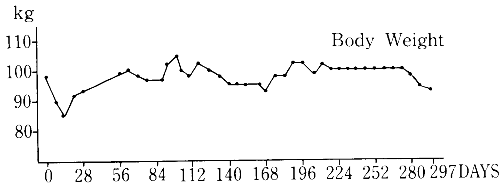


Fig. 7. Preoperative body weight was 97 kg and was kept around 100 kg after recovering from the operation.

during the first 65 days of the experiment. When the right atrial pressure (RAP) monitoring port became occluded, all pressure taps were cut and sealed on the 66th postoperative day. The mean atrial pressures changed during the day (Fig. 8). The RAP in general was high, and the right heart filled completely most of the time. The heart rate was increased and subsequently the cardiac output reached 11 liters/min. An attempt was made to keep the heart rate at 110 beats/min because a high cardiac output, such as 11 liters/min, was not considered necessary for the sheep.

However, on the 39th postoperative day, ascites was found and the sheep appeared to have difficulty and pain in lying down. The highest

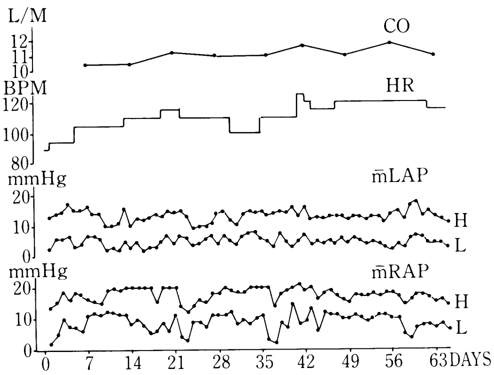


Fig. 8. Daily fluctuation of mean atrial pressures. Ascites was found on the 39th postoperative day. Highest mean right atrial pressure was 21 mmHg, despite a heart rate of 110 beats/min and a cardiac output of 11 L/min. The heart rate was increased to 125 beats/min.
H = highest, L = lowest during the day

Table 1. Results of Blood and Materials Cultures: TH82S5

Organism	No. of times isolated	No. of times sensitive to antibiotics ABPC	CBPC	CET	GM	KM
Premortem blood cultures						
Klebsiella rhinoseleaomatis	4	2	4	0	1	0
Enterobacter cloacae	3	0	3	0	3	0
Enterobacter agglomerance	3	3	3	3	3	0
Klebsiella pnemoniae	1	1	1	0	1	0
Pseudomonas sp.	1	0	0	0	0	1
Postmortem total artificial heart cultures						
Klebsiella rhinoseleaomatis	1	1	1	0	0	0
Enterobacter cloacae	1	0	0	0	0	0
Aeromonas sp.	1	0	0	0	1	1

ABPC: Ampicillin (According to the abbreviations of antimicrobial agents defined by Japan Society of Chemotherapy)
CBPC: Carbenicillin
CET: Cephalothin
GM: Gentamycin
KM: Kanamycin
(Veterinary Reference Laboratory, Salt Lake City, Utah, USA)

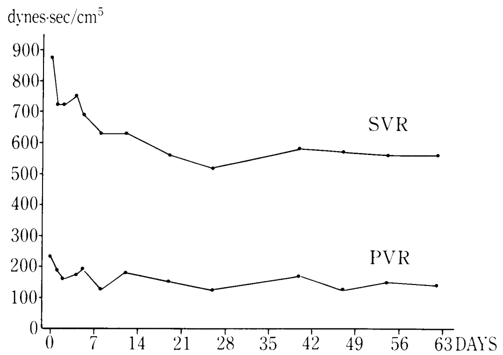


Fig. 9. Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR). The SVR elevated immediately after surgery and soon decreased to less than 800 dynes·sec/cm^5.

mean RAP during one day was over 20 mmHg, despite a heart rate of 110 beats/min and cardiac output of 11 liters/min. Because the right ventricle consistently filled completely, the heart rate was increased to 125 beats/min. The RAP slowly came down and a few days later the ascites decreased and then disappeared.

Systemic vascular resistance was elevated immediately after surgery, and soon decreased to less than 800 dynes·sec/cm^5 (Fig. 9). Mean AOP changed during the day, and was slightly high immediately after surgery (Fig. 10).

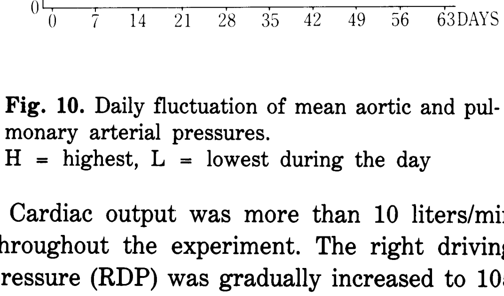


Fig. 10. Daily fluctuation of mean aortic and pulmonary arterial pressures.
H = highest, L = lowest during the day

Cardiac output was more than 10 liters/min throughout the experiment. The right driving pressure (RDP) was gradually increased to 105 mmHg in order to obtain proper emptying of the right ventricle, which indicated that there was an increased resistance of the right outflow tract. The left driving pressure (LDP) was kept at 180 mmHg after the 168th postoperative day

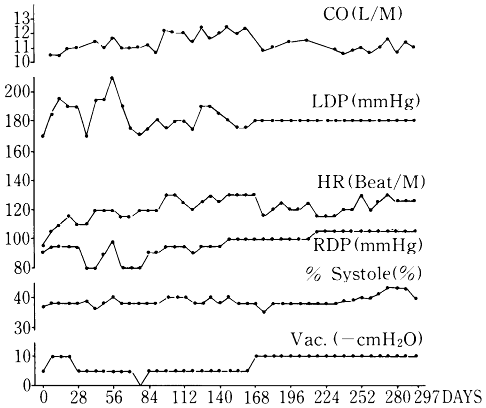


Fig. 11. Driving parameters and the cardiac output throughout the course of the experiment. The right driving pressure was gradually increased to obtain proper emptying of the right ventricle.

(Fig. 11). Both ventricles filled and emptied normally throughout the duration of the experiment with these slight modifications to the driving parameters.

Treadmill exercise was started on the 8th postoperative day, and although some fever spiking prompted temporary cancellation, the animal was exercised throughout the experiment. The COMDU airflow curve (Fig. 12) showed changes during treadmill exercise. Driving parameters were not changed. Left filling volume (LFV) was 85 ml, left cardiac output (LCO) 9.8 liters/min, right filling volume (RFV) 88 ml, and right cardiac output (RCO) 10.1 liters/min before starting exercise (Fig. 12A). During exercise LFV increased to 89 ml and RFV to 96 ml and both ventricles filled completely (Fig. 12B). This meant both driving pressures were not high enough to eject larger volumes (total emptying) and the heart rate was not high enough to pump a larger volume, even though driving pressures and heart rate were optimal at rest.

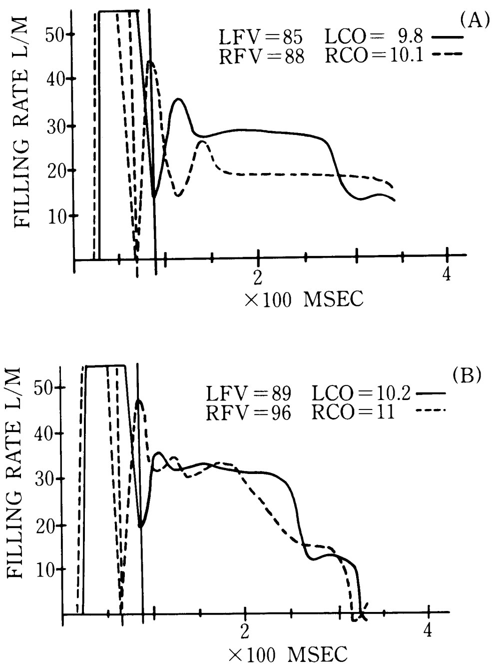


Fig. 12. The COMDU airflow curves (A) before starting exercise and (B) during treadmill exercise. During exercise both driving pressures were not high enough to completely eject larger volumes of blood and the heart rate was not high enough to pump larger cardiac outputs, although driving parameters were adequate at rest. FV = filling volume in milliliters; CO = cardiac output in liters per min.

C. Hematologic and Chemical Analyses

Hematocrit dropped after the operation and stabilized at a significant point below the preoperative control without additional blood transfusions (Fig. 13). White blood cell count often increased over 10,000/mm^3, but was not always associated with fever spikes (Fig. 14). Fibrinogen levels were not significantly associated with white blood cell counts or high fever spikes.

Total protein dropped sharply within 28 days postoperatively, but slowly increased and stabilized at a point slightly lower than the preoperative control (Fig. 15). Potassium, sodium, and calcium levels were within normal limits throughout the experiments (Fig. 16). Crystalline warfarin sodium (Coumadin™, Endo Laboratories, Inc., Subsidiary of the DuPont Company, Wilmington, Delaware, U.S.A.) was given to maintain the sheep's prothombin time (PT) at 1-1/2 to 2 times the preoperative value. Aspirin (McKesson Laboratories, Division of Foremost-McKesson, Inc., Dublin, California, U.S.A.), 1,300 mg, later 650 mg, was given to modify platelet function. Platelet count remained within normal limits but sometimes dropped un-

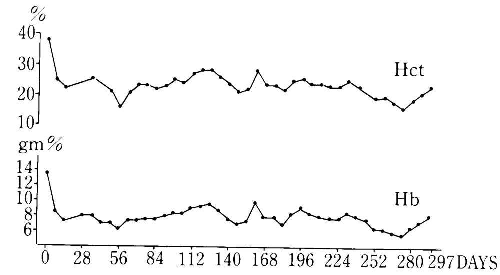


Fig. 13. Hematocrit (Hct) and hemoglobin (Hb). Hematocrit dropped after the operation and stabilized at a significant point below the preoperative control.

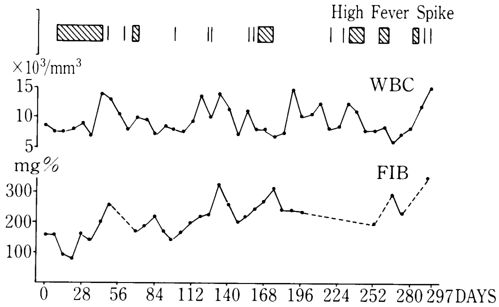


Fig. 14. White blood cell counts (WBC), fibrinogen (FIB) and high fever spikes. Leucocytosis was observed several times, but it was not a good index for infection. Fibrinogen levels were not significantly associated with white blood cell counts or high fever spikes.

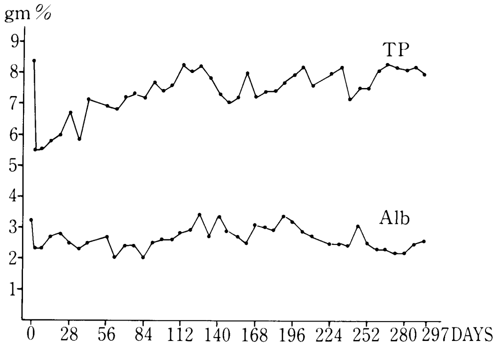


Fig. 15. Total protein (TP) and albumin (Alb). TP dropped sharply within one month postoperatively, but slowly increased and stabilized at a point close to the preoperative control.

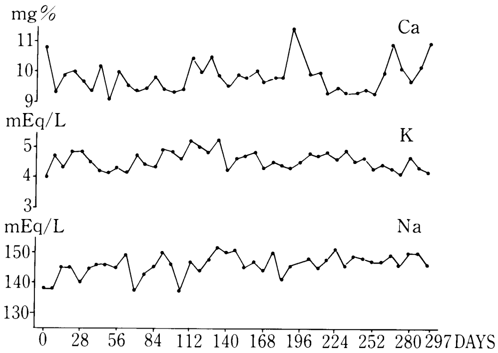


Fig. 16. Electrolytes (sodium, potassium and calcium) were within normal limits throughout the experiment.

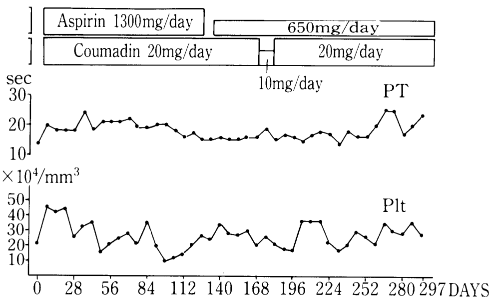


Fig. 17. Anticoagulants (Coumadin and aspirin), prothrombin time (PT) and platelet count (Plt). Platelet count remained within normal ranges but several times dropped under 200,000/mm^3.

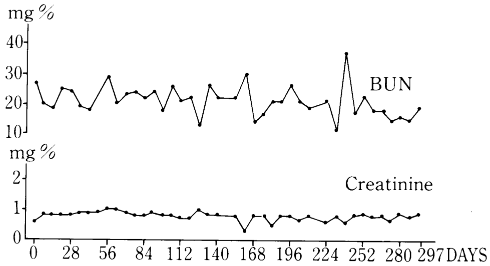


Fig. 18. Blood urea nitrogen (BUN) and creatinine levels were within normal limits.

der 200,000/mm^3 (Fig. 17). Blood urea nitrogen (BUN) and creatinine levels were within normal ranges (Fig. 18). Serum glutamic oxaloacetic transaminase (SGOT) level increased immediately after the surgery, but gradually decreased and stabilized within normal range. Lactic dehydrogenase (LDH) increased from the 161st postoperative day and remained at about 400 to 500 U/ml, and serum glutamic pyruvic transaminase (SGPT) levels were within normal limits (Fig. 19). Free plasma hemoglobin levels were as high as 6.0 mg% within two weeks postoperatively, then decreased and usually remained around 3.0 mg% (average 3.4 mg%) (Fig. 20). Total bilirubin levels were low throughout the experiments.

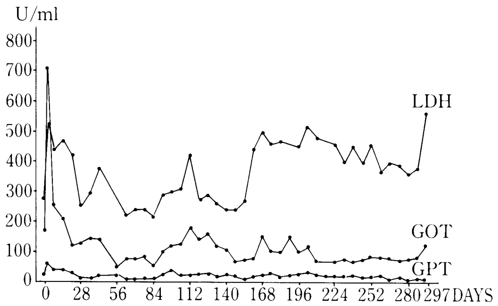


Fig. 19. Levels of GOT increased immediately after surgery, but gradually decreased and stabilized within normal ranges. The LDH increased from around the 161st postoperative day and stabilized at about 400 to 500 U/ml.

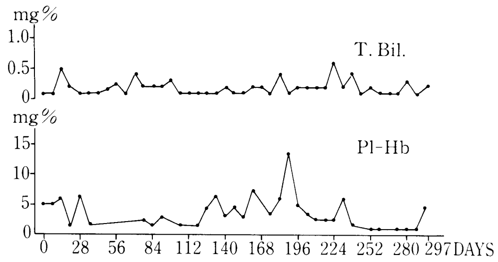


Fig. 20. Free plasma hemoglobin (Pl-Hb) and total bilirubin (T. Bil.). Free plasma hemoglobin levels were as high as 6.0 mg% within two weeks postoperatively, but decreased and usually remained around 3.0 mg%.

D. Pathophysiological Evaluation

On the 297th day the sheep suddenly fell, ceased breathing, and died within five min. The following abnormal findings were diagnosed and anticipated by the COMDU before autopsy. The COMDU airflow curve taken at the time of the sheep's death showed no blood entering either ventricle (Fig. 21). It was suspected there was either a right inflow obstruction of the valve, which stopped the disc in a closed position, or massive, acute hemorrhage in the thorax.

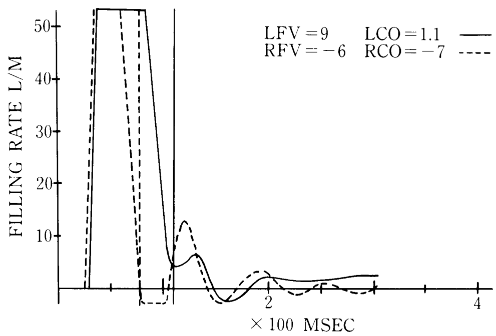


Fig. 21. The COMDU airflow curve taken at the time of the sheep's death showed no blood entering either ventricle. FV = filling volume in milliliters and CO = cardiac output in liters per min.

At autopsy the following findings were observed macroscopically:

Thorax. There was no pleural effusion nor blood in either chest cavity. In the right chest cavity, the lung adhered firmly to the right atrium. Both lungs had a normal external appearance.

Heart. There was a slight kinking of the right outflow graft because the graft was too long, which reduced the right outflow tract to about half its normal diameter. The pseudopericardium of the left ventricle was thin, but on the right ventricle it was slightly thick and adhered to the chest wall at the incision site. The distended atrium was opened and the disc of the right inflow valve was found stuck in a closed position. The disc had a small crack (Fig. 22). It could be opened with relatively little pressure; however, it could not be opened during the cardiac cycle by the existing atrial pressure. There was a small thrombus attached to the port

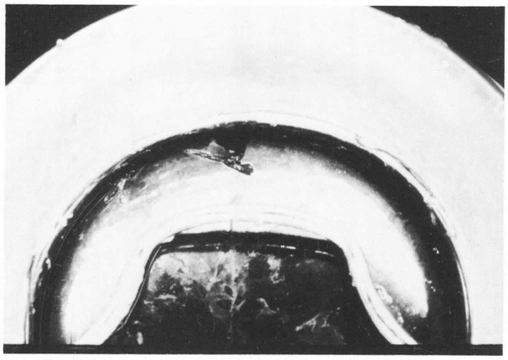


Fig. 22. The disc of the prosthetic valve had a small crack.

of the RAP line, and no pannus was evident. The other three Björk-Shiley valves were very clean and devoid of thrombus. Both pumping diaphragms were intact. No thrombus was found in either of the ventricles.

Abdomen. There was a small amount of clear ascites in the abdomen. The liver (1820 gm), spleen (240 gm) looked normal. The right kidney weighed 175 gm and the left kidney 210 gm. These organ weights were in the normal percentage of body weight for adult, healthy sheep. There were multiple old, small infarctions in both kidneys.

Driving and pressure monitoring lines. There was no infection nor abscess around these lines. Healthy connective tissue was firmly attached to the Dacron felt flanges of the skin buttons.

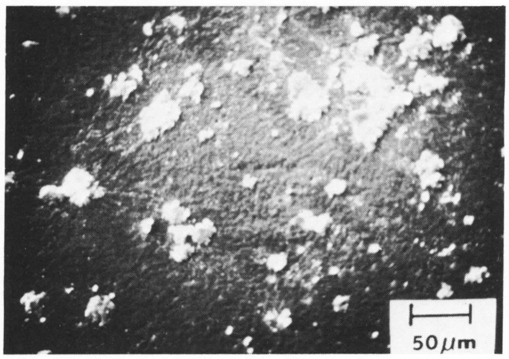


Fig. 23. Mineralization of the pumping diaphragm was observed microscopically.

Histopathology. There were multiple, old renal infarctions which were wedge-shaped from the corticomedullary junctions. Liver tissue demonstrated congestion with focal areas of fibrosis in the parenchyma. There was some mild, localized, chronic inflammation in the hepatic tissue. There was also mild interstitial pneumonitis (L. D. McGill, D.V.M., Veterinary Reference Laboratory, Salt Lake City, Utah, U.S.A.). The pumping diaphragm was examined microscopically, and early signs of mineralization were observed (Fig. 23).

E. Analyses of Sheep Implanted in Utah with Total Artificial Hearts

From 1980 through 1983, the JARVIK-7 pneumatic total artificial heart, made from Biomer was implanted in 43 sheep in Utah. The average survival time of these sheep was 63 days in 1980 (5 cases), 12 days in 1981 (15 cases), 71 days in 1982 (8 cases), and 30 days in 1983 (15 cases) (Table 2). Body weight of the sheep was between 53 kg and 110 kg (average 84 kg), and the cardiopulmonary bypass (CPB) times were between 94 min and 260 min (average 147 min).

The primary causes of death or termination of the experiment were: hemorrhage (10 cases, 23%), pulmonary failure (8 cases, 19%), infection (7 cases, 16%), mechanical accident (6 cases, 14%), and others (Table 3). Hemorrhage and pulmonary failure were the main causes of death in sheep sacrificed within two weeks (9 cases, 35% and 6 cases, 23%, of 26 sheep) (Table 4). Infection was the main cause of death in sheep surviving over two months (5 cases, 50% of 10 sheep). Mechanical accidents were classified into 3 categories: 1) valve-holding ring failure (broken quick connect, 2 cases), 2) pneumatically related failure (air leak, 1 case), and 3) cardiac valve failures (3 cases). Four of those 6 mechanical accidents (67%) were the direct cause of death. There was no diaphragm failure in these experiments. The causes of pulmonary failure were: pneumothorax (2 cases), hydrothorax (2 cases), hemothorax (1 case), pneumonia (1 case), atelectasis (1 case) and the other unidentified cause (Table 5).

High blood urea nitrogen (BUN) levels were observed in the first postoperative week in 8(36%) of 22 sheep which survived over one week. Five of these 8 cases survived over two weeks. Three of these 5 cases had higher BUN

Table 2. JARVIK-7 Total Artificial Hearts Made from Biomer

Year	No.		(Days)	BW (kg)	CPB (min)	Cause of Death
1980:	TH80S	1	5.1	85	109	Infection
		2	77.0			Infection, air leak (drive line)
		3	64.1	60	151	Vegetative thrombus
		4	169.6	68	122	Valve-holding ring fail.
		5	0	73	168	Hemorrhage
	Averages:		**63.2**	**72**	**138**	
1981:	TH81S	1	0.1	53	123	Hemorrhage
		2	0	59	156	Hemorrhage
		3	0.5	85	121	Pulmonary fail.
		4	88.9	86	105	Infection
		5	0.7	78	106	Unknown
		6	26.0	95	164	Inferior vena cava compressed
		7	0.7			Left atrium compressed
		8	0.1	70	97	Aortic graft kink
		9	5.9	77	135	Hemorrhage
		10	0.1	90	120	Hemorrhage
		11	0.1	65	125	Hemorrhage
		12	55.9	110	185	Pulmonary fail.
		13	3.2	93		Hemorrhage
		14	0.4	75	155	Inferior vena cava compressed
		15	0.5	79		Valve fail.
	Averages:		**12.1**	**80**	**133**	
1982:	TH82S	1	8.2	98	155	Valve-holding ring fail.
		2	7.0	86	155	Pregnant and miscarried
		3	128.8	99	135	Infection
		4	5.6			Hemorrhage
		5	297.5	97	95	Valve fail.
		6	12.1	104	122	Blood transfusion reaction
		7	13.8	77	196	Pulmonary fail.
		8	98.2	58	166	Infection
	Averages:		**71.4**	**88**	**145**	
1983:	TH83S	1	17.8	83	260	Infection
		2	0.3	105	224	Brain death, broken membrane oxygenator
		3	3.7	92	165	Pulmonary fail.
		4	61.2	100	161	Infection
		5	19.3	95	179	Blood transfusion reaction
		6	87.9	92	180	Thromboemboli
		7	14.7	85	149	Hemorrhage
		8	17.6	87	135	Hemorrhage
		9	18.1	98	117	Pulmonary fail., renal fail.
		10	11.7	100	145	Pulmonary fail.
		11	5.8	80	110	Pulmonary fail.
		12	51.9	100	94	Thromboemboli
		13	131.0	79	186	Thromboemboli, valve fail.
		14	3.3	75	182	Unknown
		15	5.2	95	177	Pulmonary fail.
	Averages:		**30.0**	**91**	**164**	

CPB: cardiopulmonary bypass

Table 3. Cause of Death or Termination in Total Artificial Heart Sheep

	1980	1981	1982	1983	Totals
Hemorrhage	1	6	1	2	10
Pulmonary failure	0	2	1	5	8
Infection	2	1	2	2	7
Mechanical accident:					
Air leak	1	0	0	0	1
Valve-holding ring	1	0	1	0	2
Valve	0	1	1	1	3
Positioning problem	0	4	0	0	4
Thromboemboli	0	0	0	3	3
Transfusion reaction	0	0	1	1	2
Vegetative thrombus	1	0	0	0	1
Miscellaneous	0	1	1	2	4
Totals	6	15	8	16	45

Table 4. Cause of Death or Termination of Total Artificial Heart Sheep

		Survived for:								
	Imp.	1	2	1	2	3	4	5	6	10
		wk.	wk.	mo.	mo.	mo.	mo.	mo.	mo.	mo.
Hemorrhage	5	3	1	1	0	0	0	0	0	0
Pulmonary failure	1	3	2	1	1	0	0	0	0	0
Infection	0	1	0	1	0	3	1	1	0	0
Mechanical accident:										
Air leak	0	0	0	0	0	1	0	0	0	0
Valve-holding ring	0	0	1	0	0	0	0	0	1	0
Valve	1	0	0	0	0	0	0	1	0	1
Positioning problem	3	0	0	1	0	0	0	0	0	0
Thromboemboli	0	0	0	0	1	1	0	1	0	0
Transfusion reaction	0	0	1	1	0	0	0	0	0	0
Vegetative thrombus	0	0	0	0	0	1	0	0	0	0
Miscellaneous	2	2	0	0	0	0	0	0	0	0
Totals	12	9	5	5	2	6	1	3	1	1

Table 5. Cause of Pulmonary Failure in Total Artificial Heart Sheep

No.	Days	Cause of Pulmonary Failure
TH81S 3	0.5	Pneumonia
TH81S12	55.9	Hydrothorax
TH82S 7	13.8	Unknow
TH83S 3	3.7	Hemothorax
TH83S 9	19.1	Hydrothorax
TH83S10	11.7	Pneumothorax
TH83S11	5.8	Pneumothorax
TH83S15	5.2	Atelectasis

Table 6. High Blood Urea Nitrogen, Creatinine and Lactic Dehydrogenase Levels in Total Artificial Heart Sheep Surviving Over One Week

Animal	No. :	81S6	82S1	82S6	83S1	83S5	83S7	83S9	83S10	83S13
Days:		26	8	12	17	19	14	18	11	131
BUN	(1 wk)	114	70	56	52	53	46	89	74	14
(mg/dl)	(2 wk)	56	—	—	92	29	134	101	—	17
Cr	(1 wk)	3.0	2.1	1.3	1.5	1.6	1.4	4.4	4.2	0.9
(mg/dl)	(2 wk)	1.0	—	—	7.2	1.5	7.3	6.0	—	1.0
LDH	(1 wk)	447	501	1021	1893	2802	2187	2790	2505	1760
(U/ml)	(2 wk)	356	—	—	—	5000	6672	1028	—	702
Ht	(1 day)	34	28	14	24	18	21	17	23	18
(%)	(1 wk)	22	13	16	16	17	17	15	17	15
	(2 wk)	24	—	—	14	15	14	13	17	13
Blood*		(−)	(+)	(+)	(−)	(−)	(+)	(−)	(−)	(−)
CPB time	(min)	164	155	112	260	179	149	117	145	186

*Additional blood transfusion after the first postoperative day

Table 7. Hematocrit in Total Artificial Heart Sheep Surviving Over Two Weeks

		Hematocrit (%)					Free plasma hemoglobin (mg%)		LDH (U/ml)	
No.	Days:	Postop.	1 day	1 wk	2 wk	Average	1 wk	2 wk	1 wk	2 wk
80S 3	64	32	30	25	22	26	12	3	674	453
80S 4	169	28	23	24	24	26	12	7	664	677
81S 4	88	25	23	20	16	20	40	26	—	—
81S 6	26	34	32	22	24	—	33	28	447	356
81S12	55	27	25	20	18	18	27	44	733	562
82S 3	128	30	28	23	17	26	—	8	478	424
82S 5	297	31	30	22	21	23	5	6	442	468
82S 8	98	28	24	18	20	28	28	4	498	498
83S 1	17	26	24	16	14	—	2	23	1893	—
83S 4	61	40	32	27	23	25	28	18	907	561
83S 5	19	23	19	17	15	—	43	24	2802	5000
83S 6	87	22	21	18	18	18	—	42	—	794
83S 8	17	34	30	22	20	—	51	18	870	597
83S 9	18	22	17	15	13	—	42	55	2790	1028
83S12	51	26	21	13	16	20	52	162	439	876
83S13	131	29	18	15	13	22	14	22	1760	702

Table 8. Platelet Count and Prothrombin Time in Total Artificial Heart Sheep Surviving Over Fifty Days

No.		Valves	I	Anti.	Platelet count	Ave.	Prothrombin time Pre.		Ave.
	(days)				(×10000/ml)		(sec)		
80S 2	77	3 BS/nat	(–)	None	—	—	—	—	—
80S 3	64	BS/nat	(–)	None	9-68	45	15	16-21	18
80S 4	169	HK/HK	(–)	A	7-110	29	18	18-25	21
81S 4	88	HK/HK	(+)	C,H	20-55	36	18	29-37	32
81S12	55	HK/HK	(+)	C,H	20-33	26	17	17-37	22
82S 3	128	BS/HK	(+)	C,H	24-79	50	13	13-25	15
82S 5	297	BS/BS	(+)	C,A,H	10-46	25	14	14-25	18
82S 8	98	BS/BS	(–)	A	21-90	48	14	13-15	14
83S 4	61	BS/HK	(+)	C,H	26-44	34	13	14-25	17
83S 6	87	HK/HK	(–)	C	19-93	51	12	12-19	14
83S12	51	HK/HK	(+)	C,A,H	27-98	67	13	13-22	17
83S13	131	BS/BS	(+)	A,H	38-108	60	12	12-22	15

Valves: BS = Björk-Shiley, HK = Hall-Kaster, nat = natural
I: instrumented with open pressure-monitoring lines
Anti.: anticoagulant: A = aspirin, C = Coumadin, H = heparin

levels in the second postoperative week, with high creatinine levels (Table 6), which died, respectively, of sepsis, hemorrhage, and hydrothorax within 3 weeks. High lactic dehydrogenase (LDH) levels were seen in the first postoperative week in 7(32%) of 22 sheep surviving over one week, and 6(86%) of these 7 cases had high BUN levels as well.

Hematocrit (Hct) was well maintained at the first postoperative day's value in one sheep;

however, in the other 15 sheep surviving over two weeks, it dropped at a rate of between 3% and 11% (average 7%) from the first postoperative day's value within two weeks (Table 7). Average Hct throughout the experiment of each sheep which survived over 50 days was between 18% and 28%.

Out of those 43 cases, 12 sheep survived over 50 days (51.9 days to 297.5 days, average 109 days) (Table 8). In 2 sheep, pulmonary or both pulmonary and aortic natural valves were retained[49], and no anticoagulant was given. Seven sheep were instrumented with open pressure monitoring lines, and heparin was added in the flush solution. Coumadin was given to 5 sheep, aspirin was administered to 3 sheep, and both Coumadin and aspirin were used in two sheep. Thrombocytopenia (under 100,000/ml) was observed in 3 cases. Prothrombin time (PT) was well maintained 1-1/2 to 2 times the preoperative value in 2 of 7 cases with Coumadin; however, in the remainder of the 5 cases with Coumadin, PT fluctuated between normal value and two times the preoperative value.

Leucocytosis (over 10,000/cc) was observed in 2 of 5 cases which died of infection, and in 3 of 4 cases which died of thrombus-related causes (Table 9). Cardiac output was recently measured in 6 cases using the COMDU. Cardiac output per body weight at rest while in satisfactory condition, was between 130 and 150 ml/kg/min in one sheep, 110 to 130 ml/kg/min in 3 sheep, 95 to 110 ml/kg/min in one sheep, and 80 to 90 ml/kg/min in one sheep (Table 10).

There was no mineralization or thrombus formation on the diaphragm or the blood-contacting surface inside the ventricle, macroscopically. Three of 11 left ventricles were free from thrombus on their inflow or outflow tracts (Table 11). Three sheep had massive vegetative thrombus on the inflow or outflow tract of the left ventricle, obstructing 80%, 50%, and 20%, respectively, of the blood flow. There were multiple infarctions in 4 kidneys, some infarctions in 11 kidneys, one abscess in one kidney, and 50% necrosis in one kidney. Five kidneys (23%) were normal.

Apparent signs of systemic infection towards the end of the experiment were observed in 6 sheep. Four of those sheep had massive vegetative thrombus on the inflow or outflow tracts of the ventricles. Thromboemboli to the brain or the legs was the direct cause of death or termination in 2 sheep (TH83S6 and TH83S13). Infected percutaneous leads or drive lines were found in 4 cases (5 of 22 drive lines, 23%). There was no definite relation between the renal infarctions and the amount of vegetative thrombus on the inflow or the outflow tract of the left ventricle.

Five of 11 right ventricles were free from thrombus on their inflow or outflow tracts (Table 12). Infarctions or severe atelectasis of the lungs were observed in 3 cases which had massive vegetative thrombus on the inflow tract of the right ventricle obstructing 99% (fungal endocarditis), 25%, and 15% respectively, of the blood flow.

Table 9. White Blood Cell Counts in Total Artificial Heart Sheep Surviving Over Fifty Days

No.	WBC(× 1000/ml)	Average	Cause of Death or Termination
80S 2	—	—	Infection, air leak
80S 3	5.5-13.0	8.8	Vegetative thrombus
80S 4	4.5-8.5	6.8	Valve-holding ring failure
81S 4	4.0-8.0	6.0	Infection
81S12	2.8-9.5	6.0	Pulmonary failure
82S 3	5.2-13.4	8.2	Infection
82S 5	5.8-15.1	9.4	Valve failure
82S 8	2.6-9.5	5.1	Infection
83S 4	5.0-24.0	12.8	Infection
83S 6	4.8-11.8	8.0	Thromboemboli (brain)
83S12	4.9-12.0	8.0	Thromboemboli (lungs)
83S13	3.6-9.6	6.6	Thromboemboli (legs), valve failure

Table 10. Cardiac Output Per Body Weight of Total Artificial Heart Sheep

No.		Body Wt.	Cardiac Output per Body Wt.
	(days)	(kg)	(ml/kg/min)
82S 5	297	100	110-130
83S13	131	70	110-130
82S 8	98	65	130-150
83S 6	87	75	110-130
83S 4	61	95	80-90
83S12	51	100	95-110

Table 11. Infection, Vegetative Thrombus in the Left Heart, and Kidney Infarctions in Total Artificial Heart Sheep

	Inst.	S. Buttons		Infect.	Left Heart				Kidney Infarcts	
No.		L	R		LA	IN	Out	LV	L	R
80S 3	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(+)	(+)
80S 4	(–)	(+)	(+)	(–)	(–)	(–)	(–)	(–)	(–)	(–)
81S 4	(+)	(–)	(–)	(+)	(–)	1%	(–)	(–)	(++)	(++)
81S12	(+)	(–)	(–)	(+)	1%	1%	1%	(–)	1*	(–)
82S 3	(+)	(–)	(–)	(+)	(–)	50%	(–)	(–)	(+)	(+)
82S 5	(+)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(++)	(++)
82S 8	(–)	(–)	(+)	(+)	(–)	(–)	20%	(–)	(+)	(+)
83S 4	(+)	(–)	(–)	(+)	(–)	2%	2%	(–)	(+)	(+)
83S 6	(–)	(–)	(+)	(+)	2%	5%	(–)	(–)	50%	(+)
83S12	(+)	(–)	(–)	(–)	(–)	1%	(–)	(–)	(–)	(+)
83S13	(+)	(+)	(–)	(–)	(–)	(–)	80%	(–)	(–)	(+)

*abscess

Inst.: Instrumented

S. Buttons: infected skin buttons: L = left, R = right

Infect.: signs of systemic infection

Left Heart: vegetative thrombus, rate of obstruction (%) of the area.
LA = left atrium, In = inflow, OUT = outflow, LV = left ventricle

Kidney Infarcts: (–) = no infarction, (+) some infarctions, (++) = multiple infarctions

Table 12. Vegetative Thrombus of the Right Heart and Lungs in Total Artificial Heart Sheep

No.	Right Heart				Lung
	RA	IN	OUT	RV	
80S 3	—99%—		(–)	(–)	R: multiple infarctions L: unremarkable
80S 4	(–)	(–)	(–)	(–)	R: congestive L: congestive
81S 4	(–)	(–)	(–)	(–)	R: some atelectasis L: unremarkable
81S12	—25%—		1%	(–)	R: hydrothorax, 99% atelectasis L: unremarkable
82S 3	(–)	15%	(–)	(–)	R: some infarctions L: some infarctions
82S 5	1%	(–)	(–)	(–)	R: unremarkable L: unremarkable
82S 8	(–)	(–)	(–)	(–)	R: unremarkable L: unremarkable
83S 4	(–)	(–)	(–)	(–)	R: some atelectasis L: unremarkable
83S 6	2%	5%	5%	(–)	R: edematous L: edematous
83S12	(–)	(–)	5%	(–)	R: some atelectasis L: unremarkable
83S13	(–)	(–)	2%	(–)	R: unremarkable L: unremarkable

Right Heart: vegetative thrombus, rate of obstruction (%) of the area.
RA = right atrium, IN = inflow, OUT = outflow, RV = right ventricle

Suspected acute pulmonary hypertension due to pulmonary thromboemboli was the main cause of death in one sheep (TH83S12), which had small vegetative thrombus obstructing 5% of the outflow tract of the right ventricle. In two cases there were no thrombus on either inflow or outflow tracts of either ventricle (TH82S5 and TH80S4). Macroscopically, a congested liver was found at autopsy in 5 sheep (Table 13). Right heart failure was evident in 2 of those 5 sheep during the experiment. Abscess in the liver was found in 2 sheep which had systemic infection. Multiple infarctions, mild congestion of the liver with 20 liters ascites were found in one sheep (TH83S6), which died of thromboemboli to the brain.

Table 13. Pathological Changes of the Liver in Total Artificial Heart Sheep

No.	RHF	Cause of RHF	Ascites	Liver
80S 3	(+)	Right inflow vegetative thrombus 99% obstructed	6 L	Congested, fibrosis
80S 4	(−)		(−)	Unremarkable
81S 4	(−)		3.5 L	Slightly congested
81S12	(−)	Right inflow vegetative thrombus 25% obstructed	2.8 L	Some abscess
82S 3	(−)		(−)	Atrophic
82S 5	(−)		(−)	Unremarkable
82S 8	(−)	Pericardial abscess	5 L	Congestive, abscess
83S 4	(−)		1 L	Unremarkable
83S 6	(−)		20 L	Mild congestion Multiple infarctions
83S12	(−)		7.5 L	Unremarkable
83S13	(+)	Broken right inflow valve disc	23 L	Congestive

RHF: right heart failure

DISCUSSION

A. Materials

1. The heart. The size and shape of the artificial heart were investigated, coupled with improvements in materials. Previously, collapsable, sack-type hearts made from smooth Silastic were used in this laboratory. In 1970, the design was changed from sack-type hearts to hemispherical hearts, to reduce the rate of hemolysis[33]. However, thrombosis and thromboemboli were still problems with Silastic hearts.

Then Silicone Rubber was covered with a Dacron-fibril coating (Thermo-Electron Corporation, Waltham, Massachusetts, U.S.A.) developed by Bernhard and LaFarge[3]. The fibril was intended to affix a pseudoneointima derived from the blood proteins and to prevent further thrombus formation. However, the pseudoneointima was not self-limiting, and could become very thick and rigid, causing the focus of infection, producing embolization, and readily calcified in the calf[48].

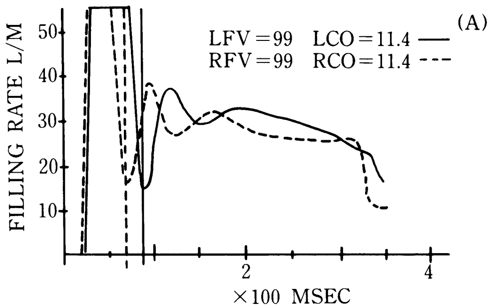
A polyurethane, hemispherical artificial heart was developed and showed better blood compatibility[41]. Since Avcothane-51 Elastomer™ (Avco-Everett Corporation, Waltham, Massachusetts, U.S.A.) and Biomer became commercially available, these materials were used for fabricating hearts. Dacron fibril-coated surfaces proved inferior to smooth surfaces (Avcothane-51 Elastomer, Biomer, and Silastic)[53]. Several fit trials, including one in a human cadavor, resulted in better fit and were performed in order that the artificial heart would not compress large vessels. In 1973 the JARVIK-3™ heart was developed, which showed better fit in the calf's chest.

However, thrombus formation in the ventricle was a problem with the JARVIK-3 heart. A seamless, internal surface was used in the JARVIK-5™ heart to eliminate thrombus formation at the diaphragm-housing junction (DH junction)[30]. Then the JARVIK-7 heart was developed for human use, and has been implanted in calves and sheep since 1978.

The artificial valves continued to be a potential problem with thrombosis, hemolysis, and occasional fracture. It was assumed that four mechanical valves in the human would result in serious anemia. In 1975 a technique was developed to excise the natural heart in the calf, leaving the pulmonary artery and aortic valves *in situ*[49]. The natural outflow valves had no regurgitation; if undamaged at surgery, the cardiac output was approximately 12% higher with the natural valve than when replaced with a Björk-Shiley valve[52].

However, outflow obstruction due to vegetative thrombus became a problem as an obstacle to the long-surviving animals. Vegetative thrombus was found at the remnant myocardium at the left outflow. The mechanism was not clearly understood, but the following hypothesis was considered: infection (endocarditis, local infection around the left outflow quick connect), turbulent flow or jetting flow, high pressure, and degeneration of the myocardium were involved in forming vegetative thrombus[19].

Two recent calf experiments with four mechanical valves (TH82C1 and TH83C2, survived 72 and 68 days, respectively) also developed severe left outflow obstruction due to vegetative thrombus during the extended episodes of systemic infection. Thus, the outflow obstruction due to vegetative thrombus was not unique to calves with natural outflow valves. The cause of death of one sheep (TH82S5) was a cracked right inflow valve disc, which swelled to a larger diameter and stuck in a closed position. This valve was purchased in 1976 and used in 10 earlier experiments (total valve-days in animals were 854). After the 47th postoperative day, the COMDU airflow curve of the right ventricle consistently dropped to zero after the decompression phase, which indicated the inflow of blood was slightly prevented by delayed opening of the inflow valve (Fig. 24).



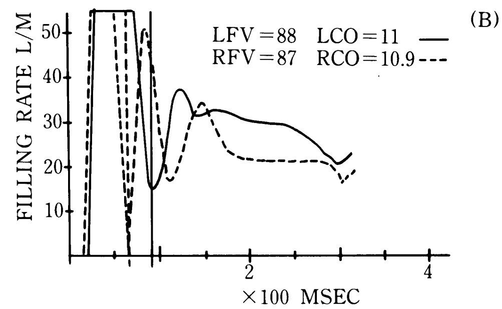


Fig. 24. Since the 47th day, the COMDU airflow curve of the right heart consistently dropped below zero after the decompression phase, which indicated the inflow of blood was prevented slightly by delayed opening of the inflow valve: (A) before the 47th day, (B) after the 47th day.

Cardiac valve failures (strut or disc) were encountered in 7 (26%) cases, and valve-holding ring failures in 2 (7%) of 27 animals surviving over 100 days, from 1975 through 1982 in this laboratory[5]. For long-term survival, prevention of mechanical accident is an important factor. When weak or failure-prone points were identified, design and fabrication techniques were modified to achieve improved reliability[14].

2. The Cardiac Output Monitor and Diagnostic Unit. Monitoring functions of the pneumatic total artificial heart by analyzing the driving air pressure waveforms has been used for many years[9,18,43]. Since 1982, the COMDU was used in studies on calves and sheep with pneumatic total artificial hearts. It was found that several conditions could be diagnosed by analyzing and correlation of the driving air-pressure waveform, stroke volume, filling rate, and shape of the filling curve of the COMDU, which proved to be very useful for clinical application of the pneumatic total artificial heart. The COMDU airflow curves led to diagnosis of the following conditions: hypovolemia (Fig. 25), pericadial tamponade (Fig. 26), malpositioning of the ventricles (Fig. 27), malfunctioning valves (Figs. 28, 29, and 30), pumping diaphragm problems (Figs. 31 and 32), malfunctioning heart driver (Figs. 33 and 34), and maladjustment of the heart driver (Figs. 35 and 36).

The COMDU was connected at the initial pumping of the heart, and driving parameters were adjusted while weaning off cardiopulmonary bypass. Any inflow obstruction was avoided by changing the heart's position. The optimal circulatory blood volume was obtained by monitoring cardiac output. In the early postoperative period, hypovolemia and the pericardial

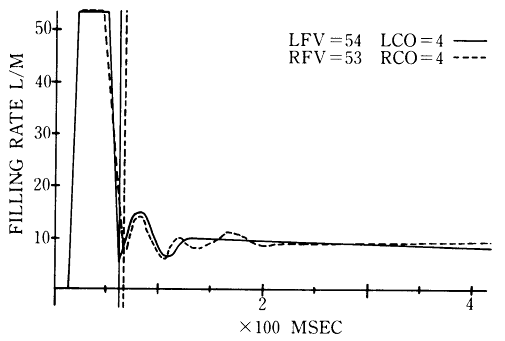


Fig. 25. The COMDU diagnosis: hypovolemia. The COMDU tracing was taken immediately after the operation. Low filling volume and low filling rate of both ventricles indicated hypovolemia.

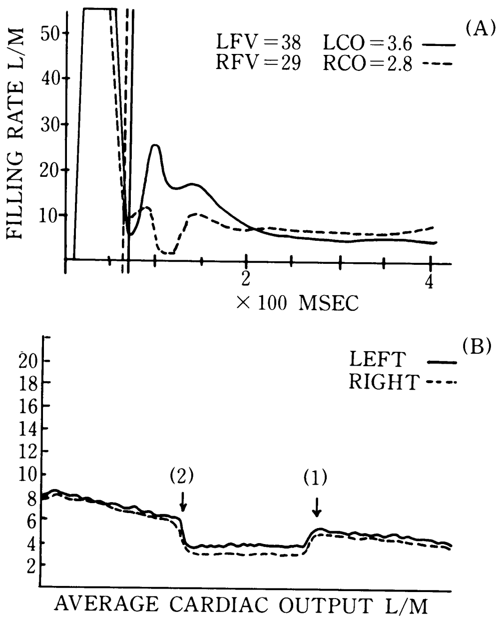


Fig. 27. The COMDU diagnosis: malpositioning of the ventricles. Early downswing of the airflow curve of the right ventricle, which was followed by low filling, indicated inflow obstruction (A). The IVC was compressed by the artificial heart when the animal was placed on its sternum after surgery (B-1). The chest was reopened and the position of the ventricles was corrected (B-2). Consecutive average cardiac output showed dramatic increase in cardiac output when the position of the ventricles was corrected.

tamponade were detected. Later postoperative inflow or outflow obstruction, diaphragm

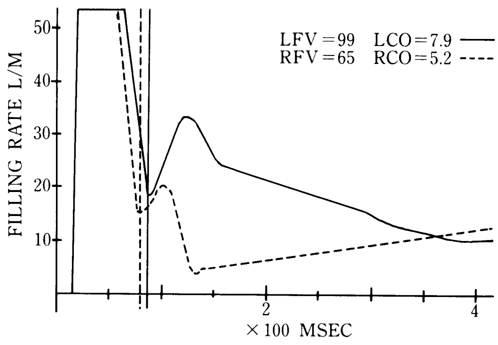


Fig. 26. The COMDU diagnosis: pericardial tamponade. High initial upswing of the airflow curve followed by limited low blood filling indicated pericardial tamponade.

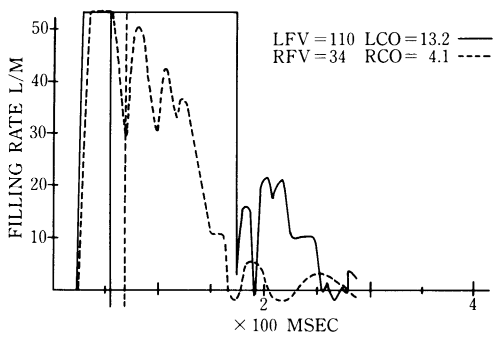


Fig. 28. The COMDU diagnosis: malfunctioning valve. Early, quick filling (the filling rate was over 50 liters/min) indicated regurgitation due to a dislodged disc of the inflow or outflow valve in the left ventricle. Entry of the blood could not be signalled to the computer. The starting point for integration was placed at the wrong point, so the left filling volume was not correct. Because of the high left atrial pressure and subsequent high pulmonary arterial pressure, the right ventricle could not eject blood.

problems, or malfunctioning valves were diagnosed. Any malfunctioning external heart driver was immediately replaced. The heart drivers were adjusted to have a reserve volume in each resting diastole by monitoring the stroke volume. This permitted larger cardiac output during exercise without changing the driving parameters. The COMDU allowed easy and noninvasive, precise monitoring and evaluation of the hemodynamic performance of the ventricles.

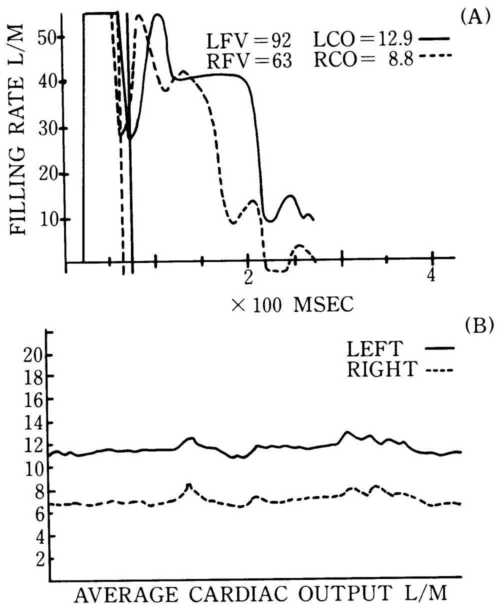


Fig. 29. The COMDU diagnosis: malfunctioning valve. High filling rate of the left ventricle and the clear difference in cardiac output between left and right ventricle, suggested left inflow or outflow valve regurgitation. High pulmonary arterial pressure was diagnosed by the airflow curve of the right ventricle, which showed incomplete ejection at the previous driving pressure.

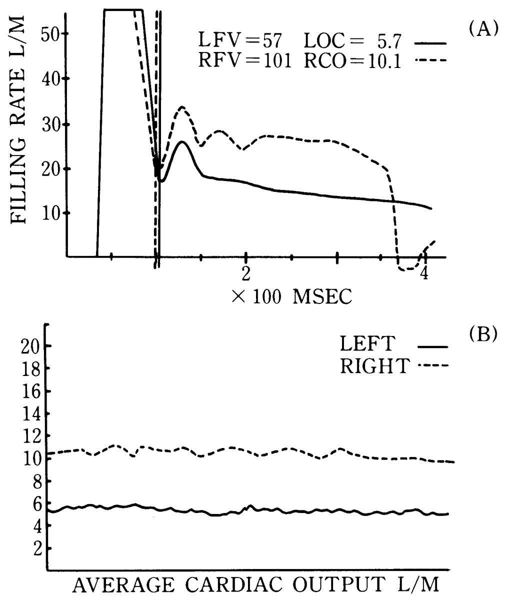


Fig. 30. The COMDU diagnosis: malfunctioning valve. The consistent, definite difference in cardiac output between left and right sides indicated right inflow or outflow valve regurgitation.

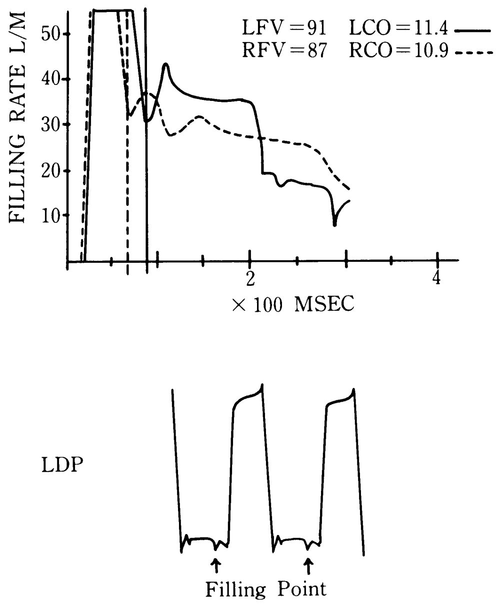


Fig. 31. The COMDU diagnosis: pumping diaphragm problems. During diastole, the pumping diaphragm sometimes occluded the orifice of the air drive line inside the base before the ventricle completely filled. Early filling point, previously indicated, appeared on the driving air pressure tracing, but was not a true filling point.

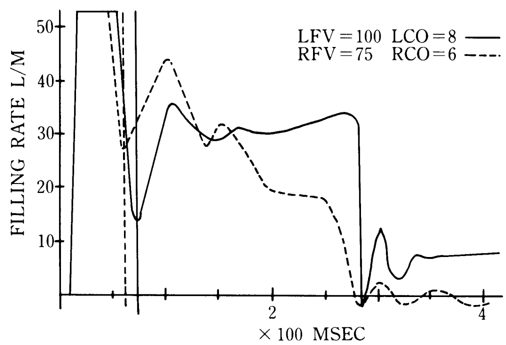


Fig. 32. The COMDU diagnosis: pumping diaphragm problems. Consistent, limited stroke volume was observed in a calf with a JARVIK-5 artificial heart (stroke volume 165 ml). A broken diaphragm was diagnosed and replacement of the left ventricle was performed. The air was trapped between the layers.

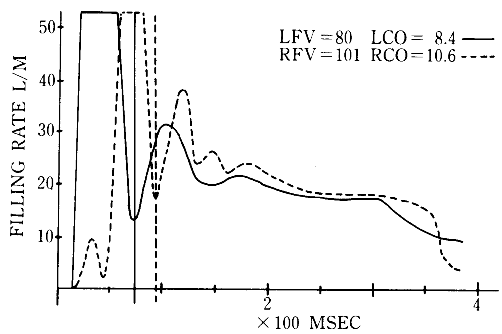


Fig. 33. The COMDU diagnosis: malfunctioning heart driver. Late beginning of the decompression phase of the right heart suggested malfunction of the driver.

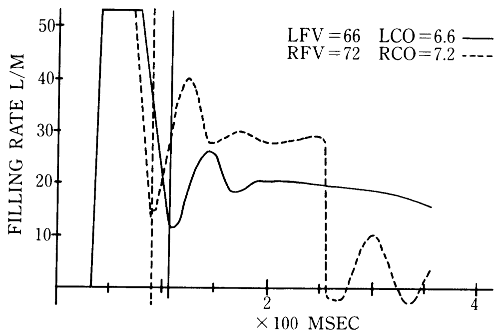


Fig. 35. The COMDU diagnosis: maladjustment of the heart driver. The right ventricle completely filled with only 72 ml of the filling volume, which meant the right ventricle was underdriven. The heart could not follow the Starling-like response because the right cardiac output was limited.

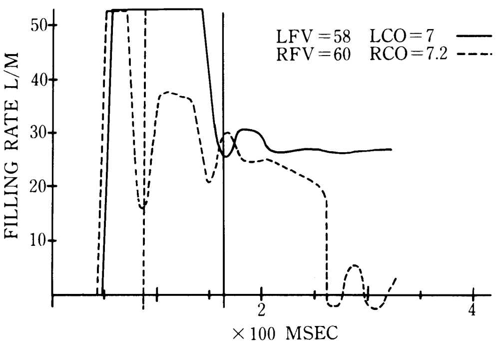


Fig. 34. The COMDU diagnosis: malfunctioning heart driver. Prolonged decompression phase of the left ventricle indicate the malfunction of the driver. Because of the shortened real diastolic phase, the blood could not properly enter the left ventricle, the pulmonary congestion appeared.

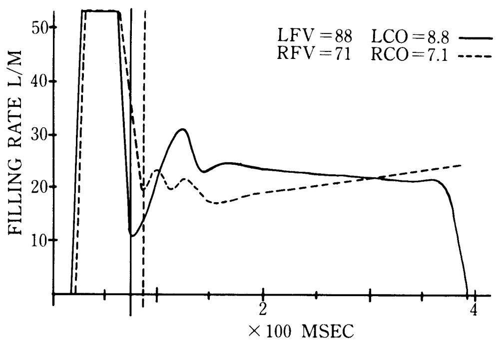


Fig. 36. The COMDU diagnosis: maladjustment of the heart driver. The left ventricle completely filled with only 88 ml of filling volume, which meant the left ventricle was underdriven. Because the left cardiac output was limited, the increased venous return would cause pulmonary congestion.

B. Methods

Since 1978, the JARVIK-7 heart has been implanted in calves and sheep. The average survival days of calves with JARVIK-7 hearts in 1978 were 80.8 days (4 cases), while those of sheep were 1.3 days (5 cases). From 1978 through 1983, 17 calves survived over 2 months on the JARVIK-7 heart (Table 14). TH83C14, which survived 226 days, began showing mild ascites at approximately day 150. Body weight increased from a preoperative value of 75 kg to a postmortem weight of 177.5 kg, with 17.2 liters of ascites. TH78C15, which survived 221 days, showed visible edema after 20 weeks when body weight exceeded 160 kg[43]. It was obvious that the growing calf needed a higher heart rate to obtain proper cardiac output with the JARVIK-7 heart. After a period of time, the calf outgrew the capacity of the JARVIK-7 heart and could not gain further body weight while still tolerating the mild exercise.

The primary cause of death or termination of these 17 calves were: mechanical accident (7 cases, 44%), pannus formation (3 cases), infection (3 cases), and others. Mechanical accidents included broken valves (3 cases), broken left out-

Table 14. Long-Surviving Calves with JARVIK-7 Total Artificial Hearts

No.	Days	Type	Valves	Cause of Death or Termination
83C14	226	B	HK/HK	Congestive heart failure, infection
78C15	221	B	BS/nat	Intestinal bleeding, pannus
82C18	162	B	BS/BS	Valve failure
81C 5	145	B	HK/nat	Air leak
82C19	137	B	BS/BS	Valve-holding ring failure
83C 4	136	B	HK/HK	Valve-holding ring failure
82C15	124	B	BS/HK	Valve failure
80C26	113	B	HK/HK	Infection
83C10	97	B	HK/HK	Thromboemboli to legs
78C 4	96	A	BS/nat	Thromboemboli
82C 7	89	B	BS/BS	Suspected valve failure
80C 8	82	B	BS/nat	Valve failure
82C 1	72	B	BS/BS	Valve-holding ring failure
83C 2	68	B	BS/BS	Infection
79C19	67	B	BS/nat	Elective termination
83C 8	63	B	HK/HK	Pharmacological study
80C14	62	A	BS/nat	Pannus

(From 1978 through 1983)
B = Biomer
A = Avcothane
BS = Björk-Shiley
HK = Hall-Kaster
nat = natural

flow valve-holding ring (3 cases), and air leakage between the housing and base (1 case).

Higher frequency of heart rate and subsequent higher driving pressures, which put excessive mechanical stress on the artificial heart, were necessary to maintain proper cardiac output for the growing calf. Those conditions were considered physiologically abnormal. Because of this limitation, the sheep was developed as a non-growing, adult animal model for the long-term testing of the JARVIK-7 heart.

C. Results

1. Infection. Infection was one of the major problems encountered in long-surviving animals with total artificial hearts[16,45]. Systemic infection was indicated by episodes of high fever spikes (over 40.0°C), loss of appetite, and leucocytosis. When high fever spikes were observed, a blood culture was taken and antibiotics were administered intravenously. If there were no more fever spikes and the blood culture was negative, antibiotics were stopped. If the blood culture was positive, appropriate antibiotics were given for at least two weeks. Subsequently, another blood culture was taken. High fever spiking was the most reliable parameter to detect infection, because the body temperature was taken every 4 hr, while the hematologic evaluation was made only once a week. Leucocytosis was not a good index for infection. In the experimental animal, bacteria came from various sources. It would appear that postoperative bacteremias were the source of the majority of infections with the total artificial heart[45].

The most obvious source of bacterial invasion of the blood stream came from multiple, open-port pressure lines[45]. TH82S5 had high fever spikes during the time pressure monitoring lines were open and flushed every hour, until they were cut and sealed by the 66th postoperative day. Local infection around the drive lines or pressure monitoring lines has recently been rare. The drive lines had strain-relief types of percutaneous leads, and all pressure monitoring lines had Dacron cuffs at the skin surface. The surrounding tissue was firmly attached to the Dacron cuff, thus forming a barrier to bacterial invasion.

The animals had decreased reticuloendothelial and polymorphonuclear leucocyte phagocytic function after artificial heart implantation, which might be one of the causes of prolonged bacteremias[32,57]. Luderer et al reported that the pharmacokinetics of the antimicrobial agents were different in the calves than previously reported in man, and recommended that either dosage be increased for antibiotics, or that dosing intervals be shortened when treating serious infections in calves[39].

TH82S5 suffered from high fever spikes several times, but those episodes were successfully treated with antibiotics. The sheep did not develop any endocarditis-like vegetative thrombus and overcame the symptoms of infection, although persistent bacteremias were still life-threatening. Once the animal developed vegetative thrombus in the artificial heart, it was difficult to treat with antibiotics. As early valve replacement for the patients with infective endocarditis was recommended[37,59], replacement of the artificial heart was necessary to remove the vegetative thrombus. However, the reoperation caused marked increase of secondary infection, although both ventricles were never successfully replaced at that time[20]. Recently, explantation of the total artificial heart, with no identifiable infection, was performed 2 to 3 months after total artificial heart implantation, and the calf was successfully transplanted with the normal heart of its chimeric twin[55,56]. In order to remove the vegetative thrombus, replacement of both ventricles instead of a single ventricle, could be recommended to prevent secondary infection.

2. Pneumatic Driving Parameters. Atrial pressures of the sheep (TH82S5) were higher than the normal physiological range (2 to 7 mmHg), although the sheep had approximately 110 ml/kg/min of cardiac output. Mean right atrial pressures (RAP) varied from approximately 7 to 20 mmHg daily. When the heart rate was fixed at 110 beats/min the sheep developed ascites.

There are many reports indicating that high RAP was generally observed as a complication in long-term total artificial heart animals. Honda et al reported a close relationship between anemia and the increase in venous return[25]. However, Kasai et al found that progressive anemia was not a phenomena specific to total artificial heart recipients, and the hemodilution with hypervolemia was not necessarily a major cause of this anemia[29].

Murakami et al reported a correlation between high RAP and high circulating blood volume (CBV). In order to maintain a physiological range of CBV, the cardiac output must be kept in a range close to 120 ml/kg/min, and at this range of CBV, RAP could be maintained close to 10 mmHg[44]. However, Mochizuki et al reported that their total artificial heart recipient calves showed no abnormal increase in CBV, and it was impossible to maintain both atrial pressures within normal physiological range, although the cardiac output was 110 ml/kg/min[42].

Henning et al reported that the high RAP was caused by insufficient cardiac output resulting in high CBV and subsequent low hematocrit. In order to maintain animals in normal physiological conditions, a cardiac output of 120 to 140 ml/kg/min seemed to be required[24]. On the contrary, Atsumi et al reported that the increase in circulating plasma volume was caused by high cardiac output, so that the decrease in hematocrit might be prevented by maintaining cardiac output at a range between 80 and 110 ml/kg/min[2]. Tsushima et al suggested that high RAP and CBV were correlated to possible disturbance of protein metabolism, if the total artificial heart's performance was sufficient with a cardiac output of at least 70 ml/kg/min[64]. Harasaki et al indicated that an output more than 90 ml/kg/min was necessary to maintain the calf in good physiological condition, and high RAP and CBV were reflected in the morphological changes of the atrium[22].

The true mechanism of high RAP was not clearly understood. During the early postoperative period of the sheep (TH82S5), driving parameters were set to obtain almost complete filling of the ventricle at rest, which resulted in high RAP because the ventricle filled completely while the animal changed position or walked on the treadmill. Bucherl et al[4] reported that animals with their natural heart showed a typical daily profile of cardiac output, while their RAP stayed at almost a constant level. So, a constant cardiac output during the day in animals with total artificial hearts resulted in high mean RAP profiles because their pump had a much flatter Frank-Starling curve than that of the natural heart[4].

Recent studies show that the RAP could be maintained around 10 mmHg if the heart rate was set higher when the animal was at rest, to have some reserve volume during exercise. Increase in venous return was followed by increase in cardiac output during exercise if the ventricle had adequate, Starling-like response[40,51].

If there was no reserve volume in each cardiac cycle at rest when the flow demand increased beyond the pump's capacity, the heart rate had to be set to a new, higher level manually[63]. Higher heart rate decreased the filling sensitivity of the ventricle. Recent data taken from the sheep, in which the driving parameters were set to have some reserve volume during exercise, indicated the necessary cardiac output varied from 80 to 150 ml/kg/min. Because the animal needed relatively larger cardiac output than expected, the higher heart rate was required to maintain proper cardiac output. Decrease in the filling sensitivity of the ventricle seemed to be one of the causes of high RAP.

The JARVIK-7 heart had relatively good filling sensitivity of the pumping diaphragm under conditions with low outflow resistance, low percent systole (35%), and no valving[38]. However, high driving pressure, high percent systole, and two mechanical valves might decrease the filling sensitivity of the ventricle.

Systemic vascular resistance (SVR) was not too high immediately after surgery, and soon decreased to less than 800 dynes·sec/cm^5, which showed the same trend as in previously reported cases[60].

3. Hematologic and Blood Chemistry Analyses. The most marked alterations in laboratory values were seen in the first two weeks after surgery; for instance, high SGOT, high LDH, and low total protein, as reported previously[31]. The sheep reached a stabilization period and was maintained in good health for the remainder of the survival time.

Hematocrit (Hct) of the sheep showed continuous decrease in the first one to two weeks postoperatively, then increased gradually to a stable value without the need of blood transfusion. The cause of decrease in Hct was not clear, but hemolysis and lack of a blood transfusion played a role in this phenomenon. It wa obvious that increased transfusions caused additional hemolysis. Thus, the complete hemostasis during the surgery was essential for the sheep. It was suspected that there might be some type of blood reaction after cardiopulmonary bypass, resulting in hemolysis. Some of the sheep did have extensive hemolysis and the prognosis was unfavorable. Further study is needed to identify the mechanisms and elminate postimplantation hemolysis to establish constant success in the sheep experiments.

It was difficult to maintain the sheep's prothrombin time (PT) at 1-1/2 to 2 times the preoperative value with Coumadin. The reason was that the sheep was a ruminant animal. The effect of Warfarin was affected by the amount of Vitamin K, which was adsorbed simultaneously. When the sheep lost their appetite, less Vitamin K was adsorbed, and subsequently the PT increased to two times the preoperative value. It was recommended that continuous anticoagulation with warfarin be maintained for all patients with Björk-Shiley prosthetic cardiac valves, to prevent thrombosis of the prosthesis[65]. However, anticoagulant therapy in total artificial heart animals is still under investigation.

4. Pathophysiological Evaluation. There was no mineralization or thrombus formation in the ventricle macroscopically, but early signs of mineralization were observed at the microscopic level. These signs were reported in the sheep which survived 77 days with a total artificial heart[7]. There were 12 sheep with total artificial hearts which survived over 50 days (from 1980 through 1983), and macroscopically there was no, or very little, thrombus formation in the ventricle. It would appear the incidence and severity of mineralization was dependent upon the animal's species or age. Mineralization of the diaphragm was less of a problem in adult sheep than it was in growing calves. Further study is under way to identify the mechanisms of mineralization. Pannus did not develop in these sheep. TH82S5 had no thrombus on the inflow or outflow tract of the ventricle at the quick connect, or at the junction between the stellate steel valve-holding ring and the polyurethane housing

of the heart, which were the predilection sites of thrombus formation in recent experiments. It was difficult to identify the cause of renal infarctions, because most sheep had four pressure-monitoring lines. Kidney function remained normal in all long-surviving sheep throughout the course of the experiment.

The etiology of the pulmonary dysfunction and its prevention are at this time unclear. Further study is needed to assess the relationship changes associated with cardiopulmonary bypass and ovine lung dysfunction due to platelet aggregation[15].

ACKNOWLEDGEMENTS

From March 1982 through April 1984, I participated in 126 surgeries (pneumatic total artificial heart implantation in 47 calves and 26 sheep, electrohydraulic total artificial heart implantation in 12 calves, cardiac transplantation in 4 calves, and ventricular assist device implantation in 37 sheep) at the University of Utah. I was First Surgeon in total artificial heart implantations on two calves and eight sheep, and 18 sheep implanted with ventricular assist devices. I was primary investigator (Principal Investigator) on 14 total artificial heart calves and 15 total artificial heart sheep, one of which (TH82S5) survived for a record 297 days.

Special thanks are given to Professor Willem J. Kolff, M.D., Ph.D., for his invitation to come to the University of Utah, and the kind supervision during my stay; to Don B. Olsen, D.V.M., Director, for his thorough instruction and review; and to all the staff members and other personnel of the Artificial Heart Research Laboratory, Division of Artificial Organs, University of Utah, for their supervision and cooperation.

Some sections of this manuscript were presented at the Fourth Congress of the International Society for Artificial Organs, Kyoto, Japan in 1983.

This work was supported in part by grants from the National Institutes of Health via the National Heart, Lung, and Blood Institute's grants number HL-24561 and by the Development Fund of the Division of Artificial Organs, to which contributions have been made by many generous donors including: Ethicon Laboratories, Ben Matthews, Digital Equipment Corporation, and Square-D Foundation.

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