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Abstract

A biventricular bypass type total artificial heart (BVB-TAH) utilizing two pusher-plate pumps was developed and implanted in a sheep for 48 days with excellent results. A Hall effect sensor was utilized to operate each pump independently with a full stroke at variable rates (VR). With this system, the animal's hemodynamics was kept physiologically, and all metabolic parameters except hemoglobin and hematocrit returned to normal three weeks after implantation. However, signs of infection appeared on the forty-second day, and consequently the animal fell into a state of shock. Even at that time the BVB-TAH maintained circulation by increasing pumping rate automatically. On the forty-eighth day, the animal could not stand and suffered from anuria; the experiment was then terminated after 1,140 h pumping. At autopsy, there was an enlarged heart with an atrophic change, 1,900 ml of pleural effusion, and 3,100ml of ascites fluid. Blood culture taken on the forty-seventh day yielded Acinetobacter calcoaceticus. The BVB-TAH operated in an independent VR mode maintained entire circulation, and has a capability of substituting the native heart function in any situation.

KEYWORDS: biventricular bypass, total artificial heart, pusher-plate pump, Hall effect sensor, variable rate mode

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A Sheep Survived for 48 Days with the Biventricular Bypass Type Total Artificial Heart

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A biventricular bypass type total artificial heart (BVB-TAH) utilizing two pusher-plate pumps was developed and implanted in a sheep for 48 days with excellent results. A Hall effect sensor was utilized to operate each pump independently with a full stroke at variable rates (VR). With this system, the animal's hemodynamics was kept physiologically, and all metabolic parameters except hemoglobin and hematocrit returned to normal three weeks after implantation. However, signs of infection appeared on the forty-second day, and consequently the animal fell into a state of shock. Even at that time the BVB-TAH maintained circulation by increasing pumping rate automatically. On the forty-eighth day, the animal could not stand and suffered from anuria; the experiment was then terminated after 1,140 h pumping. At autopsy, there was an enlarged heart with an atrophic change, 1,900 ml of pleural effusion, and 3,100 ml of ascites fluid. Blood culture taken on the forty-seventh day yielded *Acinetobacter calcoaceticus*. The BVB-TAH operated in an independent VR mode maintained entire circulation, and has a capability of substituting the native heart function in any situation.

Key words : **biventricular bypass, total artificial heart, pusher-plate pump, Hall effect sensor, variable rate mode**

Total artificial hearts (TAH) have been developed in the past three decades. The survival of experimental animals has gradually increased from several hours in first experiments to over 200 days as recently reported (1-3). In 1984, DeVries and his associates used Jarvik-7 TAH as a permanent cardiac replacement in four patients. Survival for as long as 620 days was achieved, but multiple complications such as thromboembolism or infection limited the patients' survival (4). His results were encouraging and thereafter, temporary use of the TAH and a paracorporeal ventricular assist device as a bridge to cardiac transplantation have dramatically increased. To date, of 400 patients who received ventricular assistance in conjunction with heart transplantation, 130 (32.5%) received biventricular support with an average duration of 11 days (5).

Since 1988, we have developed a biventricular bypass system for use in the future as a bridge to

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cardiac transplantation. This paper details our biventricular bypass type TAH (BVB-TAH) with pneumatically driven pusher-plate (PP) type pumps, and presents data on a sheep which survived 48 days after the BVB-TAH implantation.

Materials and Method

Description of the BVB-TAH system. The system consisted of a pair of pneumatically powered PP type blood pumps (Fig. 1), a pneumatic power unit, and a control system (Fig. 2). A block diagram of the BVB-TAH system is illustrated in Fig. 3. The pumps with a stroke volume of 60 ml for the left side and 40 ml for the right side were used to clarify an independency of each pumping. The pump consists of three parts, inner (blood side) and outer (air side) pump housings, and a flexing diaphragm attached to the PP on the airside. The pump diaphragm was made of segmented polyurethane (Biomer®, Ethicon, Somerville, NJ, USA) while the rigid outer housing was made of epoxy resin. The blood contacting surface including the inner surface of the blood side housing and the flexing diaphragm was coated with the segmented polyurethane. Björk Shiley monostrut valves of 25 mm and 21 mm were used in the inflow and the outflow ports, respectively. The pumps incorporated the Hall effect position sensor which was attached on the air side housing, while its companion magnet was mounted on the PP. The Hall effect signal was utilized to compute the pumping rate, beat-to-beat stroke volume, pump output per min, and to precisely regulate the PP movement (6). Inlet and outlet cannulae of 12 mm in-diameter were coated with segmented polyurethane. The transthoracic portions of the cannulae were externally covered with Dacron velours to encourage tissue growth and to provide firm fixation to the skin and connective tissues to thereby reduce bacterial invasion. A Dacron graft formed the end of the outlet cannula and permitted a standard anastomosis to the aorta or pulmonary artery.

The control-drive unit (Model 113, Yasuhisa Biomechanics Co., Tokyo, Japan) is capable of functioning in three different modes: fixed rate (FR) mode, R-wave synchronized mode, and variable rate (VR) mode. In the VR mode, the Hall effect signal is utilized to regulate the pump stroke volume at a constant level, while its rate is allowed to vary depending on its preload and afterload (6). In case of component failure, an alarm circuit, which is incorporated into each side, is activated, thus controlling an electromechanical relay to transfer the pump into the preset FR mode of operation.

BVB-TAH implantation. A male sheep weighing 50 kg was selected for the experiment. The animal was fasted overnight prior to the implantation, with free access to water. Anesthesia was induced and maintained during surgery using 1.0–1.5% Halothane and 50% nitrous oxide mixed with oxygen. Respiration was controlled by using a volume-cycle respirator with 15ml/kg of tidal volume. The chest was opened through the fifth intercostal space and a single dose of heparin sodium

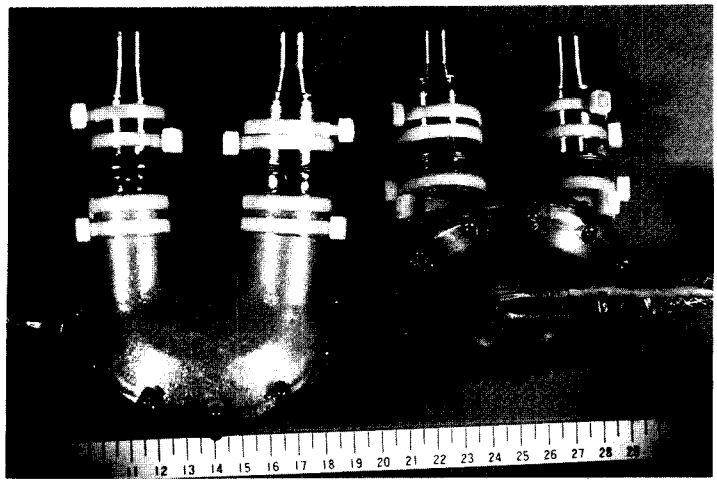

Fig. 1 A pair of pusher-plate pumps with a Hall effect sensor. Left: 60 ml stroke volume, Right: 40 ml.

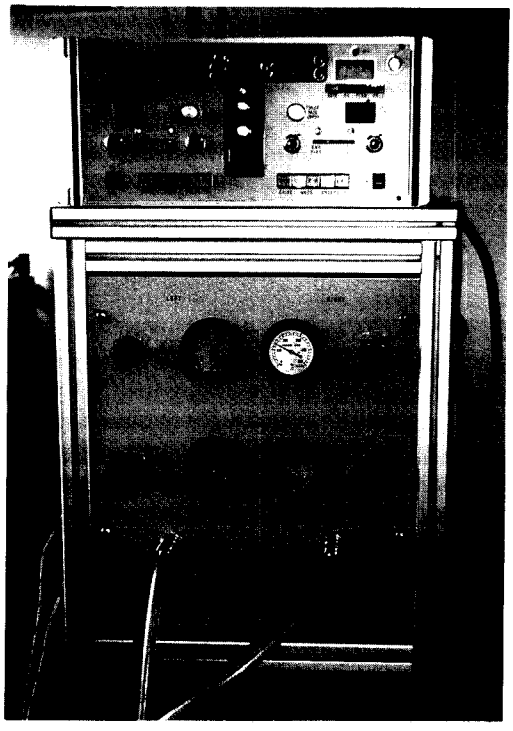

Fig. 2 Front view of control-drive unit for pusher-plate type TAH.

(1mg/kg) was injected intravenously before cannulation. The drainage cannula of the left bypass pump was then inserted into the left atrium through the Dacron atrial cuff which was sutured to its appendage, while the outflow cannula was anastomosed to the descending aorta. The PP pump primed with saline was connected to the cannula, placed on the animal's chest, and operated in the VR mode. The right bypass circuit consisted of the drainage cannula being inserted into the right atrium through the atrial cuff and the return cannula being anastomosed to the pulmonary artery. After first initiating a pumping action in the right side, both pumps were operated in an independent VR mode. Following the control data acquisition, the native heart was fibrillated by an electrical shock, and the artificial hearts thereafter maintained the entire circulation. A drainage tube was placed in the chest cavity. The chest was closed in layers, and the animal was placed in a special cage. The experiment was performed without any blood transfusion. Antibiotics, such as cefazolin, were administered for the first two weeks. Anticoagulant was not applied after the operation.

Hemodynamic and metabolic measurement. Two 16 gauge fluid-filled catheters were advanced into the ascending aorta and near the right atrium through the left internal thoracic artery and vein to monitor arterial blood pressure and central venous pressure (CVP), respectively. Both pressures were continuously recorded on a polygraph (San-ei Co., Tokyo, Japan) using pressure

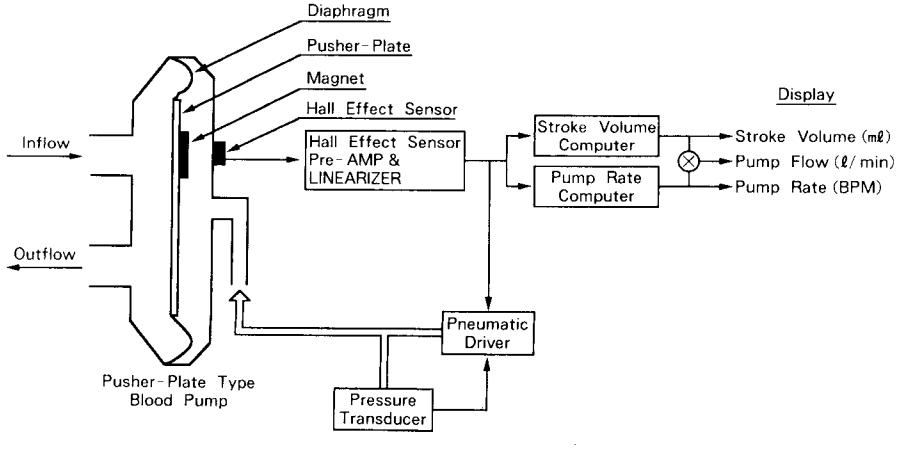

Fig. 3 Block diagram of the BVB-TAH system using pusher-plate pumps.

transducers with zero reference at the right atrium level. During the experiment, the right pump output was employed for the total flow, which was computed by multipling the beat-to-beat rate by the stroke volume of 40 ml. For metabolic information, blood samples were taken every day in the first postoperative week, and thereafter taken once a week, for the measurement of blood gases, oxygen saturation, hemoglobin, hematocrit, serum free hemoglobin, venous lactate, antithrombin-III (AT-III) and other blood chemicals.

Results

Postoperative course. Total operating time was 4 h 40 min. Recovery from anesthesia was excellent and one hour postoperatively, the animal was extubated and it was standing and urinating one hour later. From the second day, intravenous hyperalimentation of 600 cal per day was administered. On the third day, the chest drainage tube was removed. During the first week, the mean aortic pressure gradually declined despite the flow being maintained at more than 100 ml/min/kg, and the animal's activity reduced. On the seventh day, the intravenous hyperalimentation was stopped because the blood sugar level was greater than 500mg/dl. Thereafter the blood sugar level stabilized between 40 and 50 mg/dl, and the sheep could eat well, bleat and stand up almost all day long (Fig. 4). On the twenty-fourth day, a deep decubitus was found in the anterior chest wall. It was cured using a chest pad for one week. On the forty-second day, appetite decreased and the animal appeared less active. Thereafter some changes were found in the animal's physiological condition: 1. body temperature was greater than 39°C; 2. face edema was found and the abdomen became distended; 3. mean aortic pressure tended to decrease; and 4. the pump flow tended to increase. These findings indicated that the animal was in a state of septic shock characterized by hypotension, peripheral vasodilatation and normal flow. Administration of antibiotics was restarted. Nevertheless, on the forty-eighth day the animal could not stand and suffered from anuria. The experiment was terminated on August 15, 1990, after 1,140 h of artificial heart pumping.

Hematology (Fig. 5). The values of hemoglobin and hematocrit changed in parallel and had a tendency to decrease in the first week. On the twelfth day, values decreased to 5.7mg/dl and 16.8%, and inceased at 8.4mg/dl and 24.7% on

Fig. 4 The BVB-TAH sheep kept in a cage showing the location of the artificial hearts. This picture was taken on the thirty-second postoperative day.

the twenty-first day, respectively. Therefore, during the same period, a marked increase in the serum free hemoglobin level from 20.2mg/dl on the fourteenth day to 32.7mg/dl on the twenty-first day was observed. The cause of this hemolysis was not identified. Except for the third week, a serum free hemoglobin level was maintained at less than 10mg/dl. However, the resultant values of hemoglobin and hematocrit never returned to the control level.

AT-III, which is a good indicator of disseminated intravascular coagulation, decreased markedly in the first two days, and returned to the control level on the fifth day. During the subsequent 5 weeks it remained within normal levels and thereafter it declined to 76.5% by the end of the experiment.

Liver and kidney functions (Fig. 6). Total protein decreased to around 5.0g/dl for the first week but then returned to normal levels. Glutamic oxaloacetic transaminase increased markedly to over 1000IU/l immediately after surgery. However glutamic pyruvic transaminase remained within normal levels throughout the experiment. Blood urea nitrogen and creatinine remained within normal range except during terminal episode.

Hemodynamics (Fig. 7). Flow, expressed in ml/min/kg, maintained between 100 and 110 until the thirty-fifth day, and tended to increase thereafter. The mean aortic pressure was maintained at greater than 70 mmHg except for the low levels of the first week. CVP remained at between 10 and 15mmHg until the forty-fifth day and then rose to 27mmHg. Values of venous lactate, which indicates the state of peripheral circulation, were under 10mg/dl except for the last three days.

Autopsy findings. The sheep was well nourished and had well-developed skeletal muscle. No signs of infection were observed around the drive line, and all wounds were well healed. A subcutaneous edema in the face and a brisket were found. There was also a 1,900ml serous effusion in the right pleural cavity and 3,100ml of serous ascites in the abdomen.

The trachea, right lung and lower lobe of the left lung were neither edematous nor congestive. The upper lobe of the left lung was atelectatic and

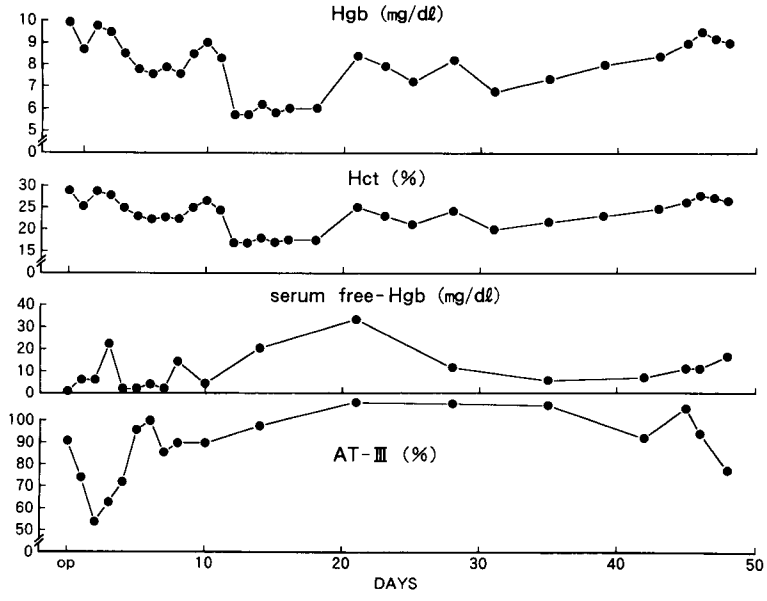

Fig. 5 Hematology and coagulation factor expressed as hemoglobin (Hgb), hematocrit (Hct), serum free-Hgb, and antithrombin-III (AT-III).

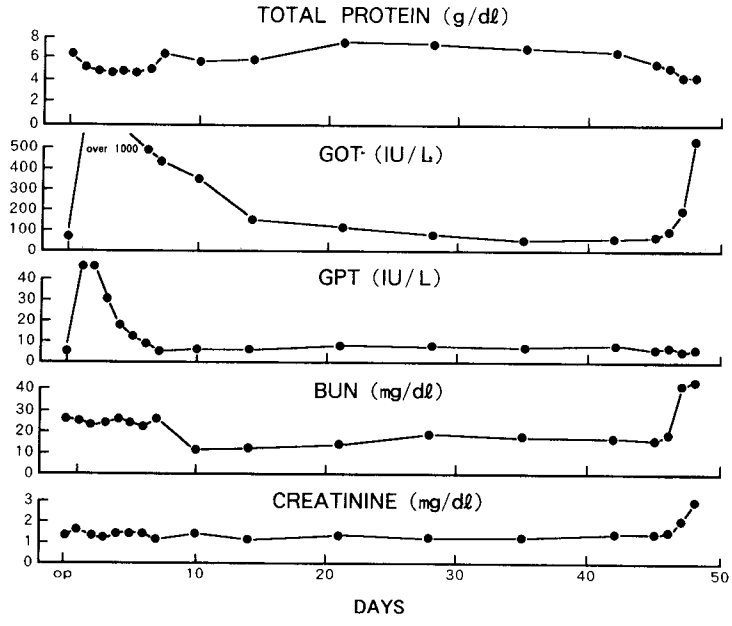

Fig. 6 Liver and kidney functions expressed as total protein, glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), blood urea nitrogen (BUN), and creatinine.

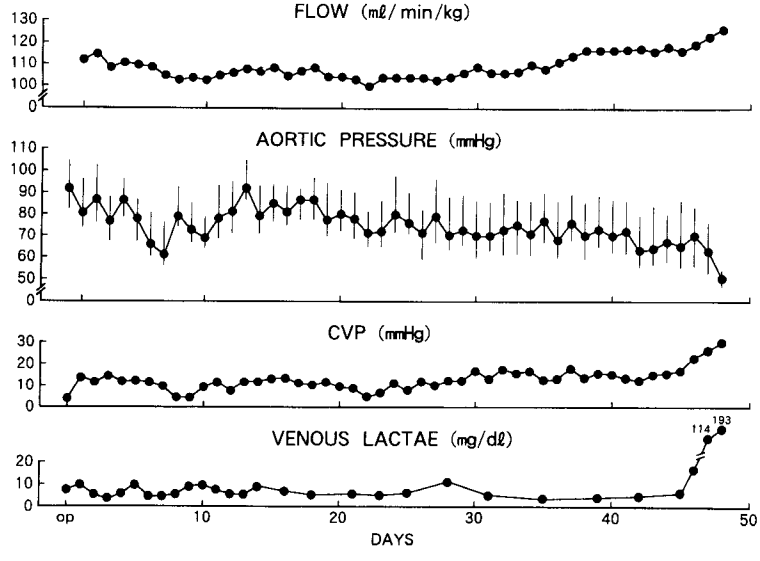

Fig. 7 Hemodynamic changes and venous lactate levels.
CVP: central venous pressure

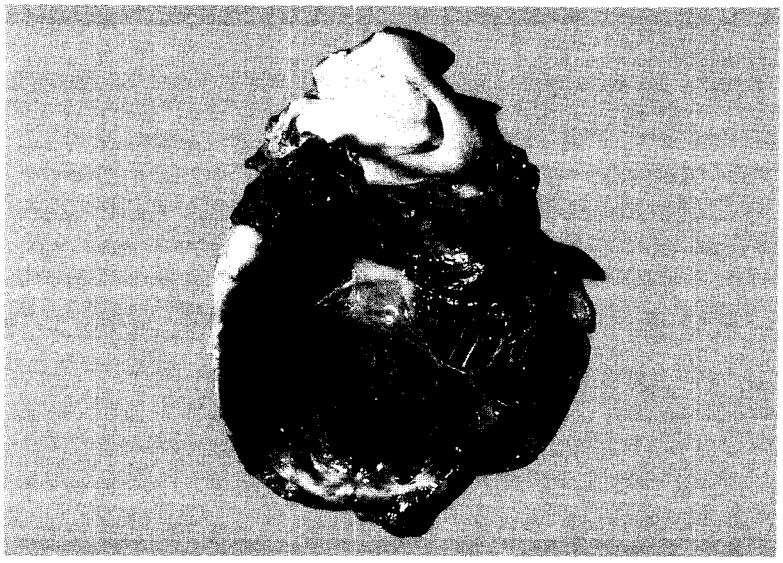

Fig. 8 The enlarged heart with atrophic changes of both ventricles.

adherent to the chest wall.

Good tissue growth occurred around the velours covering the cannulae and the native heart. Both ventricles of the native heart were markedly enlarged with extreme atrophy or thinning of the ventricular wall (Fig. 8). In the abdominal cavity there were no adhesions, hematoma, abscess, or signs of infection. No abnormal changes were observed in an outward appearance or cut surface of the liver, both kidneys, spleen and the digestive tract.

There were no serious thrombi on the blood contact surface of both artificial hearts or cannulae. However, linear thrombi were found along the artificial valve ring, and also at the junction of artificial heart and inflow cannulae.

Blood culture, which was obtained on the forty-seventh day, yielded *Acinetobacter calcoaceticus.*

Discussion

The goal of our experiment was to establish a biventricular bypass system with the ability of a total circulatory maintenance. In the present study, hemodynamic performance of our system was evaluated in the form of BVB-TAH. In TAH experiments, the control method is an important factor in optimizing pump performance. Most totally replaced type artificial hearts to date have used the atrial pressure as a parameter to control a rate filling of the ventricle. This method provides two alternatives for pumping the heart; constant frequency with variable stroke volume, and variable frequency with constant stroke volume (7). The former control method, so called FR mode, operates two pumps in the fill-limited mode. Therefore, a large stroke volume is necessary to insure adequate flow from a pump, and pressure measurement is also required to regulate atrial pressure. The latter control method, so called VR mode, insures complete filling and ejection of the pump, and the pumping rate is allowed to vary from beat to beat with changes in filling pressure and afterload. In this fill-empty operation, blood stagnation in the pump is eliminated and invasive measurement is no longer required.

It was for above reasons that we employed the VR mode as a control method for our BVB-TAH. Although hemodynamic performance of

totally replaced TAH operated in the independent VR mode was fully justified (8), in the case of the BVB-TAH a question arises concerning the pump flow sensitivity to the filling pressure due to its thin cannulae.

During the 48 day experiment, the BVB-TAH with a varied stroke volume pump capacity was able to pump independently and to yield enough flow at greater than 100ml/min/kg. It also maintained a mean aortic pressure of between 70 and 90 mmHg except for the first hyperglycemic period and toward the end of the experiment. Readjustment of the driving condition was not necessary after the operation. For the last 5 days when the sheep was in a state of shock, an interesting phenomenon observed was the increase of pump output resulting from increase in the pumping rate. This is similar to the functioning of a native heart when a patient is in a state of septic shock.

One problem concerned with a hemodynamic state is the tendency to increase flow as observed from the thirty-sixth day, despite the sheep's excellent condition. Regarding the dilated and atrophic native heart, there is a possibility that aortic or pulmonary regurgitation caused the increase of flow. Otherwise it would seem to be an initiation of sepsis. In BVB-TAH animal experiments with fibrillating hearts, Atsumi *et al.* reported the occurrence of peripheral circulatory insufficiency due to the aortic and mitral valve regurgitation which were caused by atrophic change of the native heart (2). Harasaki *et al.* indicated that atrophy of unloaded ventricles and enlargement of atria were apparent in the animals with non-pulsatile BVB-TAH which survived for longer than 34 days (9).

The blood compatibility of the biolized material was excellent without anticoagulant therapy. Although the linear thrombi adhered to the valve ring and the conjunction of inflow cannulae, there were no serious thrombi in both circuits. Transient hemolysis of unidentified origin occurred on the fourteenth and twenty-first days, and consequently caused the decrease of hemoglobin and hematocrit. This severe anemia improved in about 7 days. However, another problem was a slight anemia which persisted throughout the experiment. Imachi *et al.* indicated that slight anemia in animals with BVB-TAH without native heart beating or totally replaced TAH was caused by a deficiency of impulse to sympathetic and vagal nerves (10). AT-III decreased markedly in the first two days, and returned to the normal level five days after the operation. This reduction of AT-III was not a phenomenon specific to BVB-TAH recipients.

Major problems previously identified in experimental and clinical TAH recipients were local and general infections (3, 11, 12). In this case, the bacteremia was identified from the blood culture in spite of systemic aseptic procedures, precise application of antibiotics, and treatment of local infections. Although no infectious regions were found in the autopsy, two intravascular catheters or four cannulae which directly penetrated the chest wound might be a cause of infection.

In conclusions, the BVB-TAH using pusher-plate pumps which operated in the independent VR mode was developed and were implanted in a sheep for 48 days. Hemodynamic parameters were kept at near normal levels. Advantages of the VR mode are as follows: manual adjustments and invasive monitorings are no longer required once the pump operating conditions are established. To prolong the survival of the animal, further study into the causes of anemia and infection is necessary.

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