A Case Report of 17 Days Survival with an Implanted Artificial Heart in a Calf

Masaaki Nakazono, M.D.,* Kenkichi Koiso, M.D.,**
Takashi Komai, M.D.,*** Tetsuzo Agishi, M.D., Jorge Urzua, M.D.,
Raymond Kiraly, M.D., Helen Kembic, M.D., Richard Surovy, M.D.,
Charles Carse, M.D., and Yukihiko Nose, M.D.

Summary

We established a 17 days survival with an implanted total artificial heart in a calf. The blood contact surface was made of aldehyde treated bovine pericardium and the outer surface was reinforced with specially treated natural rubber. The artificial heart used could pump by pneumatical driving system more than 11 L/min of water in vitro and around 10 L/min of blood in the experimental animal and was able to maintain hemodynamics within normal ranges for 17 days without difficulty. Though to keep hematological and biochemical parameters within normal ranges was relatively difficult, thromboembolism and disseminated coagulopathy characterized by bleeding were not large troubles at all. The main cause of death was breakage of the heart terminated in air embolism in the cerebral arteries.

Additional Indexing Words:
Total artificial heart Survival time Aldehyde treated bovine pericardium Breakage of heart

The first report concerning with the implanted total artificial heart in dogs with the maximal survival of 2 hours after implantation was performed by Akutsu and Kolff in 1958.1) In 1963 Atsumi et al2) reported a successful experiment of 5 and 1/2 hours survival in dog.

Cooley et al3) performed an implantation of total artificial heart in human and were able to keep the patient alive for 3 days in the first step and in the second step they gave a cardiac allograft but he expired 32 hours after the second procedure. Kawai et al,4) utilizing hypothermic procedure during implantation, achieved 10 days survival in a calf. More recently Akutsu’s group5) achieved an average survival of 156 hours in 15 total artificial heart
experiments and discussed the systemic hemodynamics and the lung circulation.

In the Department of Artificial Organs of the Cleveland Clinic Foundation, continuous efforts have been made to improve all phases involved in the total artificial heart implantation project. The major hindrances to successful development of a cardiac prosthesis are; 1) blood clotting inside the device and 2) poor hemodynamic function.

We proposed heterologous pericardium treated with aldehyde could meet these conditions.6) Recently we had a successful experiment of 17 days survival in a calf. Here we discuss the entire course of the experiment.

**Experimental Methods**

The implanted artificial hearts are shown in Figs. 1 and 2. Their performances

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Fig. 1. The blood contact surface is made of aldehyde treated bovine pericardium and the outside air chamber is made of polyurethane.

Fig. 2. The outside looking of the artificial heart.
are also shown in Fig. 3 and the fabrication methods will be discussed in elsewhere.

A male calf weighing 90 Kg was subjected to this study.

**Anesthesia**

Induction of the anesthesia was performed through spontaneous ventilation of 3% fluothane, 66% nitrous oxide, and 30% oxygen in semi-closed circuit. Controlled ventilation was made using a Bennett anesthesia respirator with approximately 50% of oxygen, 50% of nitrous oxide, and 0.5 to 1% fluothane. After opening the chest the animal was cyanotic and 100% of oxygen was needed.

**Perfusion**

A Travenol mini-prime oxygenator was used priming with 3,000 ml of Ringer's lactate solution buffered with 40 mEq of sodium bicarbonate.

Satisfactory venous return from superior vena cava and insufficient from inferior vena cava were observed. Arterial output during the perfusion was in the range of 3 L/min.

**Surgery**

Dissection of both femoral arteries and right femoral vein and right carotid artery with tracheostomy were performed. The chest was opened through median sternotomy. After systemic heparinization cannulations of femoral and carotid arteries and cannulations of superior and inferior vena cava, via right arterial appendage were performed and the total bypass was established.

After excision of the natural heart bilateral artificial hearts were implanted using running suture of the artificial atria and slip-in technique to the arterial stumps. A magnetic flowmeter probe was placed in the pulmonary artery. After checking hemostasis the thorax was closed in a standard fashion leaving 4 thoracic drainages connected to continuous suction. Surgery was uneventful; no particular complications were observed. Pumping of the implanted artificial hearts was started gradually, simultaneous with reduction of the bypass pump flow, trying to avoid excessive decrease in atrial pressures.
POSTOPERATIVE EVOLUTION

During the postoperative period hemodynamics appeared to be acceptable and cardiac output in the range of 10 L/min was able to maintain (Fig. 4). External bleeding was limited to about 700 ml during the whole postoperative period, and transfusion during the first postoperative week amounted to less than 2 L/min, but more transfusion was needed later due to anemia. Body temperature was low at the end of the perfusion in the range of 33°C and then went up to normal values soon afterward. It was maintained normal range until 14th experimental day, then it went down to pathological range. The last temperature recorded was 31.5°C. The animal was able to hold his head and breathe by himself soon after the operation. He was able to eat, drink, defecate, and urinate in normal patterns within 24 hours after surgery. No sign of brain damage was observed. All the reflexes were normal and during the first few days the overall appearance of the animal was normal. Progressive weakness was noticed after the first week of the experiment and after 13th day the animal was unable to stand up. After 15th day the animal was unable to hold head and remained on the floor most of the time. All the reflexes deteriorated very late in the experiment and general condition looked extremely poor. Although the animal was able to breathe spontaneously, assist ventilation with an Engstrom respirator was kept maintain
to avoid CO₂ retention during most of the experiment, and limited amount of oxygen was usually required to maintain optimal saturations. Purulent secretion from the tracheobronchial tree became apparent soon after surgery. Cephaloridin and later gentamicin were administered to prevent bacterial infection. Oxygen concentration required exceeded 50% after 300 hours pumping, and even 100% was used for several hours. Compliance of the lungs decreased also at that time, remaining low until the end of the experiment. Hiccups were noticed after 225 hours (Fig. 5).

Defecation was observed after 12 hours, and several periods of diarrhea were observed during the entire course of the experiment. Abdominal distension also was observed in several instances, attributed mostly to aerophagia. Melenic depositions were noticed on 4th and 6th postoperative days. The urine appeared after 20 hours; the output exceeded 2,000 ml/day most of the time.

Diuretics were used several times to reduce the body water. After 290 hours a period of anuria was noticed, lasting 26 hours; administration of diuretics afterward evoked a limited diuretic response (Fig. 6).

The animal drank by himself until very late in the experiment (402 hours). Severe dehydration was observed on the last 2 experimental days, coupled with severe abdominal distension and diarrhea.

The systemic pressure was kept normal until 300 hours, when it rose to
Fig. 6. The kidney functions, urinary specific gravity, urinary output, and urinary pH are shown.

175/100 mmHg and then it returned to normal values up to the end of the experiment. The central venous pressures were low for 3 days; afterwards it increased, always correlating closely with the right atrial pressure. Diuretics were mostly ineffective in decreasing its values, even though good diuretic responses were obtained. Cardiac output was always in the range of 10 L/min.

**Biochemical evolution**

Hemolysis. Free plasma hemoglobin level in serum increased during bypass to 50 mg%; it remained high for 2 days, with a peak of 61 mg%. But after 60 hours pumping, it went to stabilized level to less than 10 mg%, remaining low throughout the experiment. However, crenocyte count increased steadily from 5% on the first day to 84% on the 17th day. Another hemological study will be discussed elsewhere.7)

**Acid-base equilibrium and renal function**

Apparently O₂ consumption was enough, since no metabolic acidosis was observed. From 50 hours on, the animal was in a slight metabolic alkalosis; after 300 hours, it went to slight metabolic acidosis which corrected itself spontaneously. No NaHCO₃ was used throughout the experiment. BUN and creatinine levels were normal all the time until 300 hours; at this moment
they started to rise progressively to high pathological values. Inorganic phosphate showed a parallel increase, non-related to plasma calcium level.

**Liver function**

SGOT increased markedly on the second day, returning slowly to near

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**Fig. 7.** BUN, creatinine, and uric acid levels in the serum.

**Fig. 8.** Liver function indicators.
control levels on the 8th day, to start rising again after 310 hours to pathological levels (Fig. 7). Bilirubin was normal for 4 days after surgery, going up afterwards with a peak of 3.4 mg% on the 180 hours, predominantly indirect but after 320 hours, direct bilirubin level increased correspondent with increasing of alkaline phosphatase activity (Fig. 8).

Autoptic and histological study

In external appearance, dehydration and muscle atrophy were dominant and moderate distension of the abdomen was observed. Body weight was approximately 70 Kg and some amount of foamy blood was noticed in the left driving line.

External appearance of the brain was almost normal except the presence of air bubbles in all the cerebral arteries but no pathological changes could be found in the brain tissue.

Muscles in the thoracic wall apparently showed good blood circulation. The left lung was grossly normal weighing 640 Gm and the right one was congestive and atelectatic weighing 590 Gm. Neither obvious abscesses in the lung nor free exudate and blood were accumulated in the chest cavity. The lungs were free of adherences to the chest wall. Highly cellular thickening of alveolar septa was dominant in microscopic study. Areas of atelectasis mostly resulted from septal thickening. No alveolar exudates nor hyaline alveolar lining was noticed (Fig. 9).

The implanted hearts were surrounded by a foul smelling capsule of gray color 2 mm thick sheet. The infectious process did not spread out of the capsule.

The location of the implanted hearts was quite acceptable from the point

![Fig. 9. Histological finding of the lung. H-E stain.](image-url)
Fig. 10. The blood contact surface after 17 days implantation shows a thick pseudoneointima of about 2 mm thickness which is folded following the pattern of the movement of the sac. The homogeneous area (left side) shows the original surface of the peritoneum.

of anatomy, neither compression nor kinking of main vessels were observed.

The main vessels were apparently well encapsulated. The left ventricle showed one point of rupture in the middle of free part of rubber sac with passage of air to the blood compartment. The insides of the hearts were covered by a thick pseudoneointima of 2 mm thickness which was folded following the pattern of movement of the sac. The suture lines were covered by a thin endothelial or a neo endothelial layer of glossy appearance. The valves were soft and pliable and contivent. No stenosis nor retraction were observed. No infectious processes were obvious in the valves nor other places in the ventricular sac. The sharpest gradient in ripples, and the steepest in ripples was formed at the point of failure, which could be attributed to the stress point (Fig. 10).

The abdominal wall showed some muscular atrophy and complete disappearance of fatty tissues. The stomach was partially filled with semi-digested liquid food and gas. In the colon some depositions of normal appearance were present and the small intestine was mostly empty. Exploration of mucosa did not show any pathological changes.

Liver was slightly enlarged in size, measuring 15.5 × 8.5 × 5.0 inches, weighing 4,300 Gm. External appearance was icteric with some regions of patchy congestion. The borders of the liver were sharp demonstrating absence of severe congestion. Histological study revealed that general architecture was well preserved, but slight centrolobular congestion, marked biliary stasis with dilatation of intrahepatic canaliculi—so called aspects of nutmeg liver—was observed. Some cloudy cellular changes were also noticed in some
the liver. H-E stain.

Fig. 12. Histological findings of the kidney. H-E stain.

regions (Fig. 11).

The general architecture of the kidney was well preserved but in several areas hemorrhage was seen and in the left kidney at least 1 area of about $3 \times 3$ cm of pale yellow colored and soft consistency was observed.

No macroscopic thrombi were found in the arteries but some of them were found in the veins and areas of necrosis, well delimited, with some macrophages were seen. The tubular cells degenerated generally to loose their nuclei but no severe degeneration process was found in glomeruli (Fig. 12).

Spleen and adrenal glands seemed within normal. Bone marrow revealed an increase in erythroblastic and myeloblastic series, with increase in plasma cells.
Discussion

We reported an experimental case of long time survival with implanted artificial hearts in a calf. Though the survival time of experimental animals up to 3 weeks can be expected, various problems, which should be solved and some of them could be solved by present tasks, still remain. Breakage of the heart, thromboembolism, disseminated intravascular coagulation and generalized infection are most frequent and important causes of death in long total artificial heart survivors. Breakage of the heart not only depends on the properties—(durability or toughness)—of the materials used but also on the design of heart and/or the fabrication methods. In this case we could keep the animal alive over 400 hours but the main cause of death was heart break terminated in air embolism in the cerebral arteries. From the point of antithrombogenicity, aldehyde treated bovine pericardium could be more reliable than the other materials such as silicon rubber or natural rubber, but from the point of durability, there are several problems solved. The ventricular sacs used were made of aldehyde treated bovine pericardium reinforced with specially treated natural rubber and dacron clothes but breakage of the heart is one of the main troubles in our long survival cases. To some extent we could improve the problems by changing the design and the fabrication methods, but to achieve a complete resolution in this problem probably takes long time.

Phillips et al reported the importance of the design and construction of the device showing how turbulent flows occurred in the device and how important role it played in clot formation. In clot formation 2 main conditions

Fig. 13. The blood contact surface of the cardiac prosthesis implanted for 164 days in the descending aorta. The arrow mark indicates the area where pseudointima was mobilized to show the difference.
are involved, one is the static condition—surface properties of the materials used—and the other is dynamic—manner of the ventricular movements—. An ideal device should meet these two conditions. In the past cardiac prosthesis was implanted into the aorta to study what kind of intima formation took place on the surface. The blood contact surface could move but relatively stable moved passively and did not to full strokes. Fig. 13 shows the inner surface of a cardiac prosthesis implanted in the descending aorta for 164 days. Uniform rather thin pseudoneointima formation can be seen. But the moving surface showed quite different pattern of pseudoneointima formation from actual simulation of cardiac prosthesis as shown in Fig. 10.

The nature of the pseudoneointima formation on the surface together with the problems of the thromboembolism is very difficult to determine unless it is exposed to the blood in exactly same operational condition.

Kito et al described that the kidney infarction was most frequently observed as a large amount of heparin during the experiments. They reported the use of CDP-cholin together with heparin was workable to prevent infarctions in the kidney. However, they also pointed out the importance of the fabrication procedures. When a device contaminated by improper treatments was used, CDP-cholin failed to prevent thrombus formation.

From the initiation of the total artificial heart program, disseminated intravascular coagulopathy characterized by bleeding due to progressive decrease in the platelet count and fibrinogen level, was reported as frequent cause of death. Though gradual deterioration of the peripheral circulation is still a serious problem in long time survival cases, no sign of disseminated coagulopathy was observed in this case. In this experiment the platelet counts and fibrinogen levels decreased at the beginning but later their levels increased to normal ranges and kept these levels to the end of the experiment.

Pulmonary insufficiency has been one of the most serious problems associated with total artificial heart procedures. According to Olsen et al\(^{11}\) the lungs were edematous, congested, and with atelectasis or pneumonia of the dependent portion of the apical and some times the cardiac lobes. Microscopically the edema was limited to the perivascular areas in the lighter weight lungs; this edema extended into the interstitium and alveolar septa in the heaviest lungs. We also confirmed these changes—similar changes to those of so called pump lung—in the lungs of short survived animals. Some of the longer survived animals exhibited chronic bronchial pneumonia in various stages, hypercellularity and thickening of some of the alveolar septa were commonly found in the longer survived animals. They attributed so called shipping fever, one kind of pneumonia which is common lung problem of the calf, to the basic condition of the lung trouble with artificial heart procedures.
They listed up: (A) a pasteurella infection, (B) virus reno-infection, and (C) stress, probably due to the shipment of the calves were etiological causes of shipping fever and cardiopulmonary bypass, severe thoracic surgery, and confinement often in lateral recumbency was sufficient stress to precipitate the condition.

But comparing the pathological findings of the short time survivors with those of the long time survivors, large differences were found between them. The shipping fever indubitably will play some parts of the pulmonary insufficiency but performances of the artificial heart implanted must be more responsible to this problem. Our efforts will be paid to realize an ideal artificial heart device.

We could summarize this experiment as follows: 1) our heart device was able to keep the animal alive up to 408 hours without natural heart and to pump more than 11 L/min of water in vitro and 10 L/min of blood in vivo, 2) to maintain hemodynamics in the animal within normal range was not difficult but it was relatively difficult to keep hematological and biochemical parameters within normal ranges, 3) our heart device implanted made of aldehyde treated bovine pericardium was almost free from thromboemolism, 4) breakage of the heart was still our trouble to be solved.

REFERENCES