Experimental Studies in Total Artificial Heart Replacement

FUMIO IWAYA, M.D., SHUNICHI HOSHINO, M.D.
TSUGUO IGARI, M.D., AND KENJI HONDA, M.D.

Twenty-seven calves were operated on in our institute for total artificial heart replacement. Thomasu hearts (made by the Thomasu Technical Company, Japan) were used in 21 calves from February 1980 to May 1983. Utah Jarvik 7 hearts were used for the first five calves and the 17th calf. The air-driven Thomasu heart, made of segmented polyurethane, has 95 ml and 85 ml of stroke volume in its left and right sides respectively and showed recognizable function curves in mock circulation systems.

There were no satisfactory results in the first 19 cases but the 20th calf survived for 28 days. In 1982, we adopted a new surgical method in which, instead of suturing, a sutureless artificial graft with a stainless steel ring was inserted into the aorta and pulmonary truncus. Since then two out of six calves have survived for more than one month; one of these survived for 66 days.

The causes of death after the Thomasu heart replacements were varied. Ten (48%) out of 21 cases had heart trouble and four calves (19%) died through thrombus formation at the inflow and outflow valves. Three calves (14%) died because of mechanical failure of the driving system, two (10%) due to surgical failure, one because of pneumonia, and one due to an abnormal reaction after donor blood transfusion. Our longest surviving calf died after 66 days, because of a broken left blood diaphragm though, it remained in excellent condition until its death. There was no thrombus formation in either ventricle, no fibrin net formation and no calcium deposit on the surface of the diaphragm.

The surgical technique and establishment of extracorporeal circulation in total artificial heart replacement have been confirmed as successful, especially when a sutureless technique is adopted for the outflow tract, but problems remain with the manufacture and durability of the heart. The resolution of these difficulties lies in the field of engineering science, but with development in this area we can certainly look forward to six-month survival in the calf.

The first human application of total artificial heart replacement was performed in Utah, U.S.A., on December 2, 1982. Encouraged by total artificial heart experiments using calves and sheep which had achieved survival of more than seven months, the Utah medical team decided to use an air-driven Jarvik 7 heart for permanent use in a 61-year-old dentist suffering from severe myocardial disease. The patient survived for 112 days. In Japan the longest survival period for calves with total artificial heart replacement has been less than the seven months described above.

The present study was performed to develop the artificial heart for application in humans and to evaluate the status in animals after

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The First Department of Surgery, Fukushima Medical School, Fukushima, Japan
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Mailing address: Fumio Iwaya, M.D., The First Department of Surgery, Fukushima Medical School, 4-45 Sugitsuma-cho, Fukushima-shi, Fukushima 960, Japan

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artificial heart replacement.

MATERIALS AND METHODS

Prosthesis and Instrumentation

Air-driven Thomasu (Fig. 1) and Jarvik 7 hearts, made of segmented polyurethane, have been used in our surgical department for total artificial heart replacement in 27 calves over the last three years. Björk-Shiley or Hall-Kaster valves were used as inflow and outflow valves. The atrial cuffs were made from a Gore-Tex sheet lined with rough-surfaced polyester felt; their quick connectors were of polyurethane. Both cuffs were trimmed to an oval shape on the surgical table.

A low-porosity, Cooley woven Dacron graft (with stainless steel rings on one side and quick connectors on the other) was used as an artificial outflow tract, was used in the six most recent cases. Open tap pressure lines were used, attached to both atrial cuffs and the outflow grafts for pressure monitoring. The Thomasu heart has 95 ml and 85 ml of stroke volume in its left and right sides, respectively; its function was tested in mock circulation systems.

Male Holstein calves weighing 75–100 kg (average 85 kg) were used as experimental animals.
TABLE I CAUSES OF DEATH AFTER THOMASU HEART REPLACEMENT

<table>
<thead>
<tr>
<th>Causes</th>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artificial Heart</td>
<td>10</td>
<td>(48)</td>
</tr>
<tr>
<td>Thrombus Formation</td>
<td>4</td>
<td>(19)</td>
</tr>
<tr>
<td>Mechanical Failure of Heart Driver</td>
<td>3</td>
<td>(14)</td>
</tr>
<tr>
<td>Surgical Failure</td>
<td>2</td>
<td>(10)</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>(10)</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

**Anesthesia and Surgical Procedure**

Animals were anesthetized by i.v. injection of 1.5 mg atropine sulfate and 10 mg/kg thiopental sodium and placed on the surgical table, lying in a left lateral position. Anesthesia was maintained with 0.5–1.0% Fluothane and 50% oxygen.

A right thoracotomy was performed by removal of the fifth rib. Almost all the ventricular myocardium was excised, including the atrioventricular and semilunar valves, under total cardiopulmonary bypass with moderate hypothermia. Sutureless arterial grafts, with rings, were inserted into the aorta and pulmonary truncus respectively and ligated by umbilical tapes tied around the arteries at the ring. We prefer to use one stay suture of 3–0 Prolene at the posterior wall of the artery. Both right and left atrial cuffs were inverted and placed in the right and left atria. Three mattress sutures of 2–0 or 3–0 Prolene were placed around the atrial cuff, which was attached to the remaining ventricular myocardium with single running sutures. The left atrial and aortic quick connectors were snapped onto the left artificial ventricles and the heart driver was started at a slow rate (40 beats/min) and a low driving pressure (110 mmHg), with meticulous evacuation. The right artificial ventricle was connected in the same fashion and driven by 40 mmHg pressure. As the pressure and heart rate increased, blood in the extracorporeal perfusion system was gradually returned to the body until

![Graph showing the relationship between heart rate and cardiac output of the Thomasu heart.](image1)

**Fig.4.** The relationship between heart rate and cardiac output of the Thomasu heart.

![Graph showing survival after total artificial heart replacement of 27 calves in Fukushima Medical School.](image2)

**Fig.5.** Survival after total artificial heart replacement of 27 calves in Fukushima Medical School.

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TABLE II CAUSES OF DEATH RELATED TO ARTIFICIAL HEART (THOMASU HEART)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Left Heart</th>
<th>Right Heart</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inflow</td>
<td>Outflow</td>
</tr>
<tr>
<td>Valve Failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broken Strut</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Dislocation of Valve</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Stuck Disc</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Quick Connector Failure</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Air Leakage</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Broken Diaphragm</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

both mean atrial pressures were around 10 mmHg. The cardiopulmonary bypass was turned off at optimal intracardiac pressure levels and with ideal driving pressure wave forms. Two chest drainage tubes were placed on the bottom and roof of the right chest cavity and the chest was closed. The calf was placed in the cart.

Postoperative Animal Care

The selected optimal driving parameters (160–180 mmHg for the left ventricle, 45–65 mmHg for the right ventricle, percent systolic ratio 30–40% and 5–10 cm H₂O vacuum pressure) were not changed until the growth of the animal required higher cardiac output, or some significant abnormalities in hemodynamic status were found. Blood samples for hematological examination were taken routinely.

Necropsy

Complete necropsies were performed at the end of the experiments. The inside surfaces of both the atria, the artificial ventricles, and the outflow tract were inspected for thrombus formation, pannus formation, and neointima ingrowth.

The diaphragm of the ventricle was resected and stored in glutaraldehyde solution for scanning electron microscopy and biochemical examination. Tissue samples from all the important organs (including the lungs, kidneys, liver, brain, and spinal cord) were sent for microscopic

Fig.6. Broken diaphragm at left D-H junction 66 days after surgery (TAH 82 C 25: Papafio).
Fig. 7. There was no thrombus formation in either ventricle and no calcium deposit on the surface of the diaphragm, as shown by EDX (TAH 82 C 25: Papafio).

Fig. 8. Scanning electron microscopical views of the particles of dust and polyurethane. There was no fibrin net formation on the surface of the diaphragm (TAH 82 C 25: Papafio).

examination.

RESULTS

Cardiac function in Mock Circulation Systems

The Thomasu heart showed recognizable function curves in Mock Circulation Systems. Cardiac output increased gradually, in correlation with the raised left atrial pressure, and reached a maximum at a left atrial pressure of 15 mmHg (Fig. 2). A vacuum during the diastolic phase also contributed to cardiac output.

Cardiac output increased in a linear fashion in accordance with the raised driving pressure up to a level of 180 mmHg at which maximal output was indicated. There was no increase of output at driving pressures over 180 mmHg (Fig. 3).

Cardiac output was also related to heart rate up to 130 beats/min, at which rate maximal cardiac output was reached. A vacuum during the diastolic phase also contributed to cardiac output (Fig. 4).

Animal Experiments

Twenty-seven calves were operated on for total artificial heart replacement (Fig. 5). Thomasu hearts (made by the Thomasu Technical Company, Japan) were used in 21 calves from February 1980 to May 1983. Utah Jarvik 7 hearts were used for the first Five calves and the 17th calf. There were no satisfactory results in the first 19 cases, but the 20th calf survived for
28 days. In 1982, we adopted a new surgical method in which, instead of suturing, a sutureless artificial graft with a stainless steel ring was inserted into the aorta and pulmonary truncus. Since then two out of six calves have survived for more than one month; one of these survived for 66 days.

The causes of death after the Thomasu heart replacements were varied (Table I). Ten (48%) out of 21 cases had heart trouble and four calves (19%) died through thrombus formation at the inflow and outflow valves. Three calves (14%) died because of mechanical failure of the driving system, two (10%) due to surgical failure, one because of pneumonia, and one due to an abnormal reaction after donor blood transfusion.

Nine of the 10 deaths due to heart trouble involved artificial heart problems such as valve failure (including a broken strut), valve dislocation and a stuck disc, quick connector failure, air leakage, and a broken diaphragm (which occurred on the left side of the ventricle). There was only one case with a broken strut in the right inflow valve (Table II). There were no surgical deaths among the 16 most recent cases. The sutureless method shortened extracorporeal circulation time and reduced postoperative bleeding.

Since our experimental research began, altogether three calves have survived for over four weeks. The causes of death were: thrombus formation at both inflow tracts and the left outflow tract, after 28 days; thrombus formation at the right inflow tract, after 34 days; and a broken left blood diaphragm, after 66 days (Fig. 6). This last calf remained in excellent condition until its death. There was no thrombus formation in either ventricle, no fibrin net formation and no calcium deposit on the surface of the diaphragm (Figs. 7 and 8).

DISCUSSION

Most heart diseases can now be treated by drugs and surgery. Surgical results in severe heart diseases, using cardioplegic solutions and inotropic agents such as dopamine and dobutamine, have been remarkable. However, there are several conditions, such as severe myocardial disease, extended myocardial infarction, and complicated severe congenital heart disease, which cannot be treated. These patients might be candidates for heart transplantation.

Worldwide, more than 450 heart transplants have now been performed. Recently, the Stanford group achieved a 40% five-year survival rate, which has made this method of treatment more acceptable to both the public and the medical profession. In Japan, the definition of brain death has not been established. This creates ethical, legal, social, and psychological problems which make it difficult to obtain donor hearts. The artificial heart cannot resolve all these conflicts but it can abolish the need for donor hearts and immunosuppressive therapy.

Since 1980, we have performed 27 total artificial heart replacements (six with Utah Jarvik 7 hearts and 21 with Thomasu hearts), using calves, in our laboratory. Air-driven diaphragm-type Thomasu hearts (made by the Thomasu Technical Company Japan) were modelled on the Jarvik 7 heart and demonstrated satisfactory function curves in Mock Circulation Systems.

After artificial heart replacement, most of the calves were restored to normal health and behavior, although many problems arose with the animals, relating to heart driving systems, thrombus formation, and the artificial hearts themselves. Artificial heart troubles could occur at any time and failures in different parts of the ventricles and artificial valves (such as broken struts and valve dislocation) were the main causes of death. These valve troubles occurred not only on the left but also in the right side. The inflow valve received an impact during the systolic phase, especially on the left side. Mechanical disc valves have been used for this experiment, but they proved unsatisfactory, so it will be necessary to develop a more suitable valve for the artificial heart.

To achieve durability and a leak-proof structure for the heart, we developed a manufacturing technique in which the housing, base, diaphragm, and quick connectors were constructed of the same material segmented polyurethane. We named the Thomasu heart the 'all-polyurethane artificial heart.' Ten calves had their hearts replaced by 'all-polyurethane hearts.' There was no air leakage in these hearts and three of the calves survived for over four weeks.

In the calves achieving long-term survival, there were two main causes of death: thrombus formation and broken diaphragm. Our longest surviving calf, named Papatio died from a broken diaphragm at the D-H junction on the 66th day. There was no thrombus formation in the heart, no fibrin net formation, and no calcium deposit.
on the surface of the diaphragm. It was very encouraging that our heart material was non-thrombogenic but we have yet to evaluate calcium deposit in animals surviving for over three months.

A broken diaphragm is the most serious durability problem, but we have several ideas for its solution. The Thomasu heart has a diaphragm consisting of two thin layers, each with a thickness of 0.15–0.17 mm; we altered these to 0.20–0.25 mm. We also changed the manufacturing method for the blood diaphragm. Formerly, we had made it from a stainless steel mold of the concave systolic position but it is now made from a mold of the convex diastolic position. The effects of this change have yet to be evaluated.

The surgical technique and establishment of extracorporeal circulation in total artificial heart replacement have been confirmed as successful, especially when a sutureless technique is adopted for the outflow tract, but problems remain with the manufacture and durability of the heart. The resolution of these difficulties lies in the field of engineering science, but with development in this area we can certainly look forward to six-month survival in the calf.

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