LONG-TERM HEMODYNAMIC EFFECTS OF THE TOTAL ARTIFICIAL HEART

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Effort has been made to develop an implantable total artificial heart (TAH) since 1957.\textsuperscript{1} It was difficult to break the 100-hour survival barrier of experimental animals with an implanted TAH. In 1971, two groups\textsuperscript{2,3} reported one 5-day and one 7-day survivor, respectively. Improved experimental results have allowed us to study the effects of prolonged artificial pumping on the biological system.

The present paper will describe hemodynamic effects of TAH in calves surviving longer than 100 hours.

MATERIALS AND METHODS

Device and Control-Driving System: Our air-driven TAH, consisting of an inner flexible pumping chamber and outer rigid housing, has been designed for implantation inside the pericardial sac of animals the size of adult humans. Each side of the heart consists of one ventricle, one atrium, one inlet valve, one outlet valve, and one vessel (either aorta or pulmonary artery) and is made in one-piece construction of silicone rubber. Detailed descriptions of the device\textsuperscript{4,5} and the manually operated control-driving system\textsuperscript{6,7} were previously reported.

Experimental Procedure: Twenty-seven calves weighing 70 to 96 kg (average $82 \pm 7$ kg) were used for this study. Thirty minutes prior to anesthesia the calves were premedicated with 0.6 mg Atropine. Anesthesia was induced by intravenous administration of 25% Sodium Thiamylal and maintained with 0.3% to 1.0% Fluothane. The chest was opened through the left fifth intercostal space. Heparin (3 mg/kg) was administered before cannulation for extracorporeal circulation (ECC). A Bentley's disposable bubble oxygenator and two roller pumps were used for ECC, and the circuit was primed with one liter of fresh blood and two liters of lactated Ringer's solution.

After removal of the natural heart, the TAH was connected to the natural counterparts in the following order: right atrium, left atrium, aorta, and pulmonary artery. After the chest was closed in routine fashion, the calf was placed in a special cage in the normal lying position. The pumping conditions were fixed as follows: pumping rate, 100 beats/min; systolic-
diastolic ratio, 0.6 to 0.7; driving air pressure, 220 to 240 mm Hg on the left side and 100 to 140 mm Hg on the right; vacuum during diastolic phase, approximately 20 mm Hg on both sides. Thereafter, the primary method of controlling the TAH was to maintain both atrial pressures within the normal range with a cardiac output (CO) of approximately 90 ml/kg/min.

**Measurements:** The blood pressure was measured in both atria, the aorta and the pulmonary artery through the attached side tubes with Statham pressure transducers. The CO was measured by means of an electromagnetic flow meter (Carolina Medical Electronics). These variables were continuously and simultaneously recorded on a Hewlett-Packard recorder. The zero point for the atrial pressure was set at the mid-point of the right atrium and was marked on the chest wall when the chest was closed.

Arterial and venous blood gases were periodically measured using an Instrumentation Laboratory gas analyzer, and arterio-venous (A-V) oxygen difference and oxygen consumption (OC) were calculated.

In an attempt to measure the mean systemic pressure (MSP) and the mean pulmonary pressure (MPP), the TAH pumping was stopped at the end of the systolic phase by occluding both drive lines. Procedures were repeated while the calf was lying quietly without anesthesia or sedatives.

Cineangiographic studies of the TAH were performed using 35 mm General Electric X-ray system films.

**RESULTS**

Twenty-seven calves (38.6%) survived more than 100 hours and of those, five survived over 200 hours (up to 590 hours). The causes of death in the two groups, Group A (less than 200 hours) and Group B (over 200 hours), are shown in Table 1. Thromboembolism, breakage of the device, and infection were the three main causes of death in Group B. In Group A, res-

<table>
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<tr>
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<th>GROUP A</th>
<th>GROUP B</th>
<th>TOTAL</th>
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<tbody>
<tr>
<td>Thromboembolism</td>
<td>7 (32%)</td>
<td>3 (60%)</td>
<td>10 (37%)</td>
</tr>
<tr>
<td>Breakage of Device</td>
<td>5 (22%)</td>
<td>1 (20%)</td>
<td>6 (22%)</td>
</tr>
<tr>
<td>Infection</td>
<td>3 (13%)</td>
<td>1 (20%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Respiratory Insufficiency</td>
<td>2 (10%)</td>
<td>0</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Renal Insufficiency</td>
<td>2 (10%)</td>
<td>0</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Others</td>
<td>3 (13%)</td>
<td>0</td>
<td>3 (11%)</td>
</tr>
</tbody>
</table>

Total 22 5 27
piratory and renal insufficiency in addition to these complications prevented the calves from surviving over 200 hours.

Figure 1 presents the typical hemodynamic recording in a calf with a TAH; pulsatile CO, phonocardiograms (PCG), left atrial pressure (LAP), arterial pressure (AP), left ventricular pressure and left driving air pressure. The ejection plateau of driving air pressure is equivalent to LVP providing an adequate collapse of the ventricle. Rapid release of the air pressure brings LVP below zero, but ventricular end-diastolic pressure is always around zero. A high spike in LAP seems due to bulging of the upper

![Figure 1. Hemodynamic recordings taken during total artificial heart pumping in a calf. CO: Cardiac Output; PCG: Phonocardiogram; LAP: Left Atrial Pressure; AP: Arterial Pressure; LVP: Left Ventricular Pressure. Note that the pressure phase of driving air is exactly the same as the ejection period of LV with 20 msec of time lag providing an adequate ventricular collapse. High spikes in LAP are due to inevitable bulging of the upper free portion of the inlet valve.](image-url)
Fig. 2. Cineangiograms of the left side during diastole. A: Right-to-Left View, B: Antero-Posterior View.

Fig. 3. Cineangiograms of the left side during systole. A and B: Same as in Figure 2.
portion of the monomembrane inlet valve which occurs immediately after its closure.

Figure 2 presents cineangiograms of the left heart, both the right to left view (A) and antero-posterior view (B). They show complete filling of the LV during diastole. Almost complete ejection except the outflow portion of the LV is shown in Figure 3.

Figure 4 presents the daily average hemodynamic changes in two groups; CO, total peripheral resistance (TPR), AP and RAP. In Group A, CO was approximately 6.0 L/min on the operative day, and increased gradually each day to normal valves. TPR and AP progressively decreased toward the end of the experiments. The RAP continuously increased and reached 20 mm Hg in the terminal stages.

In Group B, CO increased from 7.0 L/min to 9.0 L/min on the second postoperative day (P.O.D.) and remained constant thereafter throughout the experiments. TPR decreased until the third P.O.D., and stabilized at 0.6 to 0.7 mm Hg/ml/sec. Mean AP, however, remained high and varied from 100 mm Hg to 120 mm Hg. RAP continued to increase gradually until the seventh P.O.D., when it reached 20 mm Hg, and thereafter usually

Fig. 4. Daily average hemodynamic changes in two groups: Group A, 22 calves who survived less than 200 hours and 5 calves who survived longer than 200 hours. CO: Cardiac Output; TPR: Total Peripheral Resistance; AP: Arterial Pressure; RAP: Right Atrial Pressure. In Group A, AP and TRP tended to decrease in the early stages, although CO and RAP did not.
remained at approximately 15 mm Hg. In the longest survivor, TPR and AP began to decrease after the seventeenth P.O.D., whereas RAP began to increase again 17 days after implantation and reached 30 mm Hg.

Figure 5 shows recordings when the heart was stopped for seven seconds to measure MSP. RAP increased and AP decreased approaching nearly the same value but did not reach complete equilibration within that period of time. Figure 6 presents changes in RAP and AP during such tests in the two longest survivors. In case 1, changes in RAP were in proportion to those in final AP (r=0.9512), and were also the same in Case 2 (r=0.9064). An important difference between the two was that RAP in Case 2 did not exceed 20 mm Hg.

Figure 7 shows changes in PAP and PVR. In Group A, PVR had a tendency to decrease toward the end of the experiments. PAP remained unchanged at approximately 25 mm Hg.

**TAH (60)**

![Fig. 5. Hemodynamic recordings when the heart was stopped for 7 seconds with the intention to measure mean systemic pressure. Decrease in AP and increase in RAP did not reach complete equilibration leaving approximately 2 mm Hg discrepancy.](image)
In Group B, PVR decreased from 0.24 mm Hg/ml/sec to 0.17 mm Hg/ml/sec and remained unchanged until the 14th P.O.D. Thereafter, it decreased to approximately 0.1 mm Hg/ml/sec. PAP remained unchanged at approximately 27 mm Hg until the 9th P.O.D. Thereafter it varied from 18 mm Hg to 27 mm Hg in the longest survivors.

Fig. 6. Changes in RAP and AP frequently measured by stopping the heart for 7 seconds in two longest survivors. In both cases changes in RAP were in proportion to those in final AP.

Fig. 7. Changes in PAP (pulmonary artery pressure) and PVR (pulmonary vascular resistance). In Group A, PVR showed a tendency to decrease in early stages, similar symptom observed in systemic circulation although PAP remained unchanged.
Table 2 presents a comparison of the hemodynamic and metabolic changes by a minor movement in normal and TAH calves. Since actual movements of calves were restricted in a cage, hemodynamic changes were observed before and immediately after standing and after hemodynamic stabilization in both groups. In the TAH calves the pulse rate was fixed at 100, and no readjustment of the control-driving system was made during such movement.

In the control group, CO and OC increased from 90 ml/kg/min to 122 ml/kg/min, and from 4.1 ml/kg/min to 7.5 ml/kg/min, and stabilized within three minutes at 90 ml/kg/min and 4.9 ml/kg/min, respectively. Mean arterial pressure (MAP) and TPR decreased from 132 mm Hg to 90 mm Hg and from 0.82 mm Hg/ml/sec to 0.41 mm Hg/ml/sec, and stabilized at approximately 110 mm Hg and 0.70 mm Hg/ml/sec, respectively. Changes in CO were not significant (from 107 kg/min to 113 ml/kg/min), but OC increased from 4.1 ml/kg-min to 6.5 ml/kg/min with an increase in arteriovenous oxygen difference from 3.8% to 5.6%. MAP and TPR decreased from 113 mm Hg to 93 mm Hg, and from 0.72 mm Hg/ml/sec to 0.53 mm Hg/ml/sec, and stabilized within three minutes at 104 mm Hg and 0.64 mm Hg/ml/sec, respectively.

**DISCUSSION**

Recent progress in each phase of the entire procedure has improved the overall experimental results. The average survival time of experimental animals was prolonged from 30 hours in 1970 to over one week in 1974.

<table>
<thead>
<tr>
<th></th>
<th>Quietly Sitting</th>
<th>Immediately After Standing Up</th>
<th>After Stabilization</th>
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<tbody>
<tr>
<td><strong>CONTROL CALVES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Output (ml/kg/min)</td>
<td>90.00</td>
<td>122.00</td>
<td>90.00</td>
</tr>
<tr>
<td>Pulse Rate</td>
<td>103.00</td>
<td>117.00</td>
<td>105.00</td>
</tr>
<tr>
<td>Stroke Volume (ml)</td>
<td>91.00</td>
<td>109.00</td>
<td>90.00</td>
</tr>
<tr>
<td>Mean Arterial Pressure (mm Hg)</td>
<td>132.00</td>
<td>90.00</td>
<td>110.00</td>
</tr>
<tr>
<td>Total Peripheral Resistance (mm Hg/ml/sec)</td>
<td>0.82</td>
<td>0.41</td>
<td>0.70</td>
</tr>
<tr>
<td>Oxygen Consumption (ml/kg/min)</td>
<td>4.10</td>
<td>7.50</td>
<td>4.90</td>
</tr>
<tr>
<td>Arterio-Venous Oxygen Difference (vol %)</td>
<td>4.60</td>
<td>5.90</td>
<td>5.30</td>
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<tr>
<td><strong>TAH CALVES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>107.00</td>
<td>113.00</td>
<td>110.00</td>
</tr>
<tr>
<td>Pulse Rate</td>
<td>100.00</td>
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<td>100.00</td>
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<tr>
<td>Stroke Volume</td>
<td>87.00</td>
<td>91.00</td>
<td>89.00</td>
</tr>
<tr>
<td>Mean Arterial Pressure</td>
<td>113.00</td>
<td>93.00</td>
<td>104.00</td>
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<tr>
<td>Total Peripheral Resistance</td>
<td>0.72</td>
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<td>0.64</td>
</tr>
<tr>
<td>Oxygen Consumption</td>
<td>4.10</td>
<td>6.50</td>
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<tr>
<td>Arterio-Venous Oxygen</td>
<td>3.80</td>
<td>5.60</td>
<td>4.60</td>
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</table>
With prolongation in the survival times of the TAH calves, the primary causes of death were eventually attributed to three factors: thromboembolism, breakage of the device, and infection. Death could result from any one of these factors, but concurrence of two or all were frequently seen.

Among many possible eitologic factors causing circulatory failure, low cardiac output was of prime importance. The low cardiac output observed in this series of experiments was not caused by malfunction of the TAH, but occurred when the device was too large for the chest cavity pressing the inferior vena cava interfering with the venous inflow to the right atrium. Since CO in the normal calf was approximately 90 ml/kg/min when the calf was quietly lying or standing, 12.0 L/min of maximum pump capacity was thought to be sufficient for the calf (80 to 90 kg) to perform light exercise.

In Group A (less than 200-hour survivors), the CO was lower than that in Group B (over 200-hour survivors) in the beginning and gradually increased to normal within 24 to 48 hours. On the other hand, AP and TPR in group A were high in the early stages of the experiments and gradually decreased daily although CO had a tendency to increase.

Group B showed no significant changes in AP, varying from 100 mm Hg to 120 mm Hg. TPR, however, decreased from the initial high value during the first 24 postoperative hours and stabilized at approximately 0.7 mm Hg/ml/sec, except for the period of terminal stage. The details of changes in TPR during the first 24 hours were perviously reported.11

Progressive increase in RAP was also a serious problem in the long-term survivors.11,12 The TAH response to atrial pressure (Starling's Law) was less sensitive than that of the natural heart12,13 and the TAH maximum CO was limited. Therefore, if venous return exceeds the capacity of the TAH output, blood will stagnate in the venous system causing an increase in atrial pressure.14

In general, mean systemic pressure (MSP), RAP, and resistance to venous return are the three major determinants of venous return to the atrium.15 By our method of measuring MSP, decrease in AP and increase in RAP did not reach complete equilibration during 7-second stop of the heart. The lowest AP reached, however, gave sufficient information to estimate true MSP in these calves. One of the two longest survivors (Case 2) had no limitation or oral fluid intake and the other had strict limitation. As shown in Figure 6, RAP in both cases, however, changed in proportion to changes in the final AP which was considered to have reached nearly the same value as actual MSP during the period of a 7-second complete cessation of TAH pumping. Three of the many factors significantly affecting the MSP in TAH calves were changes in blood volume, vasomotor tone, and interstitial fluid volume. It should be pointed out that similar symptoms are observed in the failing natural heart.15

Some years ago pulmonary insufficiency in the calf immediately following implantation of the TAH15 was a serious problem. In this series of experiments, however, no pulmonary insufficiency was observed until terminal stages. In long-term survivors PAP and PVR remained within reasonable limits, and arterial oxygen saturation did not drop below 90% throughout the course of all experiments.

When the calves stood up, decreases in MAP and TPR were more sig-
significant in control calves (33% and 50%, respectively) than those in TAH calves (18% and 27%, respectively). These results imply that TPR markedly decreased in control calves and caused an increase in blood flow to the muscles and reduced the load on the heart, thus increasing the total cardiac output. In TAH calves, however, blood flow redistribution occurred, decreasing flow to less active tissues and increasing it to more active tissues because of limited total cardiac output. Accordingly, decreases in TPR were less significant than in control calves.

The most significant observations in TAH calves during exercise were 1) increases in oxygen extraction from the arterial blood resulting in increases in A-V oxygen difference, and 2) redistribution of blood flow from less active tissues (which did not require increase in oxygen supply) to the more active tissues. Therefore, the active tissues were able to utilize approximately the same amount of oxygen as in the control calves by means of an increase in oxygen extraction and an increase in regional blood flow without incurring oxygen debts.

SUMMARY

In long-term TAH surviving calves, the primary causes of death were attributed to three factors: thromboembolism, breakage of the device, and infection. Circulatory failure was observed in all long-term survivors toward the terminal stages. Although the performance of the present TAH is limited, it can maintain the life of a calf weighing approximately 80 to 90 kg without affecting the metabolic demand.

REFERENCES