CIRCULATORY PATHOPHYSIOLOGIC MANIFESTATIONS IN TWO LONG-SURVIVING CALVES WITH TOTAL ARTIFICIAL HEARTS

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INTRODUCTION

Pathophysiology of experimental animals with a total artificial heart (TAH) was vague till investigators started to obtain one-week survivals during the period from 1971 to 1972. Major problems reported involved pulmonary insufficiency, liver damage, high right atrial pressure, small atrial syndrome and right heart failure syndrome. The complex nature of experimental procedures made it difficult to understand the pathophysiology, and this difficulty in turn caused delay in the progress of this research.

Since the first 25-day survivor with TAH was obtained in our laboratory in 1973, several major pathophysiology problems have been elucidated. In the present paper emphasis has been particularly placed on circulatory pathophysiological findings in the two longest survivors.

MATERIALS AND METHODS

Device and control-driving conditions: Our air-driven TAH is fabricated from silicone rubber consisting of two parts, right and left sides (Fig. 1). Each side includes three portions—one atrium, one ventricle and one outflow vessel with integral inflow and outflow valves. The inflow valve is a mono-membrane leaflet-type valve, and the outflow valve is of S-shaped bicuspid-type with the bottom similar to the valsalva sinus of the natural aortic valve. The ventricle is basically "sac-type" and encased in a rigid outer shell. Compressed air is blown into the space between the outer shell and the inner flexible sac. The inlet and outlet orifices are provided with a stainless steel ring for quick connection. A stainless steel plate is embedded in the septum separating the atrium from the ventricle to avoid bulging during contraction of the ventricle.

The control-driving system is manually operated, and the pumping condition is determined by changing four parameters—driving air pressure, filling vacuum, systolic and diastolic duration ratio (S/D), and pulse rate. The pumping condition presently in use is as follows: driving air pressure—from 100 to 150 mm Hg for the right side and from 180 to...
Fig. 1. Akutsu Total Artificial Heart (TAH). Ao=Aorta, LA=left atrium, LV=left ventricle, PA=pulmonary artery, RA=right atrium, RV=right ventricle
230 mm Hg for the left; filling vacuum—from –10 to –25 mm Hg for both sides; systolic and diastolic ratio—from 250/375 to 275/400. With these ratios, the heart rate is maintained between 90 and 100 beats/min.

*Implantation Surgery:* The calves weighed 87 to 79 kg, respectively. After 24 hours of fasting, they were intubated and connected to a mechanical respirator. The chest was opened through the left fifth intercostal space. Cannulas were inserted into the left internal mammary artery and left femoral artery for arterial perfusion, and for venous drainage into the superior vena cava through the left jugular vein, and into the inferior vena cava through the right atrial appendage. Ventilation was maintained even during the total cardiopulmonary bypass by inflating the lung periodically. The natural heart was excised leaving major portions of both atria and the pulmonary artery and aorta as long as possible. The TAH was connected to the natural counterparts in the order of right atrium, left atrium, aorta, and pulmonary artery. Before the start of pumping the residual air was replaced first with carbon dioxide, and then with heparinized saline. Pumping was begun immediately after the cardiopulmonary bypass was stopped. Two driving air tubes, four pressure monitoring catheters, one flow meter cable, and one chest drainage tube were exteriorized through the chest wall. During the course of postoperative care, particular attention was paid to antibiotic and anti-coagulation therapies, hemodynamic studies, hematologic and biochemical studies, blood gas analyses, and pathologic examinations.

**RESULTS**

*Case 1.* The total time of extracorporeal circulation (ECC) was 74 minutes. Recovery from anesthesia and surgery was uneventful. The

![Graph](image)

Fig. 2. Daily hemodynamic data of six parameters in 25-day survivor.

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endotracheal tube was removed 8 hours after surgery, and 2 hours after extubation the calf stood up unassisted.

Daily hemodynamic data are shown in Figure 2. Immediately after the pumping was begun, all hemodynamic parameters were normal; mean right atrial pressure (RAP) was 0 mm Hg, mean left atrial pressure (LAP) 8 mm Hg, mean pulmonary artery pressure (PAP) 15 mm Hg, arterial pressure 130/180 mm Hg with the mean value (MAP) of 100 mm Hg, and cardiac output (CO) 6.5 L/min. Thereafter, MAP was always maintained above 80 mm Hg. The PAP varied between 13 and 30 mm Hg, and most of the time stayed around 20 mm Hg. The LAP changed slightly only when the calf moved. Until the 19th postoperative day, the RAP gradually rose to 20 mm Hg and upward to 30 mm Hg during the course thereafter. Readjusting the pumping condition did not help to lower this high RAP. The CO was maintained above 7.0/min through the entire course of the experiment. Total peripheral resistance (TPR) varied between 0.38 and 0.94 mm Hg/ml/sec until the 21st postoperative day, then it tended to decrease as MAP decreased and RAP increased.

Hematocrit (Ht) began to fall below 20% after the 13th postoperative day. Despite transfusion of fresh blood, the Ht tended to decrease. RAP, then, gradually rose in proportion to the decrease in Ht (Fig. 3). The correlation coefficient was calculated as $-0.525$ as shown in Figure 3.

![Graph](Fig. 3. Relationship between right atrial pressure and hematocrit in 25-day survivor.)
Fig. 4. TAH function curves obtained in 25-day survivor.

Fig. 5. Microscopic findings of liver recovered from 25-day survivor. There is extensive central necrosis with hepatocytes replaced by areas of hemorrhage. These central hemorrhagic areas are surrounded by zones of fatty degeneration and vacuole formation.
Figure 4 shows the TAH cardiac function curves of this calf. These function curves were obtained by plotting the CO (ordinate) and the RAP (abscissa) which were continuously monitored and recorded simultaneously every hour. The mean value and standard deviation of the CO were calculated at each RAP. The reason that these three different TAH function curves were obtained with the same device was probably due to decrease in resilience of the ventricular wall, or occasional readjustments of the pumping condition. The left curve was obtained in the early stage of this experiment, the middle curve after one week, and the right curve after two weeks. As shown in this figure, CO ranged from 7.5 to 12.5 L/min while RAP varied from 5 to 35 mm Hg. The calf died from cerebral thromboembolism on the 25th postoperative day.

At necropsy, remarkable liver damage was revealed which was obviously caused by persisting high RAP. Figure 5 shows a microscopic picture of the liver. There was extensive central necrosis with hepatocytes replaced by areas of hemorrhage. These central hemorrhagic areas were surrounded by zones of fatty degeneration and vacuole formation. Many focal areas of polymorphonuclear neutrophil leukocytes infiltration were present. Each portal area was normal.

Case 2. This calf survived for 18 days. The implantation surgery and postoperative course were uneventful as well as in Case 1. Figure 6 shows the daily hemodynamic data. MAP was maintained above 85 mm Hg till just before the fatal cerebral thromboembolism occurred. CO ranged between 6.0 and 9.0 L/min throughout the experiment. LAP always stayed within normal range. PAP was normal till the 8th postoperative day, and judging from other hemodynamic data, it probably stayed normal until

Fig. 6. Daily hemodynamic data of six parameters in 18-day survivor.
**Fig. 7.** Relationship between right atrial pressure and hematocrit in 18-day survivor.

**Fig. 8.** TAH function curve obtained in 18-day survivor.
the end of the experiment. Kinking of the PAP line inside the chest cavity did not allow us to continue further monitoring. RAP remained below 15 mm Hg most of the time. TPR ranged between 0.47 and 1.31 mm Hg/ml/sec.

Ht was always maintained higher than 20% except on the 10th post-operative day. With an increase in Ht following each blood transfusion, RAP obviously decreased, and it stayed normal when Ht was normally maintained. Figure 7 shows the correlation between RAP and Ht. The correlation coefficient was $-0.673$.

Figure 8 shows a TAH function curve of this calf. CO ranged from 4.7 to 9.6 L/min while RAP varied between $-2$ to 27 mm Hg.

The calf died from generalized thromboembolism. At autopsy, the liver was macroscopically normal. Microscopic findings are shown in Figure 9. There was no necrosis nor hemorrhage around the central vein. The liver structures were normal and well preserved. India ink, which was injected to examine the perfusion of liver tissue, was well distributed throughout the liver lobules.

DISCUSSION AND SUMMARY

*Cause of Death:* Both calves died from thromboembolism which resulted from mural thrombi formed inside the device. As reported else-

![Fig. 9. Microscopic findings of liver recovered from 18-day survivor. Note that liver structure is normal.](image-url)
where, thromboembolism was the most frequent cause of death (36%) in the calves with TAH which survived longer than 100 hours. Major clinical symptoms observed originated from lesions of the main organs such as brain, lungs, and kidneys. Despite continuous use of beef lung heparin (4 mg/kg/day), thrombus formation inside the device was not prevented.

Although silicone rubber has long been used as one of the best materials for cardiovascular prosthetic devices, in terms of antithrombogenicity, it has been difficult to keep the device free of thrombi for longer than ten days. Handling of the material and design of the device have to be considered in relation to thrombus formation. However, it is obvious that the surface property of silicone rubber needs to be improved. Segmented polyurethane and Avcothane, which have recently been developed, may be good materials for future use.

![Diagram](image_url)

**Fig. 10.** Graphic analysis of TAH function curve and venous return curve. Point A is normal equilibrium point of the natural heart. Point B is the initial equilibrium point of TAH. Point C is a new equilibrium point established when high right atrial pressure exists.
Low hematocrit and high RAP: Ht tended to decrease in all our TAH experiments. This might have been due to various causes such as hemo-dilution during ECC, destruction of red blood cells by suction during cardiotomy, ECC and TAH pumping, blood loss, postoperative malnutrition, infection, etc. Anemia causes low viscosity of blood, decrease of oxygen transport, peripheral vasodilatation, increase in circulating blood volume, and eventual increase in venous return to the heart.

Referring to Figures 4 and 8, the TAH function curves were less steep as compared with that of the natural heart, and our present TAH has only one available function curve under a certain set pumping condition. This means that the TAH cannot accommodate excessive venous return after its maximum pumping capacity has been reached. Consequently, an abnormal rise in RAP takes place.

As illustrated in Figures 3 and 7, RAP sensitivity responded to changes in Ht. In the first calf, RAP gradually rose in proportion to decrease in Ht, whereas RAP in the second calf did not rise by maintaining normal Ht.

Figure 10 explains the relationships between venous return, cardiac output, and RAP. Point A indicates the normal equilibrium point of cardiac output and venous return of the natural heart. Point B is the initial equilibrium point of those in the TAH. The RAP stays within normal range unless the venous return curve shifts. When the venous return curve shifts to the right, a new equilibrium point is established at point C because the cardiac function curve of the TAH is constant. Accordingly, high RAP results.

In case 1, which had persisting high RAP, the liver structure was severely damaged as shown in Figure 5. This can be explained as follows: continual stretching of the liver sinusoids due to such high RAP (high venous pressures) caused hepatic congestion and blood stagnation, gradually leading to necrosis of a large number of liver cells in the hepatic cellular plates. Since hepatic arterioles which supply arterial blood to the interlobular septal tissue also empty directly into the hepatic sinusoids, when the hepatic vascular resistance increases, the hepatic arterial blood flow decreases leading to insufficient perfusion and liver necrosis.

After we found these pathogenic mechanisms, efforts were made to maintain all physiologic factors within normal range which otherwise might cause anemia, leading to excessive venous return and high RAP. Thereafter, liver damage was successfully prevented, as described in the second calf.

In summary, thromboembolism still remains one of the major problems to be solved, and one of the contributing factors to high right atrial pressure is low hematocrit.

REFERENCES