

Assessment of a New Silicone Tri-leaflet Valve Seamlessly Assembled with Blood Chamber for a Low- cost Ventricular Assist Device

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ABSTRACT

We have developed a practical, low-cost ventricular assist device (VAD) comprising a newly designed blood chamber with a silicone lenticular sac and two silicone tri-leaflet valves (STV), made *en bloc*. This new VAD is seamless, can be made cost-effectively and assembled with the blood chamber and valve as one body. This novel design should reduce the incident of thrombus formation because of the absence of a junction at the connecting ring and because of the use of flexible silicone materials which have both antithrombogenicity and biocompatibility. In *in vitro* hemodynamics testing, a batch of 3 consecutively manufactured VADs with STVs underwent hydrodynamic functional testing. These showed less regurgitation, a lower value of water hammer phenomenon, and a slightly greater pressure gradient across the valves than a mechanical valve (MV) [Björk-Shiley monostrut valve]. The flow and pulsatile efficiency were adequate and similar to that of a VAD with MVs. In *in vitro* durability and hemolysis tests, a VAD with STV functioned well for 54 days and showed similar hemolytic profiles to a VAD with MVs. In an *in vivo* acute experiment using an adult sheep, our device was problem-free providing sufficient output as a left ventricular assist device (LVAD). Although it will be necessary to decrease the pressure gradient across this STV in the future, our device showed efficient performance as a practical and cost-effective VAD for short term use.

Key words: Silicone tri-leaflet valve, Silicone blood chamber, Ventricular assist device

Recently, there has been an enormous growth in the development of VADs, and these devices have become increasingly important for patients with endstage cardiac failure. Needless to say, the pulsatile VAD is functionally excellent in maintaining cardiac performance without negative physiologic effects on other organs^{24,25}. Multiple organ failure (MOF) can be ameliorated by left univentricular assistance alone⁹. However, the current type of VAD, which has clinical mechanical valves, is expensive when considering the short period of the use, especially when used on a short-term, temporary basis for the purpose of weaning. There are also some problems in that the mechanical valve can be damaged by the water hammer phenomenon^{9,22}; hemolysis and thrombus formation at the connection of the valve can occur in the artificial heart^{1,27}. Using a silicone valve, which has antithrombotic biocompatibility, and which can be obtained inexpensively, we have developed a tri-leaflet valve which imitates the organic aortic valve in order to solve the above-mentioned problems. The desirability of a leaflet type valve design is primarily due to its large central flow orifice. It has been postulated that by achieving less turbu-

lent flow, blood trauma is reduced when compared to conventional mechanical valves³¹. We have created a new silicone tri-leaflet valve, which has been seamlessly assembled with a blood chamber, comprising a low-cost VAD. This is both easy to manufacture and has good hemodynamic performance. We propose that this cost-effective VAD is a useful alternative device available for short-term support. In this paper, the structure of this new device, as well as *in vitro* hemodynamic performance, durability, hemolysis and *in vivo* test in an adult sheep are described.

MATERIALS AND METHODS

Design of silicone tri-leaflet valve (STV)

The prototype model of the STV was produced with a silicone tube and a metal ring (Fig.1A). A short silicone rubber tube was formed through a die casting process with a side wall of varying thickness. After turning the tube inside out, its sectional shape changed from a circle to a triangle. Then the metal ring was placed at the root of the silicone tube. The performance of this first generation STV was tested using a diaphragm-type air-driven artificial heart. However, regurgitation of

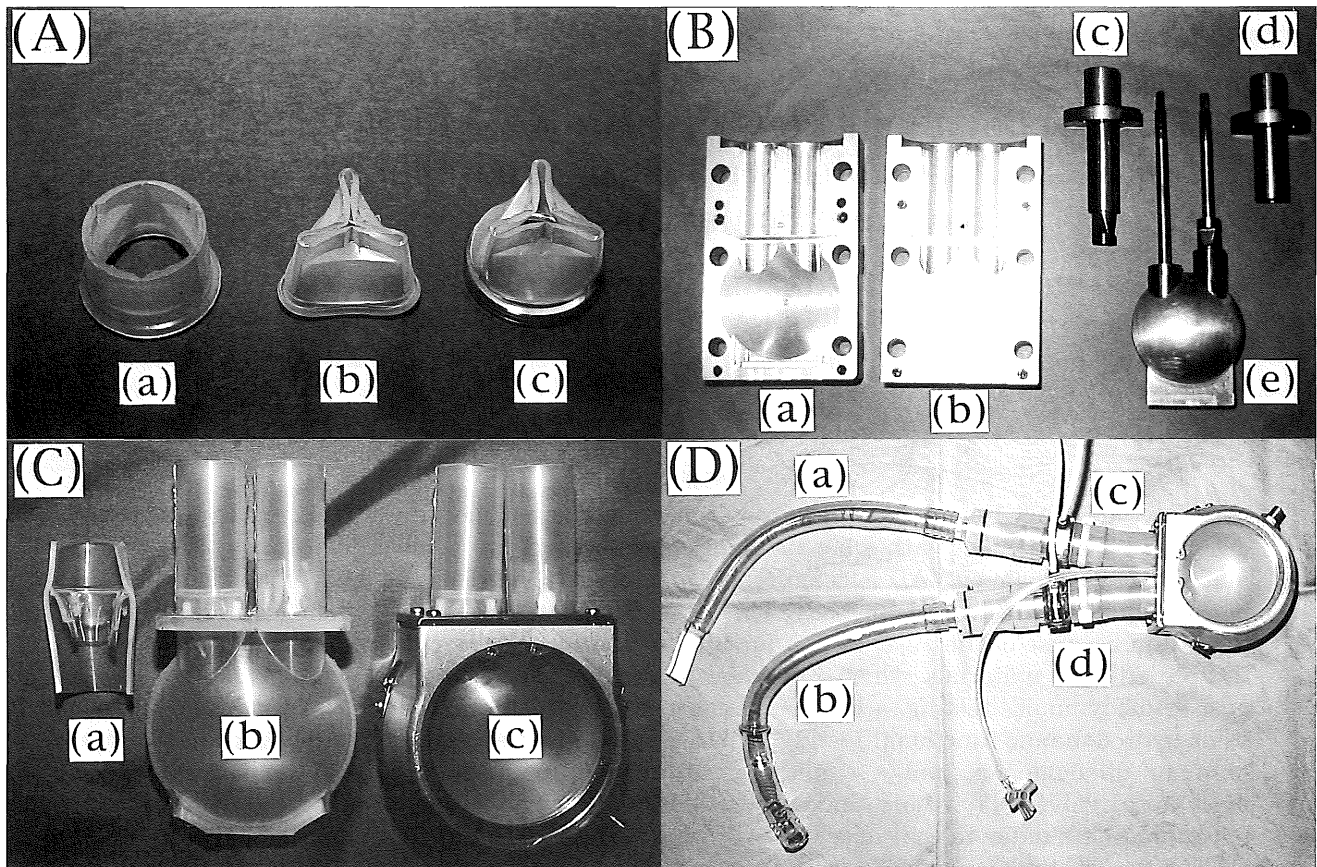


Fig. 1. Trial manufacture of a silicone tri-leaflet valve and a ventricular assist device are shown.

(A) Photographs of the prototype model of silicone tri-leaflet valves: short silicone rubber tube before it is turned inside out (a); after it is turned inside out (b); silicone tri-leaflet valves with orifice metal ring (c).

(B) Photographs of the dies for constructing a ventricular assist device *en bloc*: outer dies (a,b); dies for valve portion (c,d); core dies for blood chamber (e).

(C) Photographs of the cross-section of the valve portion (a), blood sac with tri-leaflet valve made *en bloc* (b), and ventricular assist device with casing (c).

(D) Photographs of the newly designed LVAD for an acute experiment: outflow cannula with 12 mm woven Dacron graft and inflow cannula of silicone-coating polyvinyl chloride (a,b), flow meter (c,d).

the first generation STV was considerably greater than that of commercially available artificial heart valves.

The design was improved in order to reduce regurgitation. The STVs and the silicone blood chamber were made *en bloc* with flexible silicone rubber through a die casting process with no metal ring. Photographs of dies and core for this second generation STV are shown in Figure 1B.

Design of the ventricular assist device

The valve was a hollow cylinder comprising three thick and thin portions in the side wall, turned inside out to change the shape from a short circular tube to a triangle tri-leaflet valve. After removing the core, the open bottom of the blood chamber was sealed with silicone glue. The shape of the blood chamber was a lenticular sac which was 77 mm in diameter and 38 mm in width in the central portion, with a wall thickness of 1.5 mm, and a capability of 70 ml of volume. The diameter of the inlet and outlet was 22 mm, that of the valve orifice was 17 mm, the length of the valve was 20

mm, the thickness of the valve was 0.35 mm at the thinnest portion, and the thickness of the portion connecting the blood chamber and the valve was 2.0 mm. The blood chamber was placed in a casing made with aluminum alloy and acrylic resin as a VAD (Fig.1C).

For an *in vivo* experiment, the outflow and inflow cannulas of silicone-coating polyvinyl chloride were attached to be made as a LVAD (Fig.1D).

In vitro hydrodynamic testing

A batch of 3 consecutively manufactured VADs with STVs underwent hydrodynamic function testing. The leak flow as a result of back pressure across the closed valve was measured using water at 25°C and a pressure of 100 cm H₂O. The pressure gradient across the inlet and outlet valve was measured with steady water flow at 25°C using an overflow tank and a centrifugal pump. Hemodynamic performance studies were carried out using saline as the working fluid in a Donovan-type mock circulatory system⁵⁾ connected to a pneumatic artificial heart driver (Corat 104,

Aisin Seiki Co. Ltd; Kariya, Japan) under the following conditions: preload=-10 to +25 mmHg, afterload=60 to 120 mmHg, driving positive pressure=140 to 180 mmHg, driving negative pressure=10 to 20 mmHg, percent systole=20 to 50%, and driving rate=40 to 140 beats per minute (bpm). Preload and afterload were monitored by pressure transducers (NEC San-ei Instruments Ltd; Tokyo, Japan). The flow through the VAD was measured by electromagnetic blood flow meters (Nihon Kohden Corp, Tokyo, Japan). The valve movement was observed for dynamic function visualization using a video camera. The instantaneous pressure gradient across the inlet valve was measured to examine the water hammer phenomenon under the following conditions: preload=10 mmHg, afterload=120 mmHg, driving positive pressure=140 mmHg, driving negative pressure=20 mmHg, driving rate=100 bpm, and percent systole=25 to 50%. For comparison, the above mentioned determinations were also performed on the another device in which two mechanical valves (MVs) of Björk-Shiley monostrut valves with an orifice diameter of 20 mm were placed at the inlet and outlet ports of the same silicone chamber. Hemodynamic parameters were measured under each driving condition after the hemodynamics became stable.

Durability testing

A durability test was performed in an overflow-type mock circulatory system under the following conditions: afterload=100 mmHg, driving positive pressure=140 mmHg, driving negative pressure=10 mmHg, driving rate=80 bpm, percent systole=40%. The flow curve of the outlet and inlet valves were monitored and checked once daily.

In vitro hemolysis test

An *in vitro* hemolysis study was performed using a closed test circuit with fresh heparinized bovine blood (5 units/ml) collected 2 hours before the study. The test circuit consisted of a 1500 ml blood reservoir bag as the venous reservoir. The blood flowed into the VAD from the reservoir outlet port and returned to the reservoir inlet port through the connecting polyvinyl chloride tubes (11 mm in internal diameter). This blood bag was positioned above the pump and the tube length was chosen to provide an afterload of 100 mmHg. The VAD generated 5 liters/min of flow at a driving rate of 80 bpm with the driving positive pressure of 140 mmHg in both the STV and MV. All trials were carried out at room temperature (26°C). Pumping trials lasted 5 hours with samples being drawn at the start of each run and every 30 min thereafter to measure the plasma free hemoglobin. A normalized index of hemolysis (NIH, g/100 liters) was then calculated using the following formula²³⁾:

$$\text{NIH} = \frac{\Delta \text{Free Hb} \times V \times (100 - \text{Ht})}{100 \times 100 / (\text{Flow rate} \times \text{Time})}$$

where Δ Free Hb is the increase of plasma free hemoglobin concentration during the sampling period (g/liter), V is the circuit volume (liter), Flow rate is given as liter/min, Ht is hematocrit (%), and Time is the sampling interval (min).

In vivo animal experiment

An acute *in vivo* study was conducted to evaluate the characteristics of the pump as a left ventricular assist device (LVAD) in accordance with the institutional guidelines of the Guide for the Care and Use of Laboratory Animals published by the U.S. Department of Health and Human Services. An adult sheep weighing 61 kg was used in our study. The sheep is the preferred model because its cardiac physiology, hemodynamics and coagulation parameters are similar to those of humans¹⁸⁾. The animal was anesthetized with intravenous pentobarbital (10 mg/kg) and ketamine hydrochloride (10 mg/kg) and intubated. While ventilation was maintained by a positive pressure respirator, the pump implantation was performed through a left lateral thoracotomy at the 5th intercostal space. Intravenous heparin (200 units/kg) was given in one dose before tube cannulation, and additional doses were given so that the activated coagulation time was controlled from 200 to 300 sec. The outflow cannula of silicone-coating polyvinyl chloride (12 mm in internal diameter) from the the VAD was sewn onto the sidewall of the thoracic descending aorta by a 12 mm woven Dacron graft connected at the end (4 cm in length), and the inflow cannula of the same

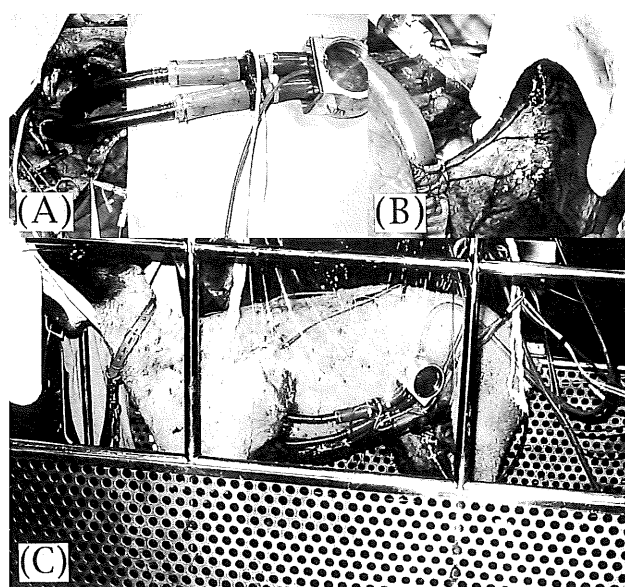


Fig. 2. Photographs of the acute *in vivo* experiment are shown: intraoperative (A), injecting 5N NaOH into the myocardium (B), an adult sheep weighing 61 kg received a newly designed left ventricular assist device (LVAD)(C).

size silicone-coating polyvinyl chloride was inserted into the left atrium through the 20 mm woven Dacron graft (10 cm in length) anastomosed to the left atrial appendage (Fig.2A). The aortic pressure, venous pressure, left atrial pressure, total flow (pulmonary arterial flow), artificial ventricular pressure, outlet flow of the LVAD, and electrocardiogram were continuously monitored and recorded. The LVAD was operated asynchronously or synchronously (counter-pulsation) under normal heart conditions and left heart failure conditions were induced by injecting 5N NaOH into the myocardium of the left ventricular free wall between the left circumflex and left anterior descending coronary arteries directly¹⁴⁾ (Fig.2B). After the chest drainage tube was positioned and the chest was closed, the LVAD was placed on the left side of the sheep (Fig.2C).

RESULTS

The mean leak flows of the closed 3 STVs were 210 ml/min and a MV was 340 ml/min, respectively.

The relationship between the pressure gradient across the valve and the steady water flow is shown in Fig.3. Mean pressure gradients across the silicone inlet valve measured with steady water flow of 4, 6, 8, and 10 liters/min, were 0.3, 0.8, 1.8, and 2.6 mmHg, respectively. Those of the outlet valve were 1.0, 1.6, 2.6, and 4.1 mmHg, respectively. The pressure gradients across the

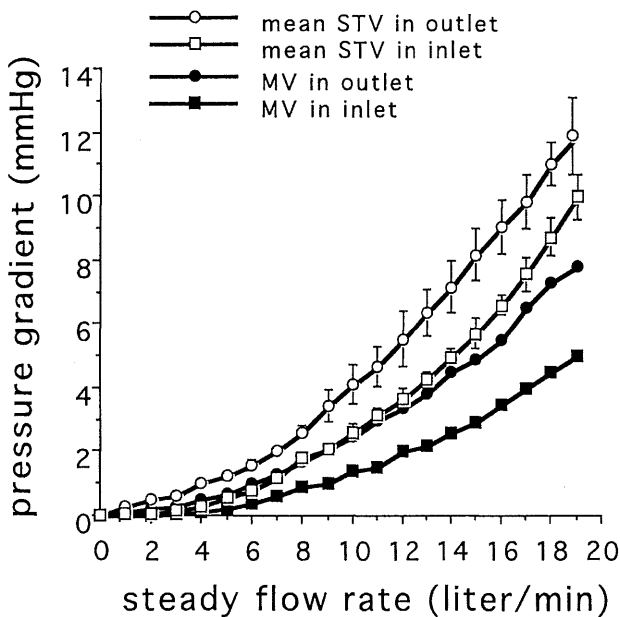


Fig. 3. Pressure gradients across the silicone tri-leaflet valve and mechanical valve [Björk-Shiley monostrut valve] under steady flow are shown. STV: silicone tri-leaflet valve, MV: mechanical valve Values for the STV are means of 3 consecutively manufactured valves; standard deviation bars are indicated at each point

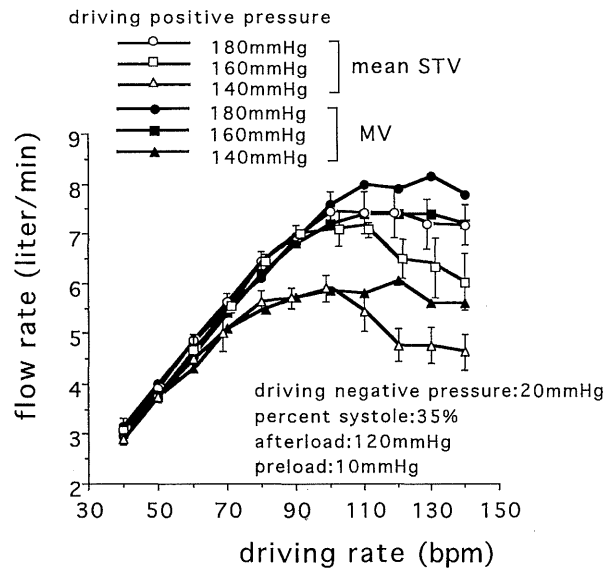


Fig. 4. The relationship between flow rate and driving rate for STV and MV types in the mock test is shown under the following conditions: driving positive pressure=140 to 180 mmHg, driving negative pressure=20 mmHg, percent systole=35%.

MV were 0.1, 0.4, 0.9, and 1.4 mmHg for the inlet and 0.5, 1.0, 1.7, and 2.5 mmHg for the outlet, respectively. The pressure gradient across 3 STVs was slightly greater than that across the MV at each flow rate in both inlet and outlet positions.

The relationship between flow rate and driving rate is shown in Fig.4. The driving rate varied from 40 to 140 bpm. The maximum mean flow rate of 7.4 liters/min (stroke volume, 74 ml) was obtained under the following conditions: driving positive pressure=180 mmHg, driving negative pressure=20 mmHg, percent systole=35%, and driving rate=100 bpm. This value for flow was similar to that of the MVs under the same conditions. Beyond this driving rate, the flow rate began to decrease. The relationship between flow rate and percent systole at 100 bpm is shown in Fig.5. Under the following conditions: driving positive pressure=180 and 160 mmHg, driving negative pressure=20 mmHg, the mean flow rate was similar to the MV until percent systole of 35%. Beyond this percent systole, the mean flow rate began to decrease. However, under the following conditions: driving positive pressure=140 mmHg, driving negative pressure=20 mmHg, percent systole =20 to 50%, the mean flow rate was similar to that of the MV. The changes in the flow rate with a fixed driving rate of 100 bpm and a driving pressure of 140 mmHg when the afterload was adjusted to 60, 90, and 120 mmHg and preload was changed from -10 to +25 mmHg is shown in Fig.6. As the preload was increased, the mean flow rate also increased

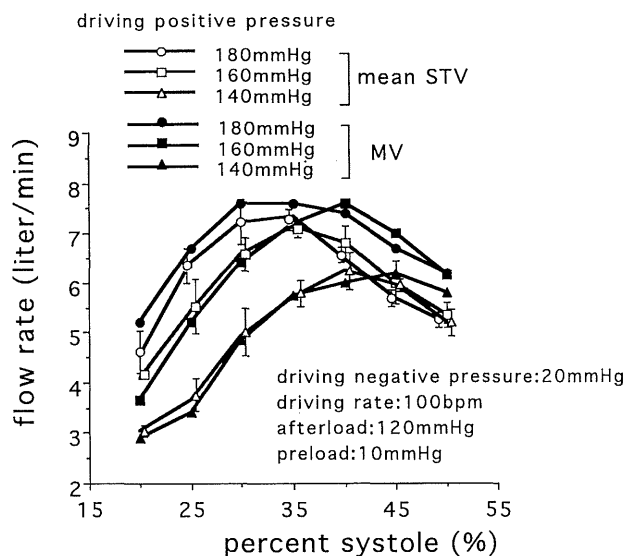


Fig. 5. The relationship between flow rate and percent systole for STV and MV types in the mock test is shown under the following conditions: driving positive pressure=140 to 180 mmHg, driving negative pressure=20 mmHg, driving rate=100 bpm.

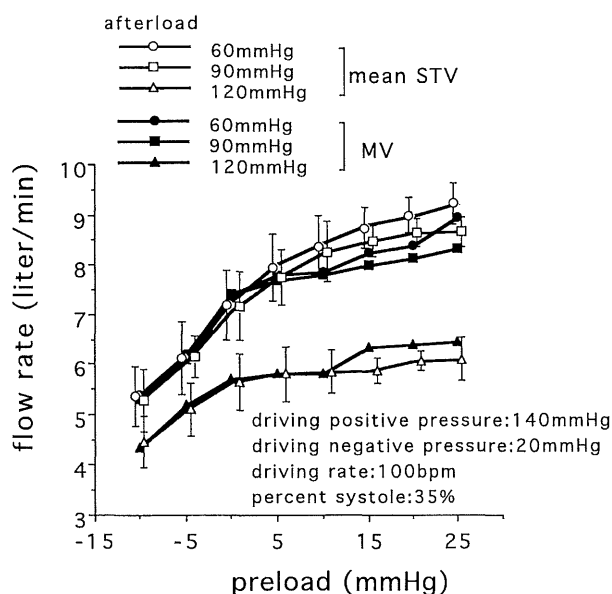


Fig. 6. The preload and afterload sensitivity tests for STV and MV types are shown under the following conditions: driving positive pressure=140 mmHg, driving negative pressure=20 mmHg, percent systole=35%, driving rate=100 bpm.

from 5.37 to 9.23 liters/min, from 5.28 to 8.67 liters/min, and from 4.38 to 6.1 liters/min at afterloads of 60, 90, and 120 mmHg, respectively. Although the flow rate dropped in accordance with the increases in the afterload, the mean flow was similar to that of the MV.

The relationship between the maximum pressure gradient and percent systole at the inlet valve is

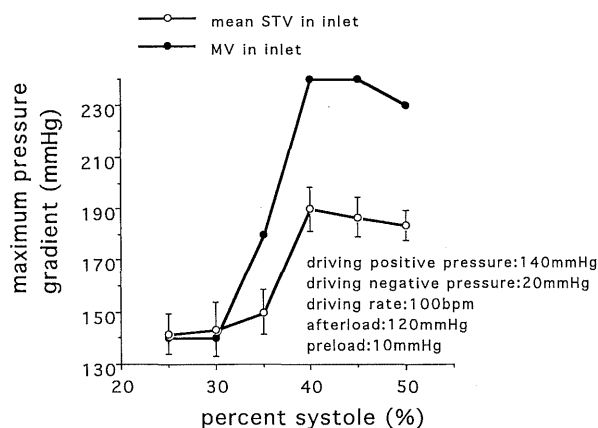


Fig. 7. The relationship between maximum pressure gradient and percent systole at the inlet valve for STV and MV types in the mock test is shown.

shown in Fig.7, under the following conditions that the mean flow was similar to that of the MV: driving positive pressure=140 mmHg, driving negative pressure=20 mmHg. The pressure gradient across the inlet valve caused by the water hammer phenomenon was 142 mmHg at a percent systole of 25%, suddenly elevated at a percent systole of 40%, and reached a maximum pressure gradient of 190 mmHg. In the MV, the pressure gradient rose precipitously at a percent systole of 35%, and reached a maximum pressure of 240 mmHg at a the percent systole of 40%. The maximum pressure gradient of STV was less than that of MV.

The hydrodynamic curves demonstrate that this newly designed VAD has a satisfactory pumping performance. From the recordings of instantaneous flow curve at the valve, we found that the sharp wave curve of flow at the silicone outlet valve closely resembled that of the MV. However, at the silicone inlet valve, the peak wave form was lower and wider than that of the MV (Fig.8). The silicone valve movement visualized by a video camera was swift and smooth (Fig.9).

In the durability testing, this newly designed VAD worked without failure for 54 days with a sufficient output of 5 liters/min, but on the 55th day the inlet valve failed with regurgitation because of a small tear in the leaflet.

In the *in vitro* hemolysis test for the STVs, the free Hb level increased from 12 to 49 mg/dl during experiments lasting 5 h and the NIH was 0.022 g/100 liters. Those of the MV were from 13 to 45 mg/dl and 0.019 g/100 liters, respectively. No remarkable hemolysis was observed in either valve.

In the *in vivo* experiment, the LVAD performed with no driving difficulties. Under the following asynchronized condition (driving positive pressure =180 mmHg, driving negative pressure=20 mmHg, percent systole=35%, driving rate=60 bpm) in a

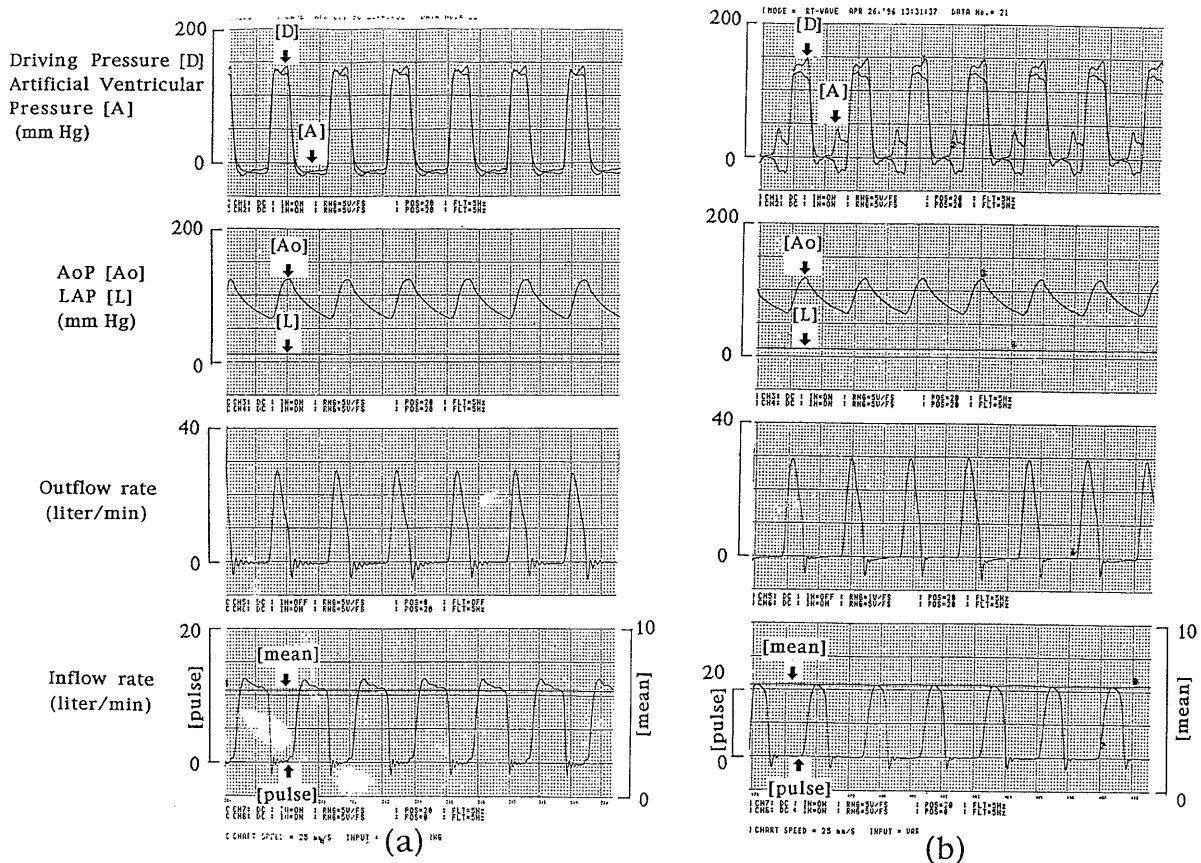


Fig. 8. Driving pressure, artificial ventricular pressure, aortic pressure (AoP), left atrial pressure (LAP), and flow rate at inflow and outflow in the mock test are shown. **(a)**STV, **(b)**MV

normal heart with the bypass flow at 2.7 liters/min (stroke volume, 45 ml), and at 33% of total flow, the systolic aortic pressure elevated from 175 mmHg to 185 mmHg, and total flow increased from 7.2 liters/min to 8.1 liters/min. The pulsatile aortic pressure was augmented by superimposing the pump on the normal heart. With severe left heart failure, the aortic pressure was maintained mainly by the VAD. When the bypass flow was 3.2 liters/min (stroke volume, 53 ml), the systolic aortic pressure increased from 60 mmHg to 80 mmHg, total flow increased from 3.5 liters/min to

5.6 liters/min, and left atrial pressure decreased from 18 mmHg to 12 mmHg (Fig.10). The mean output of the LVAD remained steady at 2.0 to 4.1 liters/min during this experiment for 29 hours without problems. The cause of termination was bleeding and this was attributed to technical failure.

DISCUSSION

Although valve prostheses have been used as the VAD valves, complications related to the use of valves such as mechanical failure caused by the water hammer phenomenon, hemolysis, thrombus formation near the junction of the connecting ring, and infection still limit the success of ventricular devices as well as the replacement of natural valves^{11,19}. Therefore, many investigators have evaluated the application of biocompatible elastomers such as polyurethane, silicone, and polyolefin rubbers to resolve these problems^{12,13,20}. With the development of biocompatible surfaces and pumping chambers, design of an effective VAD was made possible^{8,15,16,28,30}. In our laboratory, development of an artificial heart was initiated in 1966^{6,10,17,21}. We have subsequently designed a tri-leaflet synthetic valve fabricated entirely from silicone⁷ and have created a silicone blood chamber

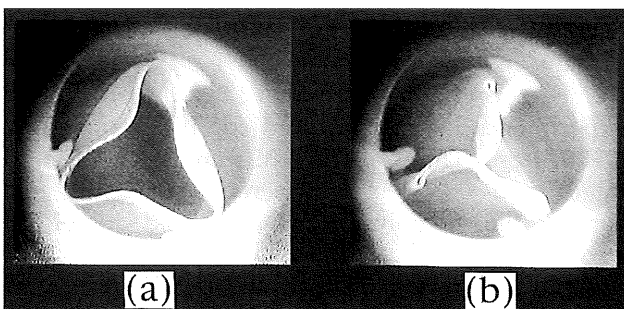


Fig. 9. Photographs of silicone tri-leaflet valve movement in the mock test are shown. **(a)** opened, **(b)** closed.

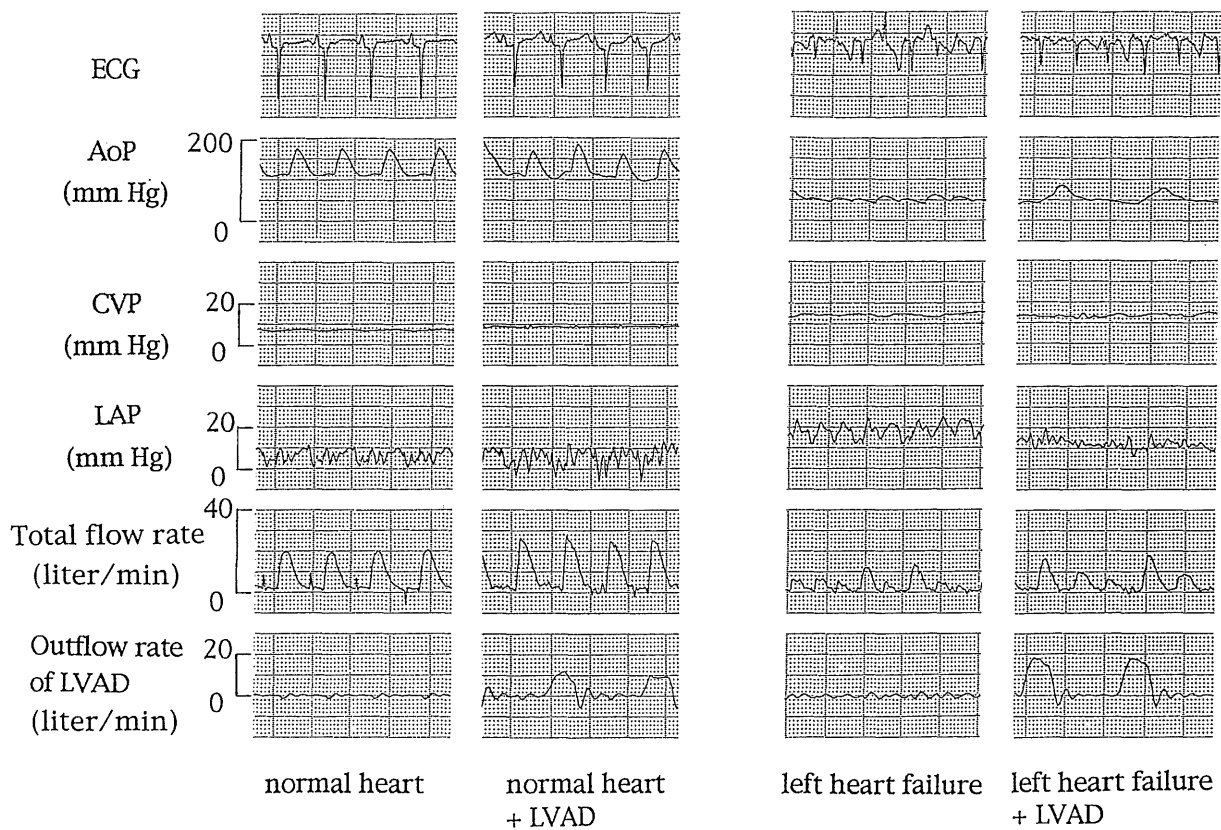


Fig. 10. Hemodynamic traces of a sheep that received a newly designed left ventricular assist device (LVAD) with a normal heart and with left heart failure are shown.

for VADs by means of a die casting process whereby tri-leaflet valves are seamlessly incorporated. The design and characteristics of the silicone pump chamber with two STVs were improved in a stepwise fashion until good performance was achieved. Notably, leaflet thickness was reduced to achieve satisfactory hydrodynamic performance.

For leakage testing of the valve under constant pressure, we used water which has a lower viscosity than blood. Therefore, we predicted that the quantity of water leakage would be greater than the actual quantity of blood leakage. However, leakage of the STV was only 210 ml/min, which was less than the MV at 340 ml/min. Therefore, we concluded that regurgitation of this valve on closing would cause no problems clinically. In a test of resistance against steady flow, the pressure gradient across the valve increased as the steady flow increased on the STV when compared with the MV. This was believed to be due to the fact that resistance upon opening of the STV was greater than in the MV, and also the effective area of the ostium of the STV was smaller than that of the MV. Furthermore, it was especially high when the constant flow rate exceeded 10 liters/min. This was believed to be due to the fact that the pressure gradient was directly proportional to the

square of flow velocity, ie, proportional to the flow rate. In the hydrodynamic test using the Donovan-type mock circulatory system, the flow and pulsatile efficiency of our STVs was adequate and similar to the MV. In an analysis of the wave forms of the flow, which were recorded in order to evaluate the characteristics of the valve, the wave forms of the outlet valve were by no means inferior to those of the MV. The wave form of the inlet valve was a little broader than that of the MV. This was probably due to the fact that the pressure gradient across the STV was greater than that across the MV, and the peak value of the inflow was lower than that of the MV under the same driving negative pressure. Therefore, the inflow time with the STV had to be longer than with the MV in order to obtain the same inflow volume. Although it will be necessary to decrease the pressure differences in this valve in the future, there were no problems with the opening and closing movement of the outlet and inlet valves, as assessed on video camera. In a test of the maximum instantaneous pressure gradient across the inlet STV caused by the water hammer phenomenon, the maximum instantaneous pressure gradient across the inlet valve in an *in vitro* mock circulatory system was evaluated. On the driving of the pulsatile pump, the water hammer phenom-

enon, which occurs in the vicinity of the valve, causes a high pressure gradient across the valve at the moment of valve closing. Therefore, the water hammer phenomenon causes valve fracture and hemolysis, especially in the inlet valve³⁰. The magnitude of water hammer phenomenon was calculated using the following formula²² :

$$\Delta p = \rho a v$$

where Δp is the magnitude of the water hammer phenomenon, ρ is the density of the fluid, a is the velocity of pressure wave propagation, v is the velocity of reverse flow at the moment of valve closing. The water hammer phenomenon is thought to be improved by diminishing the velocity of reverse flow at the moment of valve closing and the velocity of pressure wave propagation²². The water hammer phenomenon with the STV, which is composed of flexible materials, was less than that with the MV. This was believed to be due to the fact that the closing characteristics of the STV were superior to that of the MV, i.e., the v in the above formula was diminished in the STV. In a durability test of the STV, a similar wave form for the flow was observed over a 54 day period. This is more than adequate in view of the fact that the period of use for the VAD, for the purpose of weaning, is usually less than 2 weeks. Moreover, approximately 90% of discharged patients are weaned within 7 days after LVAD implantation²⁶. As such, there should be no problems with the durability of this device for the purpose of temporary short-time circulatory assistance. Clearly, a clinical need exists for a cost-effective assist device for short-term circulatory assist.

To be as practical as possible for clinical purposes in the future, in *in vivo* experiments, it is necessary to evaluate the VAD function and solve the problems of hemolysis and thrombus formation. These are significant problems in the performance of artificial hearts^{4,23,29}. Preliminary studies conducted to investigate whether this device could function and solve these problems, an *in vitro* hemolysis test and an acute animal experiment were examined. No remarkable hemolysis was observed in the *in vitro* hemolysis test. Hemolysis caused by the tri-leaflet valve, in the absence of mechanical components, is felt to be a result of forward flow and stresses not related to mechanical crushing¹. Further improvements that take full advantage of the characteristics of silicone are necessary, as evidenced by the water hammer phenomenon which is less with the STV than with the MV. Under the blood circulation kinetics in an animal experiment, the performance of our device was similar to performance in the mock test. The flow through the LVAD was sufficient to elevate aortic blood pressure, increase total flow, and decrease left atrial pressure. The results of an acute animal experiment showed that our VAD

with STVs had competent pulsatile function and was a good potential assist device in case of left ventricular failure. Although no remarkable thrombus formation was observed macroscopically over the limited course of an experiment, it is necessary to perform further microscopic observations of our device made of medical grade silicone material which can be used clinically in a living body.

Flow properties, including turbulence, shear stress, and stagnation, water hammer phenomenon, have been implicated as causes of blood cell damage, thrombus formation, and infection^{2,19}. Our device may be expected to avoid these problems in future because of the use of flexible silicone materials, a tri-leaflet valve which provides a central flow orifice, and no junction at the connecting ring.

In conclusion, the STV performed adequately in both an *in vitro* and *in vivo* hydrodynamic setting. Our device is easy to manufacture, seamless, can be made cost-effectively, and can be assembled with the blood chamber and valve as one body. Although it will be necessary to decrease the pressure gradient across this STV in the future, we would like to propose this manufacturing process as a practical and cost-effective VAD for temporary short-term using for the purposes of weaning.

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