Circulatory assistance by
linear skeletal muscle ventricle

直線型骨格筋心室による循環補助

金子幸裕

①

Circulatory assistance by linear skeletal muscle ventricle

直線型骨格筋心室による循環補助

金子　幸裕

Summary

We have developed a new skeletal muscle ventricle (LSMV) powered by linear contraction of the latissimus dorsi muscle (LD). The LSMV consists of two bellows of different diameters joined by a connector containing a valve . An additional valve is attached at the other end of the smaller bellows. The smaller bellows is connected to the left atrium, and the larger bellows is connected to the aorta. The caudal tendon of the LD is attached to the connector. LD contraction pulls the connector to compress the larger bellows and to stretch the smaller bellows. This motion closes the valve in the connector, ejects blood from the larger bellows to the aorta, and draws blood from the left atrium to the smaller bellows. LD relaxation allows aortic blood to regurge into the larger bellows. Blood regurgence stretches the LD, extends the larger bellows, and compresses the smaller bellows causing displacement of blood from the smaller bellows into the larger bellows.

In acute canine experiments, the LSMV with normal hearts generated pump output of 199 ml/min., stroke work of 0.201 J and power output of 0.137 W, equivalent to 14.1 %, 166 % and 55 % of respective normal left ventriclar values at filling pressure of 4.7 mmHg. In a setting of temporary heart failure induced by propranolol and mannitol, LSMV output, stroke work, and power output were 164 ml/ min., 0.180 J,

and 0.091 W respectively, equivalent to 15.4 %, 185 %, and 62 % of respective failing left ventriclar values. As a result of LSMV assistance, left ventricular stroke work and power output, as well as left ventricular preload and afterload, decreased significantly. This indicated that the LSMV not only assisted systemic circulation but also reduced work load of the failing left ventricle.

Thus, feasibility of this LSMV was suggested through this acute experimental study.

Background and Purpose

The concept of using the contractile power of skeletal muscle to assist the heart was first proposed in 1959.[1] However, Further work was initially discouraged by the finding that skeletal muscle fatigued rapidly when subjected to the continuous work for cardiac assistance. Discovery of fiber type transformation of the skeletal muscle by chronic, low frequency electrical stimulation (electrical preconditioning) has revived the concept that skeletal muscle can assist the failing heart.[2,3] Skeletal muscle that has been electrically preconditioned acquires favorable bioenergetics for sustained contraction as a result of changes both in the isoform of myosin, and in the kinetics of release and uptake of caucium. Simultaneously, sustained production of adenosine triphosphate (ATP) becomes possible through an increase in the capacity of oxidative pathways at the expense of anerobic glycolysis. There is an assocated increase in capillary blood supply and mytochondrial volume. With appropriate electrical preconditioning, muscle transformation can be accomplished in six to eight weeks and is associated with a greatly increased resistance to fatigue.[4-6]

Attempts to provide myocardial support with skeletal muscle have focused mainly on the use of the latissimus dorsi muscle (LD), which offers advantages suited to a cardiac assist role. Being supplied primarily by a single neurovascular

pedicle, the muscle is easily mobilized and transposed within the thoracic cavity without incurring significant impairment of shoulder function.[7] In addition, because the muscle has a bulk comparable with that of the left ventricle and skeletal muscle is capable of more work per unit weight than cardiac muscle,[4] a single LD has the potential for assuming a major part of the left ventricular workload. After division of small blood vessels to the LD during its mobilization from the chest wall, the distal half of the muscle becomes ischemic. A three weeks vascular delay period before chronic stimulation of the muscle allows recovery of normal blood flow.[8] In order to generate cardiac-type work from skeletal muscle, a burst pattern of moter nerve stimulation is necessary to induce mechanical summation of contractile force.[9]

In one form of skeletal muscle cardiac assistance, dynamic cardiomyoplasty (CM), the latissimus dorsi muscle is wrapped around the heart and then electrically stimulated in synchrony with systole to augment cardiac contraction. CM, currently undergoing clinical trials[10-13], has been performed in more than 700 patients worldwide, and excellent symptomatic improvement has been documented. A number of other methods of skeletal muscle cardiac assistance including skeletal muscle ventricles (SMVs)[6,8,14-24], aortomyoplasty[25,26], and muscle-powered cardiac assist devices[27,28] are also under experimental investigation.

Heart transplantation and mechanical cardiac assist devices are indicated for patients with severe heart failure which is otherwise untreatable. In heart transplantation, however, there are problems of donor heart shortage and immunological rejection. Mechanical cardiac assist devices are also faced with the problems of high costs and a limitation of daily activities caused by attachment to an external power unit. If SMVs become clinically feasible, these problems could be solved.

The SMV has been applied either as an aortic diastolic counterpulsator[14-16] or as an auxiliary blood pump. In both modalities, the efferent conduit of the SMV is connected to the arterial system, usually to the aorta. When the SMV works as a counterpulsator, the afferent conduit is also connected to the aorta. When the SMV works as an auxiliary pump, the afferent conduit is connected either to the left ventricle[17,18] or to the left atrium[19].

SMVs constructed with the latissimus dorsi muscle (LD) in wrap around configration, which we term wrap SMV, are the most widely investigated[8,14-24] among various blood pumps driven by skeletal muscle power. In wrap SMV, muscle preload is derived from pressure in the cardiovascular chamber to which the afferent conduit is connected.

However, the crucial problem still remains of attaining the correct filling pressure of wrap SMV as described by Spotnitz et al.[20]. That is to say, overly high filling pressure in the SMV

compresses the muscle, thereby impeding blood perfusion to the muscle causing chronic ischemic damage[21,22]. Insufficient filling pressure, meanwhile, fails to stretch skeletal muscle enough to generate necessary power[23].

Poccetino, Stephenson, and their associates[24] attempted to meet the requirement of high power output with low filling pressure by means of prolonged vascular delay period between muscle dissection and electrical stimulation. By connecting the valveless wrap SMV to mock circulation, they tested to see how much power could be harnessed from the SMV. Their SMVs at filling pressures of 10 mmHg achieved stroke work of 0.26 J and power output of 0.14 W respectively. The results obtained by Stephenson and his associates show the highest stroke work of wrap SMV at filling pressure around the atrial pressure level published as at December 1995.[24] However, when they connected their SMVs to the canine circulation in an left atrio-aortic fashion[19], the SMVs generated stroke work and power output of only 0.025 J and 0.024 W respectively at filling pressures of between 8 and 15 mmHg.

Another problem regarding the filling pressure of SMV is that the pressure may change when the patient assumes various postures (postural fluctuation). This is because of changes in the position of the SMV relative to that of the cardiovascular chamber connected to the afferent conduit.

Tacker et al.[29] suggested that a linear geometry of muscle contraction would solve many problems by improving power output and blood perfusion to the muscle. In linear geometry of muscle, however, a low filling pressure at the atrial pressure level can not stretch muscle enough to generate sufficient power. Therefore, an additional mechanism for muscle stretch is necessary. Yomo et al. used springs to stretch the LD[30], but their linear type SMV failed to work under physiological preload. The theoretical disadvantage of applying springs for muscle stretch is low pump efficiency. As the LD contracts, restitutional force of the springs increases in proportion to LD shortening. Therefore, much of the LD work is consumed in stretching the springs, resulting in low pump efficiency. Araki et al.[31] applied weights to stretch the LD. The use of weights, however, is not practical in the clinical setting.

Although several other attempts have been made to obtain sufficient skeletal muscle preload, no practically applicable system has yet been developed. Thus, the problem of attaining appropriate SMV filling pressure to achieve effective cardiac assistance remains unsolved.

We thought that the high pressure of the aortic blood could be utilized to generate LD preload. Thus, we developed an SMV in order to meet the above-mentioned requirements, that is, 1, high preload for optimal contractile force of the skeletal muscle, 2, linear geometry of muscle contraction to

prevent ischemic muscle damage, and 3, constant filling capacity despite postural fluctuation. This SMV is powered by linear contraction of the LD, and termed the linear skeletal muscle ventricle or LSMV. In the LSMV, the LD is stretched by regurgence of blood from the aorta (LSMV muscle stretch system).

This study, the first comprehensive study about the LSMV, is conducted to investigate usefulness and feasibility of the LSMV. The purposes of this study are threefold; firstly, to estimate the correct magnitude of LD stretch necessary to generate maximum pump power output, secondly, to evaluate the pumping performance of the LSMV, and thirdly, to evaluate the hemodynamic effects of the LSMV on heart failure.

Materials and Methods

Design and mechanism of the LSMV

The LSMV consists of two cylindrical bellows of different diameters joined by a connector containing a valve. This valve is termed the outflow valve. An additional valve is attached at the other end of the smaller bellows, which we term the inflow valve. Flow direction is set from the smaller bellows, the ventricular chamber, to the larger bellows, the outflow chamber. The LSMV is connected to circulation in an atrio-

aortic fashion. Both ends, which are hooped by metal rings, are anchored to the thoracic wall to keep the total length constant. The caudal end of the LD flap is attached to the connector (Fig. 1). When the LD contracts, the connector is pulled towards the aortic end, thus the LD compresses the outflow chamber and extends the ventricular chamber. As pressure in the ventricular chamber decreases, the outflow valve closes and the inflow valve opens. Blood is thereby drawn from the left atrium into the ventricular chamber, while blood in the outflow chamber is ejected to the aorta (Fig. 2 A, B). When the LD relaxes, blood in the aorta regurges into the outflow chamber, thereby extending this chamber and causing the ventricular chamber to compress. Consequently, internal pressure in the ventricular chamber increases to the level of the aortic pressure, which causes the inflow valve to close and the outflow valve to open. At this point, with the outflow valve open, force generated by the cross sectional area difference between the two chambers shifts the connector towards the atrial end, causing extension of the outflow chamber and compression of the ventricular chamber to continue. Therefore, blood in the ventricular chamber is displaced into the outflow chamber. LD preload is thereby generated (Fig. 2 C, D). The LD preload and afterload are described by the following equations, which do not take into account the restitutional force of the bellows.

Preload (N) = {(outflow chamber diameter (cm))^2
- (ventricular chamber diameter (cm))^2}
x aortic pressure (mmHg) x 1.05 x 10^{-2}

Afterload (N) = {(outflow chamber diameter (cm))^2
x aortic pressure (mmHg) - (ventricular chamber diameter
(cm))^2 x left atrial pressure (mmHg)} x 1.05 x 10^{-2}

Experiment 1

This experiment was planned to estimate the correct magnitude of LD stretch that was necessary to generate maximum pump power output. Muscle preload was generated by applying weights.

LSMV construction

We constructed LSMVs in which the two chambers were equal in size. Vascular grafts (Hemashield woven double velour, Meadox Medicals, Oakland, NJ) sealed by blood preclotting to prevent blood leakage were used as bellows. Based on a calculation, the diameter of the two chambers were decided at 22mm(see appendix 1). The length of each bellows was decided as 7.5 cm by a pilot study (see appendix 2).

Two Carpenter-Edwards porcine aortic valves of 19 mm in diameter (Edwards CVS Division, Santa Ana, CA) were used as the inflow and outflow valves. The connector was hand-made.

Both ends of the LSMV were fixed to a wooden plate. Two vinyl tubes, both 50 cm in length and 8 mm in internal diameter, were connected to both ends of the LSMV as the efferent and afferent tubes. At the other end of either tube, perfusion cannulas were connected (afferent tube; 75012 Arterial cannula DLP, INC., Grand Dapids, MI, efferent tube; V122-20 Stöckert Instrumente, Munich, Germany). A tunnel-shaped cover was placed over the ventricular chamber to prevent kinking when the ventricular chamber shortened.

Since the cross sectional areas of the two chambers are the same, no preload was generated by the muscle stretch system. Variable weights (200, 400, 600, and 800 g) were hung with threads to the connector to LD provide preload (Fig. 3).

Animal preparation

Five mongrel dogs weighing 13 to 19 kg underwent experiment 1. Each animal was anesthetized with intravenous pentobarbital (40 mg/kg), mechanically ventilated through an endotracheal tube, and then placed in the right lateral position. An oblique incision was made from the left axilla to the lowest rib. The left LD was mobilized taking care to preserve the thoracodorsal neurovascular pedicle and the humeral insertion. Two temporary epicardial pacing wires (6500, Medtronic, Kerkrade, Holland) were sutured to the LD as described by Carpentier and associates[32]. A left

thoracotomy was made at the fourth intercostal space and the pericardium was opened. An epicardial sensing lead was sutured to the left ventricle, and purse string sutures were stitched on the left atrial appendage and the descending aorta. The position of the dog was then changed to the supine position, and the left front leg was fixed to the operating table. The wooden plate on which the LSMV was placed was also fixed to the operating table, so that the LSMV was in line with the humeral tendon of the LD and the LD could reach the connector without stretching. Alignment was carefully checked to avoid kinking of either chamber. The caudal end of the LD flap was sutured to the connector, and both edges of the flap were sutured together. Heparin (100 U/kg) was given intravenously to the dogs, and the LSMV was filled with heparin-added saline (2 U/ml). The perfusion cannulas were inserted into the descending aorta and the left atrial appendage. A small amount of blood leakage was seen from the two chambers because of incomplete sealing of vascular grafts. Pacing and sensing wires were connected to an electrical stimulator (Fukuda Denshi, Tokyo, Japan) programmed to deliver burst pulses. The pulse width of 0.2 msec, the voltage of 5 V, and the frequency of 33Hz were determined for fair comparison with several other papers which adopted similar stimulator settings for muscle stimulation.[8,14-19,21,26,33] The pulse duration of 200 msec was determined so that it equals to 30 to 40 % R-wave to R-wave

duration. The synchronozation rate was set at a rate of 1:3 with the native heart beat in a counterpulsatile mode, determined by a former study in our laboratory.[34] The same stimulator setting was used throughout the study.

Measurement

Left atrial and aortic pressures were measured by fluid-filled transducers (Cobe, Lakewood, CO). Blood flow in the aortic cannula was measured by a Doppler flow meter (T201, Transonic Systems, Ithaca, NY) in order to calculate LSMV stroke volume and output.

After each preload weight was set, the burst stimulator was switched on to induce four contractions of the LD, and then turned off. Measurements of the following were taken: LD contraction rate, mean left atrial pressure, peak systolic aortic pressure, peak aortic pressure during LSMV ejection, mean aortic pressure during LSMV ejection, and LSMV stroke volume. The average values of each measurement taken during the second, third, and fourth contraction were recorded as data. The order of the weights applied was set from lighter to heavier in two dogs, heavier to lighter in two other dogs, and in random order in the last dog. One minute rest was given before the next measurement. Measurements were carried out in about 10 minutes. LSMV stroke work was defined as the energy transferred from the LSMV to blood in the cardiovascular syatem during one cycle of the LSMV

motion. Therefore, LSMV stroke work and power output were calculated by the following equations.

LSMV stroke work (J) = {mean aortic pressure during LSMV ejection (mmHg) - mean left atrial pressure (mmHg)} x LSMV stroke volume (ml) x 1.333×10^{-4}

LSMV power output (W) = stroke work (J) x contraction rate (contraction/min.) / 60

Experiment 2

This experiment was planned to evaluate the pumping performance of LSMVs in which muscle preload was generated by the muscle stretch system using dogs with normal cardiac function.

Experimental Setting

We constructed LSMVs in which the two chambers were different in diameter. We set the diameters of the ventricular and outflow chambers at 20 mm and 32 mm respectively based on the result of experiment 1(see appendix 3). Vascular grafts (Cooley low porosity graft 20 mm and 32 mm, Meadox Medicals, Oakland, NJ) were used for the two chambers, and an SJM valve (29 mm, St. Jude Medical, St. Paul, MN) was used as the inflow valve. This valve was too large to be attached to

the ventricular chamber directly. Therefore, the valve was placed in a hand-made container, and the container was attached to the ventricular chamber. A Starr-Edwards valve (Model 2310, 12A 27 mm, Edwards Laboratories, Santa Ana, CA) was used as the outflow valve.

Six mongrel dogs weighing 15 to 23 kg underwent experiment 2. General anesthesia was induced and the LD was mobilized as described above. Because the circumference of the outflow chamber was too large to be covered with the LD alone, a polytetrafluoroethylene sheet (Gore-tex sheet 0.6 mm, W.L. Gore and Associates, Flagstaff, AZ) was patched between the connector and the LD. The rest of the experimental setting was the same as that of experiment 1.

Measurement

Left atrial and aortic pressures, and blood flow in the aortic cannula were measured as described above. Blood flow in the ascending aorta was also measured by the Doppler flow meter in order to calculate cardiac stroke volume and cardiac output. During the nine heart beats before the stimulator was switched on, measurements of the following were taken and the average values for each of the nine heart beats were recorded as data: heart rate, left atrial pressure, mean aortic pressure, mean systolic aortic pressure, cardiac stroke volume, and cardiac output. The burst stimulator was then switched on to induce five contractions of the LD, and then turned off.

The volume of blood ejected to the aorta from the LSMV during LD contraction, the volume of regurgence from the aorta to the LSMV during the preceding LD relaxation period, and the difference between the two volumes were defined as LSMV stroke volume, LSMV regurgitant volume, and LSMV forward stroke volume respectively. The sum total of cardiac output and LSMV output was defined as total output. During the nine heart beats from the start of the second contraction of the LD until the start of the fifth contraction, measurements of the following were carried out and the average values for each of the nine heart beats were recorded as data: heart rate, left atrial pressure, mean aortic pressure, mean systolic aortic pressure, peak aortic pressure during LSMV ejection, mean aortic pressure during LSMV ejection, mean aortic pressure during LSMV regurgence, cardiac stroke volume, cardiac output, LSMV stroke volume, LSMV regurgitant volume, and LSMV output. LSMV stroke work, left ventricular stroke work and left ventricular power output were calculated by the following equations.

LSMV stroke work (J) = {(mean aortic pressure during LSMV ejection (mmHg) - mean left atrial pressure (mmHg)) x LSMV stroke volume (ml) - (mean aortic pressure during LSMV relaxation (mmHg) - mean left atrial pressure (mmHg)) x LSMV regurgitant volume (ml)} x 1.333×10^{-4}

Left ventricular stroke work (J) = (mean systolic aortic pressure (mmHg) - mean left atrial pressure) x cardiac stroke volume (ml) x 1.333 x 10^{-4}

Left ventricular power output (W) = Left ventricular stroke work (J) x heart rate (beats / min.) / 60

LSMV motion was recorded on a video tape by a video recorder (Canon, Tokyo, Japan) for measurement of the excursion of the connector. The restitutional force of the vascular grafts was measured with a spring scale under dry and static conditions.

Experiment 3

This experiment was planned to evaluate the hemodynamic effect of the LSMV in dogs with heart failure. The hemodynamic effects of the LSMV were assessed in comparison with those of dynamic cardiomyoplasty (CM) in a setting of temporary heart failure induced by propranolol and mannitol.

Experimental setting and measurement of LSMV

This experiment was carried out after experiment 2 using the same dogs and LSMVs. After experiment 2, the efferent tube of the LSMV was occluded with a tube clamp, and 100

mL of heparin-added saline (2 U/ml) was infused into the LSMV to prevent blood clotting. Propranolol (3 mg/kg) was infused intravenously to induce temporary heart failure. Mannitol solution of 20 % concentration was also infused to increase left atrial pressure to 18 mmHg. The tube clamp applied to the efferent tube was then released. Hemodynamic measurements were carried out in the same way as in experiment 2.

Experimental setting and measurement of CM

Six mongrel dogs weighing 16 kg to 23 kg underwent CM. General anesthesia was induced, the left LD was mobilized, and pacing wires were sutured as described above. A left thoracotomy was made at the sixth intercostal space. A short segment of the second rib was resected, and the LD flap was introduced into the thoracic cavity through the space at the second rib. After the pericardium was opened, a sensing wire was sutured to the left ventricle. The LD flap was wrapped around the heart in the posterior to anterior fashion. The flap was secured by suturing it to the pericardium and to itself. Pacing and sensing wires were connected to the stimulator. The position of the dog was then changed to the supine position, and the left front leg was fixed to the operating table. Left atrial pressure, aortic pressure, and flow in the ascending aorta were measured as described above, and recorded as control data . Mannitol solution of 20 % concentration was

infused intravenously to increase left atrial pressure to 18 mmHg following propranolol infusion (3ml/kg). Data was obtained during the nine heart beats before the stimulator was switched on, and during the nine heart beats from the start of the second contraction of the LD until the start of the fifth contraction.

Statistical Analysis

Statistical analysis was performed by the paired or unpaired Student t test, where appropriate. Statistical significance was set at a p value of less than the 0.05 level. All data were expressed as the mean ± the standard error of the mean.

Results

Experiment 1

The recorded data are summarized in Table 1. Contraction rate, peak systolic aortic pressure and mean left atrial pressure did not show significant differences among the four weight groups. Peak aortic pressure during LSMV ejection obtained at 600 g preload weight was significantly higher than that obtained at 200, 400, and 800 g weights.

Mean aortic pressure during LSMV ejection obtained at 600 g weight was significantly higher than that obtained at 200 and 800 g weights. The stroke volume of the LSMV at 600 g weight was also higher than that obtained with 200 and 800 g weights. Maximum stroke work of 0.168 ± 0.019 J and maximum power output of 0.100 ± 0.008W were obtained with a 600 g weight. These values were significantly greater than those obtained at 200, 400, and 800 g weights.

Experiment 2

Hemodynamic values before and during LSMV assistance are summarized in Table 2. As a result of LSMV assistance, mean aortic pressure increased significantly from 64.3 ± 3.7 to 81.5 ± 4.4 mmHg, whereas heart rate, systolic and diastolic aortic pressure, left atrial pressure, cardiac stroke volume, left ventricular stroke work, and left ventricular power output did not show significant changes. Total output during LSMV assistance was 1606 ± 72 ml/min., which was significantly higher than cardiac output before LSMV assistance of 1407 ± 72 ml/min..

As shown in Table 5, LSMV output, LSMV stroke work and LSMV power output were 199 ± 13 ml/min., 0.201 ± 0.014 J, and 0.137 ± 0.010 W respectively, equivalent to 14.1 %, 166 % and 55 % of respective normal left ventriclar values before LSMV assistance. The ejection fraction of the ventricular

chamber was 19 % (forward stroke volume / volume of the ventricular chamber).

The connector shifted 1.3 cm on the average towards the atrial end at LD relaxation from the resting position, and 1.5 cm towards the aortic end at LD contraction. Excursion was 2.8 cm in total, compared to the estimated value of 1.8 cm ($4 / \pi \times$ stroke volume x outflow chamber diameter^{-2}).

The restitutional force of the vascular grafts was measured as 72 N/m at a 1.5 cm excursion in each direction.

Experiment3

Temporary heart failure induction

As shown in Table 3, before the infusion of propranolol and mannitol, left atrial pressure, mean and systolic aortic pressure, stroke volume, left ventricular stroke work and left ventricular power output were significantly lower in the LSMV group than in the CM group. These differences are attributable to bleeding during experiment 2.

Propranolol and mannitol infusion resulted in a significant decrease in heart rate, cardiac output, left ventricular stroke work and left ventricular power output, as well as a significant increase in left atrial pressure, in both the LSMV and CM groups. In CM group, a significant decrease in aortic pressure was also seen.

Statistical differences in hemodynamic values dissapeared between the two groups as a result of propranolol and mannitol infusion. There was no significant difference in dog body weights between the two groups ($p = 0.85$)

Hemodynamic effect of LSMV and CM

A typical record during LSMV assistance in this experiment is shown in Figure 4. Marked aortic pressure increase and left atrial pressure decrease are seen during the LSMV contraction. LSMV regurgitant flow is seen starting just after the LSMV contraction and during cardiac systole. Hemodynamic effect of LSMV and CM on heart failure dogs is summarized in Table 4. LSMV assistance resulted in a significant decrease in left atrial pressure, mean systolic aortic pressure, left ventricular stroke work and left ventricular power output, and a significant increase in mean aortic pressure. Total output with LSMV assistance was significantly higher than cardiac output before LSMV assistance. In the CM group, CM assistance resulted in a significant increase in mean systolic aortic pressure. However, left atrial pressure, mean aortic pressure, stroke volume, and cardiac output did not change significantly.

The increment of mean aortic pressure by LSMV assistance was significantly greater than that achieved by CM assistance. The difference between total output with LSMV assistance and cardiac output before LSMV assistance was

significantly greater than the increment of cardiac output as a result of CM assistance. Left atrial pressure decreased because of LSMV assistance while remained unchanged as a result of CM assistance.

LSMV function in heart failure dogs

LSMV function in a setting of heart failure is summarized in Table 5. LSMV output, LSMV stroke work and LSMV power output were 164 ± 17 ml/min., 0.180 ± 0.017 J, and 0.091 ± 0.008 W respectively, equivalent to 15.4 %, 185 % and 62 % of respective failing left ventriclar values before LSMV assistance. Induction of heart failure resulted in a significant decrease of LSMV contraction rate and LSMV power output, whereas LSMV output and LSMV stroke work did not change significantly.

Discussion

Pumping Function of the LSMV

In this study, the LSMV was found to achieve a stroke work that exceeded normal canine left ventriclar stroke work, at filling pressure lower than normal canine left atrial pressure[18]. The LSMV showed better stroke work and pump power output than any other skeletal muscle ventricle

connected to circulation in an atrio-aortic fashion reported as at December 1995.

In experiments 2 and 3, regurgitant volume was about two thirds of LSMV stroke volume. Blood regurgence into the LSMV occurred mainly during cardiac systole, and blood ejection from the LSMV occured during cardiac diastole. This counterpulsatile action can be expected to assist the failing heart by systolic unloading and diastolic augmentation. However, LSMV output was equivalent to only 14.1% of normal canine cardiac output despite the high power output of the LSMV. Improvement of LSMV output is desired before its clinical application.

In experiment 3, LSMV stroke volume and stroke work were found to be similar to those in experiment 2. This implies that LSMV pump function is relatively independent of recipient's heart function, and the LSMV can maintain steady pump function even if the patient's heart failure worsens.

Hemodynamic effects of LSMV

In experiment 2, total output of the heart and LSMV was higher than cardiac output before LSMV assistance by 14.1 %, aortic pressure increased by 26.7 % and left atrial pressure remained unchanged as a result of LSMV assistance. Similarly, in experiment 3, total output was higher than cardiac output before LSMV assistance by 12.5 %, aortic pressure increased by 23.5% and left atrial pressure decreased by 17.8 % as a

result of LSMV assistance. Thus, hemodynamic improvement was obtained both in experiments 2 and 3.

In experiment 2, left atrial pressure and aortic pressure during systole, as well as left ventricular stroke work and left ventricular power output, remained unchanged when the LSMV was driven. The LSMV did not reduce work load of normal heart.

In experiment 3, on the other hand, left ventricular preload and afterload, as well as left ventricular stroke work and power output, decreased significantly as a result of LSMV assistance. The LSMV not only enhanced hemodynamics but also reduced the preload and afterload of the failing heart.

Judging from the results of experiment 3, hemodynamic enhancement by LSMV was obviously greater than that by CM. CM is currently not indicated to New York Heart Association functional class 4 patients because they are too severely ill to be treated by CM as it has limited effectiveness[4,6]. It is suggested in this study that the LSMV could be beneficial to patients for whom CM treatment is not indicated.

LSMV Muscle Stretch System

As shown in experiment 1, for an LSMV without the muscle stretch system, the LD must be stretched with a preload weight of 600 g to attain the maximum power output. In the LSMV with the muscle stretch system tested in

experiment 2, however, the LSMV showed better pump performance than in experiment 1, indicating that the LD was adequately stretched by this muscle stretch system. Results obtained from experiments 1 and 2 suggest that the requirements of high power output with low filling pressure as described by Spotnitz[13] could be attained by the enhanced muscle preload provided by the muscle stretch system.

The muscle stretch system used in the LSMV has four theoretical beneficial characteristics as compared to the muscle stretch method used in wrap SMVs. Firstly, filling capacity is improved by the muscle stretch system in the LSMV since blood is actively drawn from the left atrium by LD contraction. In wrap SMV, on the other hand, filling capacity is impaired since the LD contracted by previous stimulation must be stretched by filling pressure during SMV filling. Secondly, in the LSMV a steady muscle preload is provided by the muscle stretch system since aortic pressure is relatively stable as compared to left atrial pressure. In wrap SMV, meanwhile, muscle preload varies due to postural fluctuation. Thirdly, muscle preload and afterload can be easily determined by calculation based on arterial pressure and ventricular and outflow chamber diameters. If muscle force after preconditioning can be measured or predicted, the most appropriate preload and afterload can be decided upon by selecting suitable ventricular and outflow chamber diameters. And lastly, as LD power output correlates with LD preload, LD

preload correlates with arterial pressure, and arterial pressure correlates with the degree of body activity, one characteristic of the LSMV is that it increases power output in proportion to an increase in body activity. Therefore, the LSMV may have the capability to autoregulate power output.

Study Limitations

In this study, the two chambers were made of collapsible, incompletely sealed vascular grafts, and the diameters of the two chambers were determined based on rough estimation. As the material used and the design of the LSMV were perhaps not optimal, there is room for improvement in LSMV pump performance. In addition, the LDs were neither electrically preconditioned nor given vascular delay. Therefore, pump performance shown here may differ from that in the chronic setting.[34] Since we did not measure blood flow to the LDs in this study, the hypothesis that blood perfusion is not impaired in linear geometry of muscle contraction could not be tested.

Future Problems

Difficulties that may arise in chronic use of LSMV are as follows: 1, technical difficulty of making bellows suitable for the LSMV, 2, difficulty in fixing the LSMV to the body and the LD to the LSMV, and 3, difficulty in preventing muscle motion attenuation caused by adhesion and friction.

As for the technical aspect of making bellows, the bellows must meet the following requirements. Firstly, the bellows should be durable enough to be used chronically, and secondly, the LSMV should be flexible enough not to impede muscle motion yet short enough to be placed in the hemithorax. The LSMV made with bellows meeting these requirements would show a better ejection fraction than the 19 % observed in this study. Improvement in ejection fraction also seems favorable in preventing thrombosis.

In order to achieve rigid fixation of the LSMV to the body, a metal plate which fixes both ends of the LSMV could be attached to the dorsal part of three or four ribs with orthopedic techniques using screws. As for fixation of the LD to the LSMV, in the present study we fixed the LD to the connector with a simple running suture, and observed muscle tearing where the muscle was sutured. To avoid this, the LD should be securely attached to the LSMV with sutures buttressed by felt. After a period of electrical preconditioning, the LD, the felt, and the connector should stay adhered securely so as to prevent muscle tearing when the LSMV is driven by muscle power.

Possible adhesion and friction problems could be solved by wrapping an omental flap around the LSMV and the LD. This flap should help smooth movement between the LSMV-LD complex and the organs surrounding it. Such an omental

flap would also supply blood to the ischemic LD, which might be another advantage of omental wrapping.

Conclusion

In conclusion, we have developed a new skeletal muscle ventricle (LSMV) in which the latissimus dorsi muscle is optimally stretched by regurgence of blood from the aorta. In acute canine experiments in a setting of normal heart, the LSMV generated pump output of 199 ml/min, stroke work of 0.201 J and power output of 0.137 W, equivalent to 14.1 %, 166 % and 55 % of respective normal left ventricular values at filling pressure of 4.7 mmHg. In a setting of temporary heart failure induced by propranolol and mannitol, LSMV output, stroke work, and power output were 164 ml/ min., 0.180 J, and 0.091 W respectively, equivalent to 15.4 %, 185 %, and 62 % of respective failing left ventricular values. Left ventricular preload and afterload, as well as left ventricular stroke work and power output, decreased significantly as a result of LSMV assistance. It is indicated that the LSMV not only assists systemic circulation but also reduces work load of the failing left ventricle.

The study has suggested the possibility of practical use of this LSMV.

Appendix 1

Our assumptions were as follows. The optimal LD preload and afterload ratio for maximum mechanical external work in dogs weighing 12 kg on average were 0.4 kgf and 0.8 kgf, respectively, as measured by Isoda et. al.[35]. The optimal preload and aafterload of the LD muscle would be in proportion to the number of the muscle fibers in the LD, and thereby to the body weight multiplied by the power of two thirds. Assuming that the dogs used in this study weighed 18 kg on average, then the optimal preload and afterload would be 0.46 kgf and 0.92 kgf as calculated by the following equations.

$0.4 \times (18/12)^{2/3} = 0.46$ $0.8 \times (18/12)^{2/3} = 0.92$

In experiment 1, the muscle preload equals to the force to the connector generated by a weight, and the afterload equals to the force to the connector generated by the same weight and by aortic pressure. Therefore, the desirable force generated by aortic pressure for maximum LSMV power output would be 0.46 kgf, which is the difference between the optimal preload and afterload. Assuming that aortic pressure of the dogs would be around 90 mmHg, the desirable diameter of the two chambers was calculated by the following equation.

$\textit{desirable diameter (cm)} = \{(0.46 \times 4)/(\pi \times 90 \times 0.00136)\}^{1/2} = 2.19$

The softest bellows we could obtain was vascular grafts of which diameter was available in 2 mm increments. Therefore, we decided the diameter of the bellows as 22 mm.

Appendix 2

Longer bellows would lead to better pump performance because of smaller restitutional force of the bellows. However, kinking of the bellows which destroys LSMV pump performance must be avoided. The LSMVs, in which length of both bellows were 5, 7.5, 10, 12.5, and 15 cm, respectively, were used in this pilot study. The materials used were the same as in experiment 1. Weight weighing 800 g were hung with threads to the connector of each LSMV as in experiment 1. The LSMV was connected to a mock circulation made with cardiopulmonary bypass circuit filled with water. Filling pressure and aortic pressure were set at 10 mmHg and 80 mmHg, respectively. The connector was pulled towards the aortic end by hand, and then released. In result, the bellows of the ventricular chambers longer than 7.5 cm kinked while the weights pulled the connector towards the atrial end. We, therefore, decided the length of the bellows as 7.5 cm.

Appendix 3

The optimal muscle preload of 0.6 kgf was suggested from the results of experiment 1. The muscle afterload was

calculated as 1.2 kgf when the preload was 0.6 kgf by the following equation.

$(2.2/2)^2 \times \pi \times (122 - 6) \times 0.00136 + 0.6 = 1.2\ (kgf)$

Assuming mean aortic pressure of 82 mmHg, aortic pressure during LSMV of 122 mmHg, and left atrial pressure of 6 mmHg as suggested in experiment 1, the desirable outflow chamber diameter (α) and ventricular chamber diameter (β) were calculated by the following simultaneous equations.(see pages 6 and 7)

$0.6 \times 9.8 = (\alpha^2 - \beta^2) \times 82 \times 1.05 \times 10^{-2}$

$1.2 \times 9.8 = (122 \times \alpha^2 - 6 \times \beta^2) \times 1.05 \times 10^{-2}$

$\alpha \fallingdotseq 3.1\ ; \beta \fallingdotseq 1.9$

Therefore, we determined the outflow chamber diameter of 3.2 cm, and the ventricular chamber diameter of 2.0 cm.

References

1. Kantrowitz A, McKinnon WMP. The experimental use of the diaphragm as an auxiliary myocardium. Surg Forum 1959; 9: 265-8.
2. Salmons S, Vrbova G. The influence of activity on some contractile characteristics of mammalian fast and slow muscles. J Physiol 1969; 201: 535-49.
3. Sreter FA, Gergely J, Salmons S, Romanul F. Synthesis by fast muscle of myosin light chains characteristic of slow muscle in response to long term stimulation. Nature 1973; 241: 17-20.
4. Salmons S, Jarvis JC. The working capacity of skeletal muscle transformed for use in a cardiac assist role. In Chiu RCJ, Bourgeous IM, eds, Transformed muscle for cardiac assist and repair. Mount Kisco, NewYork: Futura Publishing Company, 1990: 89-104.
5. Salmons S, Jarvis JC. Cardiomyoplasty: a look at the fundamentals. In: Carpentier A, Chachques JC, Grandjean P, eds. Cardiomyoplasty. New York: Futura publishing company,1991: 105-22.
6. Guldner NW, Eichstaedt HC, Klapproth P, Tilmans MHI, Thuaudet S, Umbrain V, Ruck K, Wyffels E, Bruyland M, Sigmund M, Messmer BJ, Bardos P. Dynamic training of skeletal muscle ventricle. Circulation 1994; 89: 1032-40

7. Laitung JKG, Peck F. Shoulder function following loss of the latissimus dorsi muscle. Br J Plast Surg 1985; 38: 375-9

8. Mannion JD, Velchik MA, Acker M, Hammond R, Staum M, Alavi A, Duckett S, Stephenson LW. Transmural blood flow of multi layered latissimus dorsi skeletal muscle ventricles during circulatory assistance. Trans Am Soc Artif Intern Organs 1986; 32: 454-60.

9. Dewer ML, Drinkwater DC, Wittnich C, Chiu RCJ. Synchronously stimulated skeletal muscle graft for myocardial repair. J Thorac Cardiovasc Surg 1984; 87: 325-31

10. Carpentier A, Chachques JC. Myocardial substitution with a stimulated skeletal muscle: first successful clinical case. Lancet 1985; 1: 1267.

11. Carpentier A, Chachques JC, Acar C, Relland J, Mihaileanu S, Bensasson D, Kieffer JP, Guibourt P, Tourney D, Roussin I, Grandjuan PA. Dynamic cardiomyoplasty at seven years. J Thorac Cardiovasc Surg 1993; 106: 4254.

12. Moreira LFP, Seferian P, Bocchi EA, Pego-Fernandes PM, Stolf NAG, Pereira-Barretto AC, Jatene AD. Survival improvement with dynamic cardiomyoplasty in patients with dilated cardiomyopathy. Circulation 1991; 84 [suppl III]: III-296-302.

13. Grandjean PA, Austin L, Chan S, Terpstra B, Bourgeois IM. Dynamic cardiomyoplasty: clinical follow-up results. J Card Surg 1991; 6: S 80-8.

14. Mannion JD, Acker MA, Hammond RL, Faltemeyer W, Duckett S, Stephenson LW. Power output of skeletal muscle ventricles in circulation: short-term studies. Circulation 1987; 76: 155-62.

15. Mocek FW, Anderson DR, Pochettino A, Hammond RL, Spanta A, Ruggiero R, Thomas GA, Lu H, Fietsam R, Nakajima H, Nakajima H, Krakovsky A, Hooper T, Niinami H, Colson M, Levine S, Salmons S, Stephenson LW. Skeletal muscle ventricles in circulation long-term: one hundred ninty-one to eight hundred thirty-six days. J Heart Lung Transplant 1992; 11: S 334-40.

16. Thomas GA, Lelkes PI, Isoda S, Chick D, Lu H, Hammond RL, Nakajima H, Nakajima H, Stephenson LW. Endotherial cell-lined skeletal muscle ventricles in circulation. J Thorac Cardiovasc Surg 1995; 109: 66-73.

17. Lu H, Fietsam R, Hammond RL, Nakajima H, Mocek FW, Thomas GA, Ruggiero R, Nakajima H, Colson M, Stephenson LW. Skeletal muscle ventricles; left ventricular apex to aorta configuration. Ann Thorac Surg 1993; 55: 78-85.

18. Geddes LA, Janas W, Hinds M, Badylak SF, Cook J. The ventricular synchronous, skeletal-muscle ventricle: preliminary feasibility studies. PACE 1993; 16: 1310-22.

19. Hooper TL, Niinami H, Hammond RL, Lu H, Ruggiero R, Pochettino A, Stephenson LW. Skeletal muscle ventricles as left atrial-aortic pumps: short-term studies. Ann Thorac Surg 1992; 54: 316-22.

20. Spotnitz HM, Merker C, Malm JR. Applied physiology of the canine rectus abdominis force-length curves correlated with functional charactaristics of a rectus powered "ventricle": potential for cardiac assistance. Trans Am Soc Artif Intern Organs 1974; 20: 747-756.

21. Badylak SF, Wessale JE, Geddes LA, Tacker WA, Janas W. The effect of skeletal muscle ventricle pouch pressure on muscle blood flow. ASAIO Journal 1992; 38: 66-71.

22. Gealow KK, Solien EE, Lang GR, Evanson CM, Bianco RW, Chiu RCJ, Shumway SJ. Blood flow to the latissimus dorsi muscle pouch during chronic counterpulsation stimulation. J Heart Lung Transplant 1992; 11: S 306-14.

23. Bridges CR, Brown WE, Hammond RL, Anderson DR, Anderson WA, Dimeo F,Stephenson LW. Skeletal muscle ventricles: improved performance at physiologic preloads. SURGERY 1989; 106: 275-82.

24. Pochettino A, Spanta AD, Hammond RL, Anderson DR, Bridges CR, Samat P, Niinami H, Hohenhaus E, Salmons S, Stephenson LW. Skeletal muscle ventricles for total heart replacement. Ann Surg 1990; 212: 345-52.

25. Pattison CW, Cumming DVE, Williamson A, Clayton-Jones DG, Dunn MJ, Goldspink G, Yacoub M. Aortic counterpulsation for up to 28 days with autologous latissimus dorsi in sheep. J Thorac Cardiovasc Surg 1991; 102: 766-73.

26. Lazzara RR, Trumble DR, Magovern JA. Dynamic descending thoracic aortomyoplasty: comparison with intraaortic balloon pump in a model of heart failure. Ann Thorac Surg 1994; 58; 366-71.

27. Frey M, Thoma H, Gruber H, Stöhr H, Havel M. The chronically stimulated psoas muscle as an energy source for artificial organs: an experimental study in sheep. In Chiu RCJ, ed. Biomechanical cardiac assist. Cardiomyoplasty and muscle-powered devices. Mount Kisco, NewYork: Futura Publishing Company, 1986: 179-91.

28. Ugolini F, skeletal muscle for artificial heart drive: theory and in vivo experiments. In Chiu RCJ, ed. Biomechanical cardiac assist. Cardiomyoplasty and muscle-powered devices. Mount Kisco, NewYork: Futura Publishing Company, 1986: 193-210

29. Tacker WA, Geddes LA, Janas W, Babbs CF, Badylak. Comparison of canine skeletal muscle power from twitches and tetanic contractions in untrained muscle: a preliminary report. J Cardiac Surg 1992; 6(1 Supple): 245-51.

30. Yomo T, Shimizu H, Fujikawa T, Suesada H, Hirayama T, Ishimaru S, Furukawa K. Study on development of linear-traction type skeletal muscle powered pump. J Jpn Assn Thorac Surg 1994; 42: 1925-32.

31. Araki K, Nakatani T, Sasaki M, Matsuo Y, Taenaka Y, Konishita M, Matsuzawa T, Akagi H, Baba Y, Inoue K, Anai H, Takano H. Diastolic mechanics of a skeletal muscle pump system actuated by in-situ bilateral latissimus dorsi muscle. Jpn J Artif Organs 1993; 22: 739-42.

32. Carpentier A, Chachques JC. Cardiomyoplasty: surgical technique. In: Carpentier A, Chachques JC, Grandjean P, eds. Cardiomyoplasty. New York: Futura publishing company, 1991: 105-22.

33. Nakajima H, Thomas GA, Nakajima H, Hammond RL, Fietsam R, Mocek FW, Hooper T, Lu H, Spanta AD, Stephenson LW. Update on skeletal muscle ventricles as aortic diastolic counterpulsators. Eex Heart Inst J 1993; 20: 105-11.

34. Naruse Y, Takahama T, Furuse A. Cardiomyoplasty at a high heart rate. In: Carpentier A, Chachques JC, Grandjean P, eds. Cardiomyoplasty. New York: Futura publishing company, 1991: 105-22.

35. Isoda S, Jin Y, Yano Y, Kajiwara H, Tobe M, Imoto K, Kondo J, Matsumoto A. External work of canine latissimus dorsi muscle after vascular delay. J Jpn Assn Thorac Surg 1993; 41: 2349-53.

Preload weight (g)	200 (N=5)	400 (N=5)	600 (N=5)	800 (N=5)
Contraction rate (contraction / min)	36.4±1.7	36.6±1.9	36.4±2.0	36.2±2.0
Left atrial pressure (mmHg)	5.6±0.4	5.4±0.4	5.6±0.6	5.8±0.6
Systolic aortic pressure (mmHg)	81.2±3.7	80.6±3.1	82.4±3.8	82.0±2.1
Peak aortic pressure during LSMV ejection (mmHg)	134.4±7.8	140.2±8.1	153.2±12.1	139.8±10.6
Mean aortic pressure during LSMV ejection (mmHg)	107.8±4.4	111.4±4.6	121.8±7.6	110.8±6.3
LSMV stroke volume (ml)	8.7±0.5	9.8±0.5	10.7±0.7	9.4±0.9
LSMV stroke work (mJ)	119±11	139±11	168±19	133±18
LSMV power output (mW)	71.2±5.3	83.6±4.9	100.0±8.0	78.6±7.9

Table 1. LSMV function in experiment 1 ○ : P < 0.05 ◎ : P < 0.01

Stimulation		(−)	(+)
Heart rate	(beat / min)	123.0±4.8	123.0±4.8
Left atrial pressure	(mmHg)	4.7±0.6	4.7±0.6
Mean aortic pressure	(mmHg)	64.3±3.7	◎ 81.5±4.4
Systolic aortic pressure	(mmHg)	86.8±4.0	84.7±5.1
Peak aortic pressure during LSMV ejection	(mmHg)		174.0±8.5
Mean aortic pressure during LSMV ejection	(mmHg)		145.3±7.4
Mean aortic pressure during LSMV regurgence	(mmHg)		69.3±4.1
Cardiac stroke volume	(ml)	11.5±0.6	11.5±0.7
Cardiac output	(ml / min)	1407±72	1407±74
LSMV output	(ml / min)		199±13
Total output	(ml / min)	◎	1606±72

Table 2. LSMV effect on normal dogs (N=6) ◎ : P < 0.01 ○ : P < 0.05

Heart failure			Before induction	After induction
Heart rate	(beat / min)	LSMV	123.0±4.8	91.5±3.5
		CM	119.7±8.6	89.3±4.4
Left atrial pressure	(mmHg)	LSMV	4.7±0.6	18.0±0.0
		CM	10.2±1.5	18.0±0.0
Mean aortic pressure	(mmHg)	LSMV	64.3±3.7	61.0±4.0
		CM	92.8±7.7	62.3±3.7
Systolic aortic pressure	(mmHg)	LSMV	86.2±4.0	82.6±4.1
		CM	118.8±8.6	84.7±5.7
Stroke volume	(ml)	LSMV	11.5±0.6	12.0±1.1
		CM	13.6±0.6	12.0±8.9
Cardiac output	(ml / min)	LSMV	1407±72	1090±89
		CM	1607±55	1067±90
Left ventricular stroke work	(mJ)	LSMV	126±8	103±10
		CM	197±18	107±12
Left ventricular power output	(mW)	LSMV	257±15	156±15
		CM	386±27	160±12

Table 3. Induction of temporary heart failure (N=6)

◎ : $P < 0.01$
○ : $P < 0.05$

		Stimulation (−)	Stimulation(+)	difference
Heart rate (beat / min)	LSMV	91.5±3.5	91.7±3.6	0.2±0.2
	CM	89.3±4.4	89.7±4.3	0.3±0.2
Left atrial pressure (mmHg)	LSMV	18.0±0.0	14.8±0.6	3.2±0.6
	CM	18.0±0.0	18.0±0.4	0.0±0.4
Mean aortic pressure (mmHg)	LSMV	61.0±4.0	79.7±2.9	18.7±1.9
	CM	62.3±3.7	63.5±3.5	1.2±0.5
Systolic aortic pressure (mmHg)	LSMV	82.6±4.1	79.3±3.9	-3.3±0.7
	CM	84.7±5.7	87.8±5.3	3.2±1.1
Stroke volume (ml)	LSMV	12.0±1.1	11.7±1.0	-3.5±1.6
	CM	12.0±0.9	12.5±1.0	5.0±1.9
			1226±90	164±17
Cardiac output (ml / min)	LSMV	1090±89	1062±85	-36±13
	CM	1067±90	1115±96	46±19
Left ventricular stroke work (mJ)	LSMV	103±10	97±9	
	CM	107±12	117±13	
Left ventricular power output (mW)	LSMV	156±15	148±13	
	CM	160±12	175±23	

Table 4. Changes in circulatory indices of heart failure dogs
(LSMV: N=6, CM: N=6) ▒ : Total output ◎ : $P < 0.01$ ○ : $P < 0.05$

Heart failure		(−)	(+)
LSMV contraction rate	(contractions / min)	41.0±1.6	−◎− 30.5±1.2
LSMV stroke volume	(ml)	14.7±0.4	14.9±0.9
LSMV regurgitant volume	(ml)	9.8±0.3	9.6±0.6
LSMV forward stroke volume	(ml)	4.8±0.2	5.3±0.4
LSMV output	(ml / min)	199±13	164±17
LSMV stroke work	(mW)	201±14	180±17
LSMV power output	(mJ)	137±10	−○− 91±8
Cardiac stroke volume	(ml /min)	11.5±0.7	11.7±1.0
Cardiac output	(ml / min)	1407±74	−◎− 1062±85
Left ventricular stroke work	(mW)	121±6	−○− 97±9
Left ventricular power output	(mJ)	247±9	−◎− 148±13

Table.5 LSMV function in normal and heart failure dogs (N=6)

◎ : $P < 0.01$ ○ : $P < 0.05$

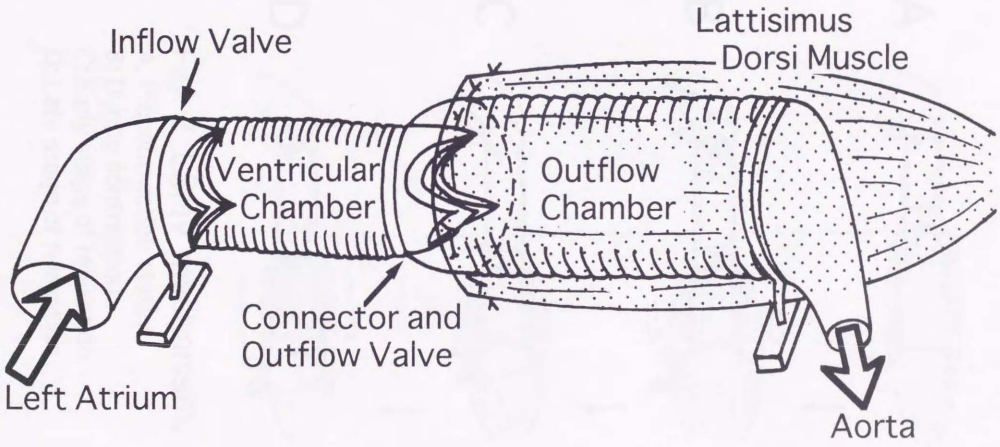


Fig. 1 Illustration of LSMV configuration

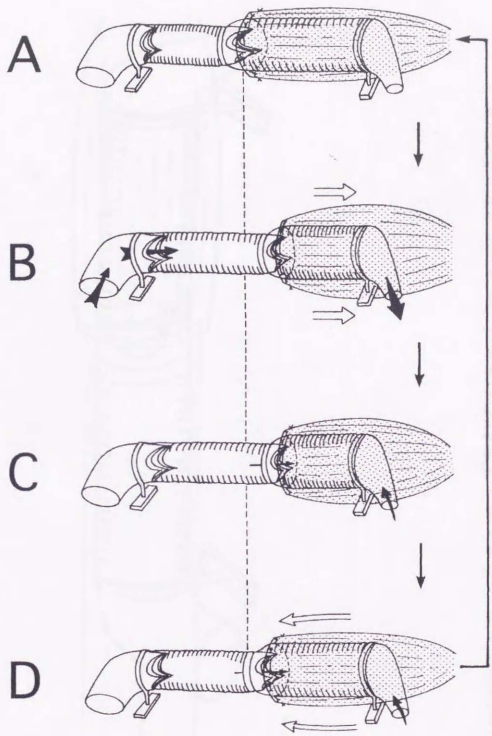


Fig. 2 LSMV mechanism.

A: Precontraction state.
B: During contraction.
C: Early stage of relaxation.
D: Late stage of relaxation

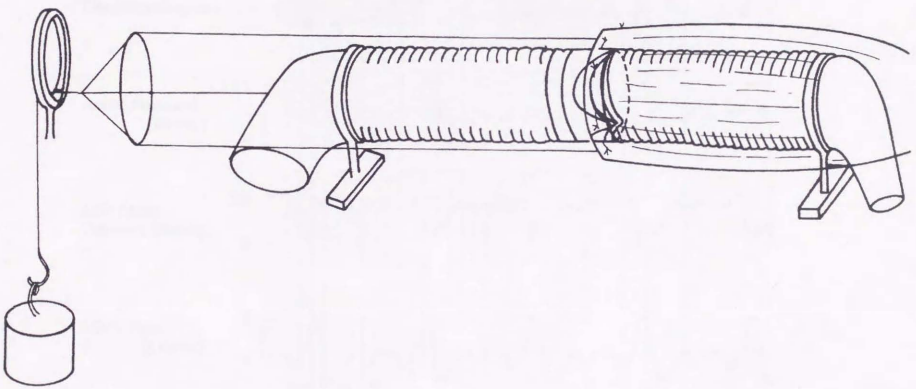


Fig. 3 Illustration of the LSMV used in experiment 1.

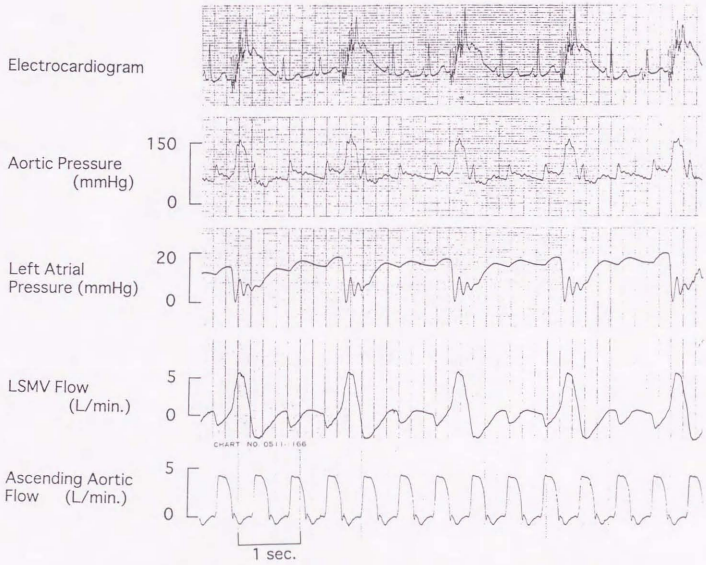
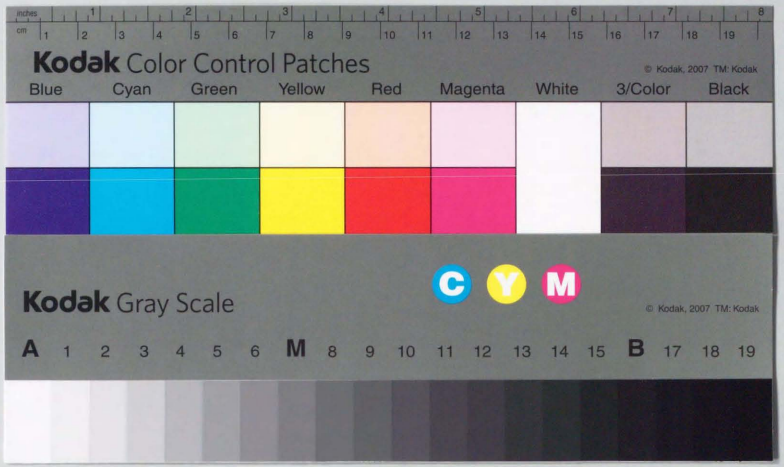


Fig 4. A typical record during LSMV driving in experiment 3. LSMV regurgitant flow is seen just after the LD contraction and during cardiac systole.


inches
cm
Kodak Color Control Patches
© Kodak, 2007 TM: Kodak
Blue
Cyan
Green
Yellow
Red
Magenta
White
3/Color
Black
Kodak Gray Scale
C
Y
M
© Kodak, 2007 TM: Kodak
A 1 2 3 4 5 6 M 8 9 10 11 12 13 14 15 B 17 18 19