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# AVAILABILITY OF OMENTAL FLAP ON PREVENTION AGAINST MUSCULAR ATROPHY OF A LATISSIMUS DORSI CARDIOMYOPLASTY

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## INDEXING WORDS

dynamic cardiomyoplasty; latissimus dorsi muscular flap; omental flap; tissue blood flow; maximal muscle strength; vascular endothelial growth factor

## SYNOPSIS

Dynamic cardiomyoplasty (DCMP) has been performed in more than seven hundreds cases world wide. However, despite symptomatic improvement in the majority of patients surviving the procedure, objective hemodynamic effects have not been consistently demonstrated. Previous studies reported that left ventricular function deteriorated and returned to preoperative level in the chronic phase. We previously reported that atrophy of the latissimus dorsi muscular flap (LDMF) was responsible for the effect of DCMP on improvement of cardiac function in the chronic phase. Ischemia of the muscle flap was proved to induce peripheral muscular atrophy of the flap, and thus

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preservation of the blood flow is important in preventing muscular atrophy. In the present study, we applied omental flap to LDMF, and postulated that the omentum would improve vascularity and perfusion of latissimus dorsi and prevent peripheral muscle atrophy. In dogs, the right and left latissimus dorsi muscles were dissected free from all attachment except for its thoracodorsal pedicles, and omental flap was wrapped around peripheral part of the left LDMF. Tissue blood flow, maximal muscle isotonic strength, morphologic features, and tissue vascular endothelial growth factor (VEGF) were examined in left LDMF with omental flap (OM group) and in the right LDMF served as the control (Control group). In the distal part of the LDMF, tissue blood flow of OM was significantly preserved than Control ( $86.4 \pm 6.5\%$ in OM and $33.6 \pm 3.4\%$ in Control, $p<0.05$). Maximal isotonic tension was significantly higher in OM as compared to Control. Microscopic findings of H and E stained specimen from distal part of LDMF showed that muscle fibers were preserved in OM. And in the distal part, VEGF expression of OM was $49.6 \pm 7.9$ pg/100μg protein and significantly higher than that of Control. Our results indicated that induced endogenous VEGF expression in the LDMF by the omental flap preserved blood perfusion and muscular strength of the LDMF, and suggested that dynamic cardiomyoplasty might not lose its long-term direct cardiac assistance when an omental flap applied for the latissimus dorsi muscle flap.

## INTRODUCTION

Dynamic cardiomyoplasty (DCMP), directly assistance by simultaneously contraction with heart, have applied to clinical case in the world, and over seven hundreds cases of DCMP had been practiced by the present (5, 21). Clinical investigation of long

term survivors that received DCMP have shown recovery of symptom and exercise. However, these clinical studies reported that left ventricular function such as cardiac output and ejection fraction deteriorated and returned to preoperative level in the chronic phase (21). Therefore, the efficacy of DCMP was mainly attributed to protection against further dilatation of the heart (girdling effect) rather than cardiac assistance (3, 18, 22, 23).

We previously reported that atrophy of the latissimus dorsi muscular flap (LDMF) was responsible for the effect of DCMP on improvement of cardiac function in the chronic phase ( Fig. 1) (28). In the study, we examined the ratio of a length of the external circumference of both ventricles covered with LDMF and a length of the total external circumference of both ventricles and found that if this ratio decreased to less than 20%, DCMP did not augment the left ventricular function. Therefore, prevention of muscle atrophy is important in keeping of cardiac assistance of DCMP.

The cause of muscle atrophy is known to be multifactorial, however, ischemia of the muscle flap was proved to induce peripheral muscular atrophy of the flap and preservation of the blood flow is important in preventing muscular atrophy (20). The blood flow of the latissimus dorsi muscle flap is constituted from the thoracodorsal artery, inter costal arteries and lumbar arteries, and dominant area supplied by the thoracodorsal artery is about fifty percents of the muscle (29). In the preparation of the LDMF, all of the collateral circulation was ligated and only the thoracodorsal artery was preserved. Therefore, peripheral blood flow of the LDMF would decrease and peripheral LDMF would become ischemic by the chronic state, resulting in about 25 to 50 percents of LDMF becoming atrophic and fibrotic (19).

We postulated that application of an angiogenic factor would improve vascularity

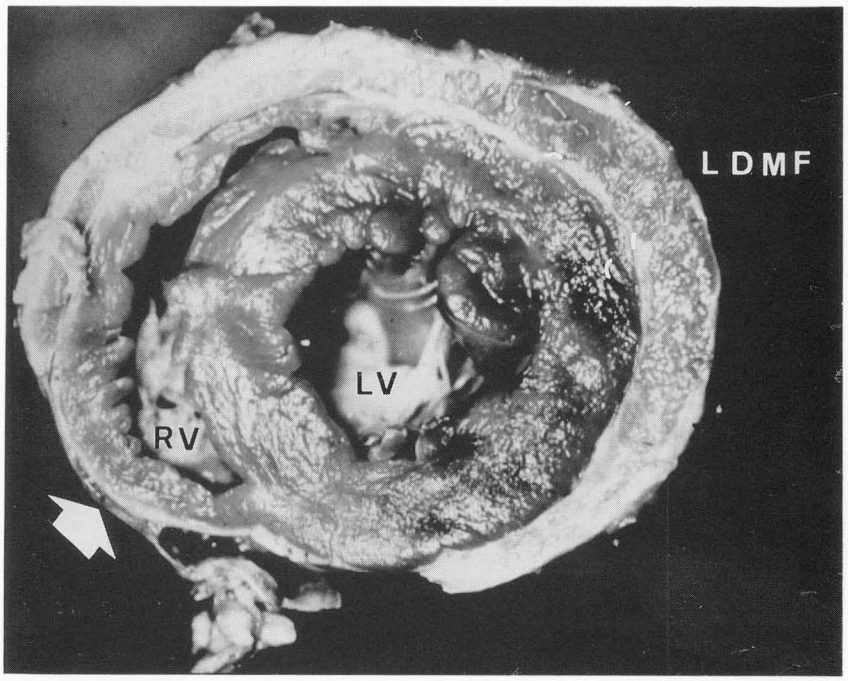


Figure 1. Transverse section of the ventricles 3 months after dynamic cardiomyoplasty (DCMP). Latissimus dorsi muscle flap (LDMF) was well preserved in the proximal part. Distal part of the LDMF was appeared atrophic (white arrow). LV: left ventricle; RV: right ventricle; LDMF: latissimus dorsi muscle flap.

and perfusion of latissimus dorsi and might prevent peripheral muscle atrophy. An omental flap was selected in this study for application of an angiogenic factor, as the

efficacy of an omental flap (omentopexy) against refractory broncho-pleural fistula or perforation of duodenal ulcer is widely known (8, 25), and also omental flap is experimentally effective in healing ischemic tissue (10) . The mechanism of omentopexy has recently been clarified that angiogenic factors are upregulated in the omentum and increased in ischemic tissue attached to the omentum (6) . Vascular endothelial growth factor (VEGF) is one of specific angiogenic factors that the omentum secretes at the highest level of proteins of all tissues. And it is proved that hypoxia upregulates the expression of VEGF and augmentation of expression of VEGF may be responsible for enhancing the angiogenic activity in the setting of ischemia (12, 30).

## MATERIALS AND METHODS

Twenty adult mongrel dogs, weighing 12 to 18 kg, were used in this study. All animal experiments were conducted according to the "Guidelines for Animal Experimentation at Kobe University School of Medicine". Each animal was anesthetized and prepared for the following sterile surgical procedures. General anesthesia was induced with ketamine hydrochloride (5mg/kg) and thiamylal sodium (30mg/kg) and was maintained with dose of sodium pentobarbital given intravenously as needed. Endotracheal intubation and positive-pressure mechanical ventilation (MA-1, Acoma INC., Tokyo, Japan) were carried out. Firstly, with the dog in the left lateral decubitus position, the right latissimus dorsi muscle was dissected free from all attachments except for its thoracodorsal pedicles. The origin of the latissimus dorsi muscle was reattached to ribs to maintain resting tension of the muscle, and then skin was closed. Secondly, with the dog in the right lateral decubitus position, the left latissimus

dorsi muscle was dissected free from all attachment except for its thoracodorsal pedicles, and origin of the latissimus dorsi muscle was reattached to ribs to maintain resting tension of the muscle. Then, under midline incision of the upper abdomen, an omentum was dissected free except for the right gastroepiploic artery. An omental flap was brought to outside of the left chest wall through a subcutaneous tunnel, and wrapped around peripheral part of the left LDMF. Twelve weeks after the first operation, the animals were anesthetized and prepared for the following sterile surgical procedures. General anesthesia was induced with ketamine hydrochloride (5 mg/kg) and thiamylal sodium (30 mg/kg) and was maintained with dose of sodium pentobarbital given intravenously as needed without endotracheal intubation. Arterial blood pressure and the electrocardiogram were monitored. Tissue blood flow, maximal muscle isotonic tension, morphologic features, and tissue VEGF were examined in left LDMF with omental flap (OM group) and in the right LDMF served as the control (Control group).

*Tissue blood flow*

Blood flow of the LDMF was measured by a laser tissue blood flow system (PERIMED Laser Doppler Perfusion Monitor PF3, PERIMED AB P.O., Stockholm, Sweden). Tissue blood flow was measured in three parts, including proximal (proximal one third of the muscle flap), middle (middle of the muscular flap), and distal part. Tissue blood flow was measured ten times in each part and averaged values were used.

*Maximal muscle isotonic tension*

Unipolar electrodes (model 6500, Medtronic Corp., Minneapolis, Minn.) were woven around the thoracodorsal nerve into the midportion of the LDMF. The

stimulating leads were connected to an external R wave-synchronous stimulator (cardiac stimulator model BC-03, Fukuda Densi Inc., Tokyo, Japan), which was programmed to deliver burst stimuli synchronously with cardiac systole. The pacemaker was set to the following parameters; DDD mode, atroventricular interval 20 msec, cardiac sensitivity 0.5 mV, muscular burst duration 200 msec. muscular frequency 20 Hz, pulse amplitude 2.5 to 7.5 V. Stimulation was limited to brief periods because muscle flap was not transformed before the experiment. Maximal isotonic tension was measured during burst stimulation and expressed as Newton (N).

*General latissimus morphologic features*

The right and left LDMFs were evaluated subjectively from hematoxylin and eosin (H&E) stained and silver impregnation stained sections. Biopsy specimens were taken from the proximal, middle, and distal parts of LDMF and placed in 20% neutral formalin under 4℃. The sample were embedded in Paraplast medium and 7 μm sections were prepared. Each slide was reviewed at x20 magnification. The percentage of muscle fibers replaced by fat and fibrous tissue was estimated to evaluate change of general latissimus morphologic features. Fatty areas were unstained and had a size similar to that of the muscle fiber they replaced.

*Vascular endothelial growth factor (VEGF)*

Biopsies were taken of proximal, middle, and distal parts of LDMF. The biopsies were extensively washed with saline and then electrically homogenized in protein extraction buffer (10 mM Tris, pH 8.0, 0.14 M NaCl, 0.025% sodium azide, 2% Triton X-100, 1 mM phenylmethlsulfonyl fluoride (PMSF), and 1μM leupeptin) and

homogenates were subsequently centrifuged for 10 min. (13,500 rpm, 4℃). Total protein was quantified using the bicinchroninic acid (BCA) protein assay kit (Pierce Chemicals, Rockford, IL). Equal amount of total proteins (100 μg) from each specimen was incubated with preequilibrated heparin at 4℃ for 2 hours. A competitive VEGF enzyme immunoassay kit (QuantikineTM, Human VEGF Immunoassay, R&D Systems, Minneapolis, MN) was used to quantify the level of VEGF in each specimen. A standard curve was included every time and triplicate wells were conducted for each specimen.

Statistical analyses were performed with a statistical program (Statview 4.0, Cricket Software Inc., Philadelphia, PA). All values are expressed as the mean ± standard error of the mean. An unpaired t-test was used to assess differences in tissue blood flow, muscle strength, morphologic features, and tissue VEGF. Differences were considered significant when $p<0.05$.

## RESULTS

*1. Tissue blood flow*

As proximal blood flow of LDMF varied significantly in each individual dog even with controlled hemodynamics, tissue blood flow of middle and distal part of LDMF were expressed by percent change from proximal tissue blood flow. Table I summarized the change of tissue blood flow of the LDMF. In the middle part, tissue blood flow was 60.5±4.8% in OM and 50.7±6.8% in Control. There was no statistically significant difference between two groups. However, in the distal part,

tissue blood flow of OM was significantly higher than Control ( 86.4±6.5% in OM and 33.6±3.4% in Control, $p<0.05$). These results showed that omental flap significantly increased blood flow of the LDMF.

Table I. Tissue blood flow of the latissimus dorsi muscle flap.

| Group | proximal | middle | distal |
|---|---|---|---|
| OM (n = 7) (percent change) | 100 | 60.5 ± 4.8 | 86.4 ± 6.5* |
| Control (n = 7) (percent change) | 100 | 50.7 ± 6.8 | 33.6 ± 3.4 |

All values are represented as mean ± standard error of the mean. OM, left latissimus dorsi muscle flap with omental flap; Control, right latissimus dorsi muscle flap; proximal: one-third proximal part of the muscle flap; middle: middle part of the muscle flap; distal: distal one-third part of the muscle flap; percent change, percent change from the proximal value. Statistical analysis by an unpaired *t* test; *, $p< 0.05$ vs. Control

*2. Maximal isotonic tension*

Maximal isotonic tension under 2.5 V electric stimulation were 3.2±0.2 N in OM and 2.1±0.4 N in Control, and there were statistical significances between two groups. With 5.0 V, maximal isotonic tension was significantly higher in OM as compared to Control ($p<0.05$). Thus, this significant difference was also observed with 7.5 V stimulation (Table II). This improved maximal isotonic tension was well correlated with increase in tissue blood flow of LDMF (Fig. 2).

Table Ⅱ. Maximal isotonic tension of the LDMF ( N ).

| Group | 2.5V | 5.0V | 7.5V |
|---|---|---|---|
| OM (n = 7) | 3.2 ± 0.2*N | 5.8 ± 0.5*N | 9.1 ± 0.4*N |
| Control (n = 7) | 2.1 ± 0.4 N | 4.1 ± 0.3 N | 6.8 ± 0.4 N |

All values are represented as mean ± standard error of the mean. 2.5V, electoric stimulation with 2.5V pulse amplitude; 5.0V, electoric stimulation with 5.0V pulse amplitude; 7.5V, electoric stimulation with 7.5V pulse amplitude. ; OM, left latissimus dorsi muscle flap with omental flap; Control, right latissimus dorsi muscle flap; LDMF, latissimus dorsi muscle flap; N, newton. Statistical analysis by an unpaired *t* test; *, $p < 0.05$ vs. Control

*3. Histological features of the right and left latissimus dorsi*

Table Ⅲ summarized the percentage of morphometric change in distal part of LDMF. Muscle fibers were significantly preserved in OM as compared to Control, and fibrous changes were significantly higher in Control as compared to OM. Microscopic findings of H&E stained specimen from distal part of LDMF showed that muscle fibers were well preserved in OM, and the silver impregnation stain demonstrated extracellular connective tissue increased in Control as compared to OM (Fig. 3).

*4. Vascular endothelial growth factor (VEGF)*

Tissue VEGF expression of proximal part of the LDMF was 44.0±4.8 pg/100μg protein in OM, and 37.8±5.0 pg/100μg protein in Control. In the middle part, tissue VEGF were 31.7±3.3 pg/100μg protein in OM and 36.3±4.3 pg/100μg protein in Control. There was no significant difference in VEGF expression between OM and Control in both proximal and middle parts. However, in the distal part, VEGF

expression of OM was 49.6±7.9 pg/100μg protein and significantly higher than that of Control. (Table IV). Increase of VEGF expression in distal LDMF was consistent with increase in blood flow of the distal LDMF (Fig. 4).

Table Ⅲ. Summary of morphometric analysis.

| | OM | Control |
|---|---|---|
| Fiber size (percent of field) (n = 5) | | |
| Mean | 70.38* | 14.13 |
| SEM | 3.71 | 6.32 |
| Collagen content (percent of field) (n = 5) | | |
| Mean | 25.54* | 71.38 |
| SEM | 4.26 | 6.25 |

SEM, standard error of the mean. OM, left latissimus dorsi muscle flap with omental flap; Control, right latissimus dorsi muscle flap. Statistical analysis by an unpaired *t* test; *, $p<0.05$ vs. Control

Table IV. VEGF expression of the LDMF.

| Group | proximal | midlle | distal |
|---|---|---|---|
| OM (n = 7) (pg /100μg protein) | 44.0 ± 4.9 | 31.7 ± 3.3 | 49.6 ± 7.9* |
| Control (n = 7) (pg / 100μg protein) | 37.8 ± 5.0 | 36.3 ± 4.3 | 30.3 ± 3.2 |

All values are represented as mean ± standard error of the mean. VEGF, vascular endothelial growth factor; LDMF, latissius dorsi muscle flap; OM, left latissimus dorsi muscle flap with omental flap; Control, right latissimus dorsi muscle flap; proximal: proximal one-third part of the muscle flap; middle: middle part of the muscle flap; distal: distal one-third part of the muscle flap. Statistical analysis by an unpaired *t* test; *, $p<0.05$ vs. Control

## DISCUSSION

In 1985, Carpentier and their associates first succeeded to use the latissimus dorsi muscle flap for the clinical case of the left ventricular dysfunction (4). Since then dynamic cardiomyoplasty (DCMP) is emerging as a promising surgical treatment for patients with end-stage heart disease who may not be candidates for heart transplantation.

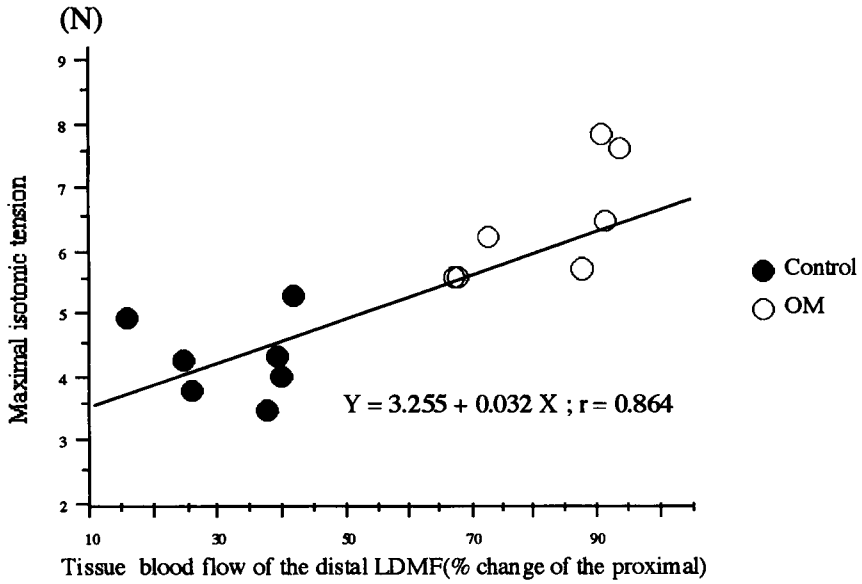


Figure 2. Relation between tissue blood flow of the distal one-third part of the latissimus dorsi muscle flap (LDMF) and the maximal isotonic tension of the LDMF. There was a linear correlation between tissue blood flow and muscle strength of the LDMF (r=0.864). OM: left latissimus dorsi muscle flap with omental flap; Control: right latissimus dorsi muscle flap.

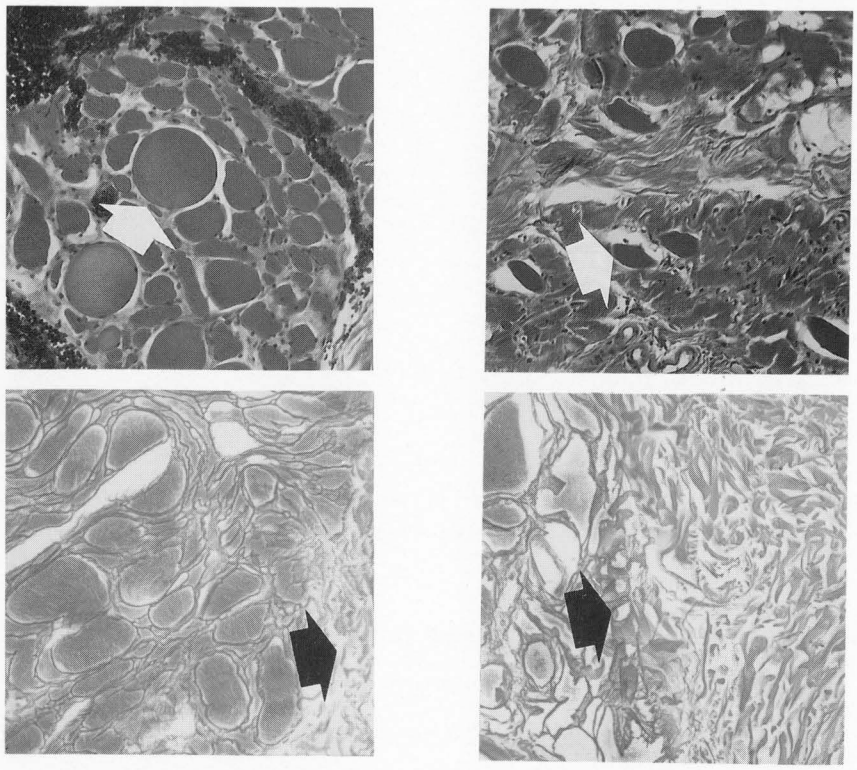

Figure 3. Representative photomicrographs of sections taken from left latissimus dorsi muscle flap (LDMF) with omenal flap (left) and right LDMF (right). Muscle sections were stained with hematoxylin and eosin (H&E) (top) and silver impregnation technique (bottom). Top panels showed that muscle fibers (white arrow) were well preserved in left LDMF with omental flap (OM). Bottom panels demonstrated that extracellar connective tissue (black arrow) increased in right LDMF (Control) as compared to OM.

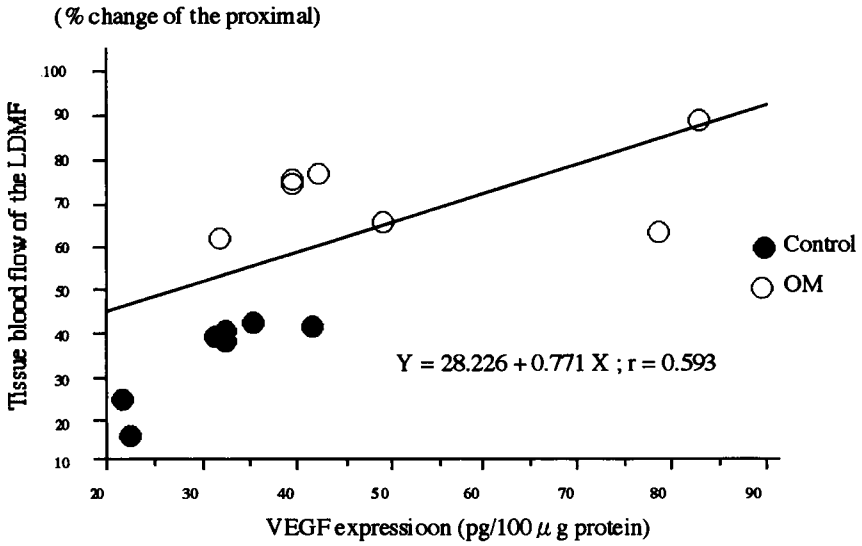


Figure 4. Relation between vascular endothelial growth factor (VEGF) expression and tissue blood flow of distal one-third of the LDMF. There was a linear correlation between VEGF expression and tissue blood flow (r=0.593). OM, left latissimus dorsi muscle flap with omental flap; Control, right latissimus dorsi muscle flap.

DCMP has been performed in more than 700 patients worldwide (5, 21) . Despite symptomatic improvement, objective beneficial hemodynamic effects or improved rates of survivor have not been demonstrated consistently (21) . The efficacy of DCMP is mainly considered to protect further dilatation of the left ventricle (so called "girdling effect") rather than direct cardiac assistance (3, 18, 22, 23).

Decrease of direct cardiac assistance of DCMP might be related with deteriorated performance of latissimus dorsi muscle flap (20). Moreira and their associates reported that despite preferable clinical outcomes, left ventricular function up to five years after DCMP tended to decrease and returned to preoperative levels at 5 years (21). And they reported that important were possibility of ischemic compromise of the muscle flap and the fact that the distal part of the latissimus dorsi muscle may eventually become fibrotic and atrophic. Kalil-Filho and their associates reported that morphologic changes in wrapped LDMF consist with fatty degeneration occurred in the patient after receiving DCMP and could be detected by the magnetic resonance imaging (16). We previously investigated the ratio of a length of the external circumference of both ventricles covered with LDMF and a length of the total external circumference of both ventricles as an index of degree of atrophy of the LDMF and this ratio ( named "cover ratio") was well correlated with direct cardiac assistance of the DCMP in the chronic state (28). We reported that if cover ratio decreased less than 20%, DCMP did not augment the left ventricular function, and that histological examination revealed atrophy and fibrosis beginning from the distal part of the LDMF (Fig. 1). Mannion and other investigators reported that an improved morphologic appearance of the latissimus dorsi muscle was associated with improved blood perfusion, and they emphasized that preservation of blood perfusion was important factor to prevent muscular degeneration (1, 7, 17, 20) . Furthermore, it has been reported that preserved morphology was associated with muscle strength (11, 17). These results are well consistent with the fact that improved muscle strength is well correlated with increase in tissue blood flow of LDMF in the present study (Fig. 2).

Induction of the neoangiogenesis may be one of the therapeutic options to

preserve blood perfusion of the LDMF. Mannion and his associates have studied that administration of basic fibroblastic growth factor (b-FGF) in the LDMF improved muscle perfusion and protected muscular atrophy (20). They also reported that improved perfusion of LDMF by administration of b-FGF eventually increased latissimus-derived collateral flow to ischemic myocardium, resulting improvement of blood perfusion of the heart. Administration of these exogenous growth factors could be potentially effective, however, exogenous b-FGF may induce systemic inflammatory reaction and mechanism of its angiogenesis is not specific and still problematic (13, 15).

Omentum flap has been widely used for the refractory broncho-pleural fistula and perforation of duodenal ulcer, and showed its efficacy to promote wound healing and to stimulate the revascularization of ischemic tissues (8, 25). The mechanism of the effectiveness of omental flap was recently proved that vascular endothelial growth factor (VEGF) expression of the omentum is greatest in the body, and moreover ischemia upregulated VEGF expression of the omentum (30). Therefore, we chose omental flap for application of an endogenous angiogenic factor to LDMF, and postulated that omentum would improve vascularity and perfusion of latissimus dorsi and prevent peripheral muscle atrophy. In the present study, application of the omental flap to the LDMF ameriolated atrophy of the LDMF and muscle strength of the LDMF was well preserved. These changes corresponded to the expression of the endogenous VEGF by the omental flap.

VEGF is one of special angiogenic factors and a heparin -binding, endothelial cell-specific mitogen (9). Recently, VEGF has focused on as a therapeutic angiogenesis for the patients with arterial occlusive disease and coronary artery disease (2, 14, 26). Zhang and their associates reported that the omentum demonstrated the highest VEGF

secretion rate as well as the highest concentration of VEGF protein of various rat tissues and organs examined (30). In addition, it was reported that hypoxia upregulated the expression of VEGF and augmented expression of VEGF may be responsible for enhancing the angiogenic activity in the setting of ischemia (12, 30) . This result is consistent with the present study in which VEGF expressed at higher level on distal part of LDMF wrapped with omental flap as compared with distal parts of LDMF without treatment (Table IV).

Dynamic cardiomyoplasty should be clinically utilized after experimental studies (24, 27). The clinical experiences with cardiomyoplasty showed that symptoms of the patients were continued to improve, however, systolic augmentation was disappeared in the chronic state. In the present study, we firstly applied an omental flap for the latissimus dorsi muscle flap to prevent muscular degeneration, and found that induced endogenous VEGF expression preserved blood perfusion and muscular strength. These results suggest that dynamic cardiomyoplasty may not lose long-term direct cardiac assistance when an omental flap applied for the latissimus dorsi muscle flap.

Omental flap to distal part of the LDMF was experimentally applied to preserve direct cardiac assistance of the DCMP in chronic state. Our result proved that an omental flap induced angiogenesis of the distal LDMF and ameliorated muscular atrophy. Clinical application of this modification during the DCMP procedure will promise the long-term direct cardiac assistance and improve performance status of the patient.

## ACKNOWLEDGEMENT

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