心大血管外科術直後からの電気刺激療法の実行可能性

（Feasibility of Electrical Muscle Stimulation Immediately After Cardiovascular Surgery）

名古屋大学大学院医学系研究科

リハビリテーション療法学専攻

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平成 26 年度学位申請論文

論文題目

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Abstract

Background Muscle wasting and muscle weakness are major clinical issues in patients immediately after cardiovascular surgery. Electrical muscle stimulation (EMS) has a possibility to be a countermeasure for postoperative muscle wasting and muscle weakness. However, the feasibility of EMS immediately after cardiovascular surgery remains unclear.

Objective The aim of this study was to determine the feasibility of EMS immediately after cardiovascular surgery as a strategy for preventing postoperative muscle weakness.

Design Pre-post interventional prospective study

Methods Adult patients who were intended for elective major cardiovascular surgery in Nagoya University Hospital were consecutively included. All of participants received EMS of the lower extremities from postoperative day (POD) 1 to 5. They also started mobilization from POD1 and walking from POD2 under supervision of physical therapists. Feasibility outcomes included the compliance, the number of the patients who presented with excessive changes in systolic blood pressure (BP) (>20 mmHg) or increase in heart rate (HR) (>20 beats/min) during EMS, and the incidence of temporary pacemaker malfunction and postoperative cardiac arrhythmias during intervention period. Secondary outcome was the change in isometric quadriceps strength from preoperative baseline to POD7.

Results Sixty-eight of 105 eligible patients participated in this study. Sixty-one of them (89.7%) completed EMS sessions. We found no patients who presented with excessive changes in systolic BP (>20 mmHg), increased HR (>20 beats/min), or pacemaker malfunction during EMS. Incidence of atrial fibrillation (AF) during the study period was 26.9% (7/26) in coronary artery bypass surgery, 18.2% (4/22) in valvular surgery, and 20.0% (4/20) in combined or aortic surgery. No sustained ventricular arrhythmia or ventricular fibrillation was observed. Isometric quadriceps strength significantly decreased on POD7 (82.5±30.8 Nm to 79.3±28.8 Nm; $P<0.01$ in right leg, 79.7±31.0 Nm to 73.0±28.0 Nm; $P<0.01$ in left leg), however, the magnitude of change was small (2.7±15.0% in right leg and 7.5±12.3% in left leg).

Conclusions The results of this study suggest that EMS immediately after cardiovascular surgery is feasible and has a possibility to prevent postoperative muscle weakness.

要旨

【背景】心大血管外科手術後は、術侵襲に伴う異化作用亢進により骨格筋の蛋白分解が起こる。筋蛋白分解は筋力低下を伴い、手術後における生活機能の円滑な回復を妨げることから、その抑制方策を開発することの臨床的な重要性は高い。電気刺激療法（Electrical Muscle Stimulation: EMS）は手術直後であっても他動的に筋収縮を誘発することが可能であることから、手術後筋蛋白分解ならびに筋力低下の抑制方策として有用性が期待できる。しかしながら、心大血管外科術翌日からの EMS の実行可能性は明らかでない。

【目的】心大血管外科手術後患者を対象に手術後筋力低下予防策としての手術翌日からの EMS の実行可能性を前向きに検証すること

【方法】名古屋大学医学部附属病院心臓血管外科にて待機的に冠動脈バイパス術・弁置換／形成術・大血管手術およびこれらの複合手術を受ける成人心大血管疾患患者で研究参加に同意を得られた連続症例を対象とした。全対象者は EMS 介入を手術翌日から手術後 5 日目まで離床プログラムと並行して実施した。研究実施に先立ち、EMS の実行可能性判定基準を設け、その基準に基づいて EMS の実行可能性を検討した。実行可能判定基準は、1）EMS 実施期間中における脱落例が 20%未満、2）EMS 施行中に収縮期血圧が、EMS 施行前と比較して 20 mmHg 以上変動しない、3）EMS 施行中に心拍数が EMS 施行前と比較

し 20 bpm 以上上昇しない、4）EMS 施行中に体外式ペーシングの異常を認めない、5）EMS 介入期間中、心房細動の新規発症率が冠動脈バイパス術後患者で 30%、弁置換／形成術後患者で 40%、大血管あるいは複合手術後の患者で 50%を超えない、そして 6）EMS 介入期間中、持続性の心室性頻拍あるいは心室細動を認めないこととした。また、手術前と手術後 7 日目に最大等尺性膝伸展筋力を測定し、変化量を検討した。

【結果】2011 年 11 月から 2012 年 11 月にかけて名古屋大学医学部附属病院心臓外科にて待機的心大血管外科手術の適応となった 144 例の内、除外症例を除いた 68 例で手術後 EMS 介入を実施した。68 例中 61 例（89.7%）が手術後 1 週間の EMS 介入を終了した。EMS 施行中に 20 mmHg 以上の収縮期血圧の変動、20bpm 以上の心拍数の上昇、あるいは体外式ペースメーカーの異常を認めた症例は 0 例であった。心房細動発症率は、冠動脈バイパス術後患者で 26.9%（7 例／26 例）、弁置換・形成術後患者で 18.2%（4 例／22 例）、大血管・複合手術後患者で 20.0%（4 例／20 例）であった。また、全ての対象者で EMS 実施期間中に持続性心室頻拍や心室細動は認めなかった。手術前から手術後にかけて最大等尺性膝伸展筋力は左右共に有意に低下したものの（右：82.5±30.8 Nm vs 79.3±28.8 Nm、P<0.01、左：79.7±31.0 Nm vs 73.0±28.0 Nm、P<0.01）、その低下度は少なかった（右：2.7±15.0%、左：7.5±12.3%）。

【結語】本研究結果から、EMS は心大血管外科手術翌日からでも安全に実行可能であり、手術後の下肢筋力低下を軽減させる可能性が示唆された。

Ⅰ. Introduction

Skeletal muscle wasting immediately after cardiovascular surgery

Skeletal muscle is wasted after cardiovascular surgery[1]. The maintenance of skeletal muscle mass depends on the balance between protein synthesis and degradation. Metabolic stress with surgical trauma accelerates muscle protein degradation and suppresses synthesis, leading to a net loss of muscle protein[2,3]. Immobilization and physical inactivity after surgery, even of short duration, also stimulate muscle wasting by slowing of protein synthesis, accelerated protein degradation and apoptosis of a myonuclei within muscle fibers[4,5]. Hypercatabolism of muscle protein is observed within a few days after cardiac surgery[6,7]. Moreover, during immobilization, the rapid reduction in muscle strength mostly occurs over the first week[8]. Loss of skeletal muscle mass and the accompanying muscle weakness cause long-term impairments such as limited functional capacity and difficulties for patients to return their former life. The prevention of muscle wasting early after cardiovascular surgery is, therefore, a major clinical concern in postsurgical rehabilitation.

Early mobilization therapy and its limitations

As immobilization is a key stimulus of muscle protein degradation, early mobilization after cardiovascular surgery is widely recognized as an intervention to reduce muscle wasting by increasing mechanical load to skeletal muscle. Early mobility therapy has been reported to be feasible and improve outcome such as length of hospital stay and activity of daily living at discharge[9,10]. However, whereas there is the clinical consensus about the favorable effect of early mobilization on postoperative patients' outcome, its effect on muscle wasting or muscle weakness has not been documented. Findings from previous study demonstrated that functional improvement gained from early mobilization was not associated with improvement in muscle strength[10]. In addition, despite an early mobilization, muscle proteolysis remarkably accelerated within 48 hours after cardiovascular surgery, and significant muscle weakness was observed[7]. These studies suggest the need for supplemental interventions to early mobilization therapy for preventing muscle proteolysis and muscle weakness after cardiovascular surgery.

Application of electrical muscle stimulation (EMS) as a new intervention modality to prevent muscle wasting after cardiovascular surgery

Electrical stimulation can create passive muscle contractions by depolarizing motor neurons thorough electrodes placed on the skin over the target muscles. Electrical stimulation has a possibility to be one of additional interventions to mobility therapy for preventing postoperative muscle wasting.

Using electrical stimulation as an intervention modality is not a novel procedure. In the area of rehabilitation medicine, electrical current has been applied to modify neuromuscular activity in several methods such as transcutaneous electrical stimulation (TENS), functional electrical stimulation (FES), and electrical muscle simulation (EMS). TENS is a form of electrical stimulation that has been historically used for pain relief. TENS propagates along smaller afferent sensory fibers specifically to override pain impulse. FES is the method that pair the stimulation simultaneously or intermittently with patients' volitional movement. The purpose of a FES intervention is to enable function by replacing or assisting a person's voluntary ability. EMS is typically provided to produce tetanic contraction of muscle that can be used for functional purpose. Those three forms of electrical stimulation have been utilized for various purposes such as decreasing pain, improving muscle strength, increasing range of motion, reducing edema, decreasing atrophy, and healing tissue[11].

Among these different methods of applying electrical stimulation to therapeutic interventions in rehabilitation, EMS has been commonly used to preserve or improve muscle mass, strength, and function. In early times, EMS has been mainly used in orthopedic and sports medicine for delaying muscle atrophy associated with disuse and improving muscle performance. The one of main advantages of EMS is to allow training of skeletal muscle without active exertion. Thus, during the last decade, EMS has come to be applied as an alternative form of exercise for patients who had difficulty performing physical exercise such as advanced chronic heart failure and chronic obstructive pulmonary disease patients[12]. There have been a number of studies regarding the functional effects of EMS and its metabolic response in these patients[13,14,15,16]. Even though there was a lack of large clinical trials, meta-analysis from the Cochrane Library demonstrates that EMS is effective to improve muscle weakness in adult advanced disease patients[17].

As a consequence of the widespread application of EMS, there is growing interest in a utilization of EMS to prevent muscle wasting in medical and surgical ICU patients. Several small clinical trials demonstrated the efficacy of EMS for preservation of muscle mass in patients immediately after abdominal surgery and critical ill patients[18,19,20]. The evidence to date suggests that EMS has a possibility to be an additional intervention to early mobilization for preventing muscle wasting and muscle weakness immediately after cardiovascular surgery.

Issues concerning the feasibility of EMS immediately after cardiovascular surgery

Serious adverse events due to EMS such as injuries, hospital admission, and death have not been reported in chronic advanced disease patients[12]. The majority of studies have reported that EMS was well tolerated in patients[12,21]. In chronic severe heart failure patients, EMS was reported not to cause any marked change in cardiac output[22], blood pressure and heart rate[15,23]. EMS was also reported to cause a marginal increase in blood pressure and heart rate even in critical ill patients[24]. On the other hand, there is no data regarding the feasibility of EMS in patients immediately after cardiovascular surgery. Based on the existing evidence, EMS seems to be feasible in this population. In previous studies, however, the feasibility of EMS was not a predefined primary outcome. Feasibility of a clinical intervention should be evaluated based on the clearly defined criteria[25]. In our opinion, concerns about the feasibility of EMS differ depending on patients' clinical condition. In fact, patients immediately after cardiovascular surgery are hemodynamically unstable and usually in need of inotropic or vasopressor support. Moreover, the incidence of specific cardiac complications such as postoperative arrhythmia and low cardiac output syndrome is high. Therefore, the feasibility of EMS immediately after cardiovascular surgery should be examined in detail by a study specifically designed to assess that. In general, feasibility studies are performed to assess the processes of clinical study, resource problems that can occur during the study, potential human and data management problems, or treatment safety and effect[25]. In this study, as the first step toward clinical application of EMS immediately after cardiovascular surgery, we focused on patients' acceptance and safety of EMS for assessing the feasibility.

Ⅱ. Study: Feasibility of EMS immediately after cardiovascular surgery

Objective

The aim of this study was to investigate the feasibility of EMS immediately after cardiovascular surgery as a strategy for preventing postoperative muscle weakness. In this study, as described at introduction, criteria of feasibility was determined by information on drop out and occurrence of adverse events.

Methods

Participants

Adult patients who were intended for elective major cardiovascular surgery (coronary artery bypass surgery, valvular surgery, aortic surgery, or combined surgery) in Nagoya University Hospital were consecutively included. Exclusion criteria were: chronic renal failure (estimated glomerular filtration rate <30 ml/min./1.73m^2), peripheral arterial disease (Fontein classification ≧Ⅲ), psychiatric disease, neuromuscular disease and dementia (Mini-Mental State Examination <18 points). Patients with technical obstacles such as intra-aortic balloon pumping were also excluded, but patients with pacemaker were included. Informed consent was obtained from each patient as approved by the Ethics Review Committee of Nagoya University Graduate School of Medicine (Approved No.1272).

Study design

Study design was pre-post interventional study. This study was a feasibility study for our future main study which would investigate preventive effect of EMS on postoperative muscle wasting in patients after cardiovascular surgery.

EMS Intervention

All of the patients received EMS on the bilateral quadriceps femoris and triceps surae daily from postoperative day (POD) 1 to POD5 (5 sessions). They also started mobilization from POD1 and walking from POD2 under supervision of physical therapists.

In this study, we used EMS with variable frequency train, initiating two high-frequency (200 Hz) bursts followed by low-frequency (20 Hz) stimulation, which was developed in our laboratory to be able to induce muscle contraction at the intensity of 20% of maximum voluntary contraction (MVC). The waveform of EMS was a symmetric biphasic square wave. The stimulator was configured to deliver a direct electrical current for 0.4 sec followed by a pause lasting 0.6 sec. Pulse groups consisting of 10 impulse trains were delivered at 30 seconds intervals during session. The intensities of the stimulation were set at 10% and 20% of MVC, and the repetitions of 10%-10%-20%MVC were prescribed throughout the session. The duration of the session was set at 30 minutes and extended to 60 minutes based on patient's tolerability.

The current intensity of EMS was determined for each patient prior to the operation. We measured MVC of quadriceps femoris by using a dynamometer developed for this study at semi-Fowler's position (Figure 1). Patients performed 3 maximal voluntary isometric contractions against a fixed resistance, and force generated was recorded on a personal computer through an analog-digital converter in kilogram force. After measurement of MVC, the current intensities of EMS were determined by manual adjustment to produce 10% and 20% of MVC. We kept a record of the current intensities (mA) of each patient, and prescribed the same current after surgery. The current intensities for the triceps surae muscles were set at the same as for the quadriceps. When stimulating, the self-adhering surface electrodes (62×62 mm) were placed bilaterally on the vastus lateralis, vastus medialis and triceps surae after skin cleaning. On the vastus lateralis, the upper electrode was positioned 10 cm below anterior superior iliac spine, while the lower was placed on 12 cm proximal to the lateral knee joint space. On the vastus medialis, the upper electrode was positioned 10 cm below anterior superior iliac spine, while the lower was placed on 10 cm proximal to the medial knee joint space. On the triceps surae, the upper electrode positioned 2 cm below the popliteal fossa, while the lower was placed just above the Achilles tendon. During EMS, patients were positioned in a semi-Fowler's position.

After surgery, all patients were assessed every morning for an EMS safety screen. Patients passed the screen if they did not have following conditions: systolic blood pressure (BP) < 80 mmHg, heart rate (HR) <40 or ≧120 beats/min, intubation, pulse oximetry < 88%, or agitation requiring sedative administration. Patients were excluded if they failed the screen for 2 days.

Feasibility outcomes

Prior to study implementation, we set the completion rate, systolic BP and HR response, the occurrence of temporary epicardial pacemaker malfunction, and the incidence of postoperative arrhythmias such as atrial fibrillation (AF) and sustained ventricular arrhythmia or ventricular fibrillation as feasibility outcomes. To examine feasibility, we established the criteria for each outcomes within clinically acceptable range as follows: 1) more than 80% of patients were able to complete more than 4 of 5 sessions, 2) systolic BP during EMS > 80 mmHg and change in systolic BP during EMS<20 mmHg, 3) increase in HR during EMS < 20 beats/min, 4) malfunction of temporary epicardial pacing did not occur during session, 5) incidence of new onset of postoperative AF during the study period < 30% in coronary artery bypass surgery, < 40% in valvular surgery and < 50% in combined and aortic surgery[26,27], 6) neither a sustained ventricular arrhythmia nor ventricular fibrillation occurred during the study period.

The acceptable ranges of the change in BP and HR were established based on clinical expert's opinion. To set the criterion for malfunction of temporary epicardial pacing during EMS, we referred to the findings from the previous studies investigating the impact of EMS on implanted pacemaker[28,29]. We also determined the criteria for the incidence of postoperative arrhythmias by reference to the previous studies[26,27,30].

In this study, we defined a successful EMS session as one in which the patient was able to receive EMS for 30 minutes. Thus, we countered patients who received EMS ≧ 30 minutes as compliant. EMS was discontinued if we found systolic BP < 80 mmHg, change in systolic BP from rest >20 mmHg, increase in HR from rest >20 beats/min, or new onset of cardiac arrhythmias during EMS. We also terminated EMS if patient offered to stop EMS due to symptoms such as dyspnea, fatigue, and muscle soreness due to EMS. Noninvasive systolic BP and HR were monitored by using Patient Monitor system (IntelliVue MP70, PHILIPS) 3 times at rest with a 5 minutes interval and every 10 minutes during EMS. Medical doctors of surgical ICU and cardiovascular surgery ward checked cardiac arrhythmias by continuous electrocardiography monitoring. Physical therapists monitored symptoms such as dyspnea, fatigue, and muscle soreness in patients during session. New onset of postoperative AF was defined as a new episode requiring intervention (medication / cardioversion) during study period, and ventricular tachycardia lasting >30 seconds were recognized as sustained ventricular arrhythmia.

Secondary Outcome

Secondary outcome was isometric muscle strength of quadriceps femoris. Well-trained physical therapist measured muscle strength at 1 day before surgery (baseline) and POD7.

Muscle strength of quadriceps was assessed by using an isometric dynamometer (μTas F-1; ANIMA Corp. Tokyo, Japan). Patients sat in a chair with their hips and knee at 90°. Their shin was strapped into a cuff and they performed 3 maximal isometric contractions against a fixed resistance for each leg. The measurements were separated by a 3 minutes interval. The highest value among 3 measurements was selected for analysis. Identical verbal encouragement was given during measurements before and after surgery.

Statistical analysis

Descriptive statistics are expressed as percentages or mean ±

standard deviation. For assessing BP and HR response to EMS, we analyzed the difference between mean resting value and the value every 10 minutes during EMS. Patient with temporary epicardial pacing were excluded from the analysis of HR response. The incidence of postoperative AF was deemed as significant if it exceeded the criteria values.

The changes in muscle strength from baseline to POD7 were analyzed by using Paired t-test. A $P < 0.05$ was considered statistically significant. All analyses were calculated using the SPSS ver 16.0.

Results

Patient population

From November 2011 to August 2012, a total of 144 patients intended for elective cardiovascular surgery in Nagoya University Hospital were included, and EMS was implemented in 68 patients after surgery (Figure 2). Patient demographics are listed in Table 1. Thirty of the patients (49%) were receiving inotropic agents such as dobutamine, dopamine, or milrinone, and 10 patients (16.4%) were in need of continuous vasopressor support at the first EMS session. There were only 3 patients (4.9%) who received beta-blocker drugs at the first EMS session. After surgery, two patients could not perform muscle strength measurement of both legs due to knee pain or postoperative cognitive impairment. Additionally, 2 patients could not perform muscle strength measurement of right quadriceps and 4 patients could not perform left quadriceps measurement due to pain from a wound in their lower legs produced by removal of the saphenous vein graft.

Feasibility of EMS

Criteria for success of feasibility and associated outcomes were listed in Table 2. All variables cleared the criteria for success of feasibility. Seven of 68 patients (10.3%) dropped out due to muscle soreness or fatigue at the first EMS session. The others were successfully terminated the session without those symptoms due to EMS. In 61 patients who completed EMS intervention, the 2 patients who received coronary artery bypass surgery manifested postoperative AF during EMS. Postoperative AF in these patients subsided within one day after beta blocker treatment and did not reoccur during study period.

Cardiovascular response to EMS at 1st session was shown in Table 3.

Changes in muscle strength after surgery

Changes in isometric quadriceps strength from baseline to POD7 were shown in Table4. Isometric quadriceps strength significantly decreased in both leg after surgery. However, the reductions in isometric quadriceps strength were less than 10%.

Discussion

EMS was safely implemented even immediately after cardiovascular surgery. To our knowledge, this is a first report of the feasibility of EMS in patients immediately after cardiovascular surgery.

The presence of outstanding cardiac pathology has been one of classic contraindication to electrotherapy due to risk of cardiac arrhythmias. Previous published studies have reported that EMS was well tolerant and improve functional outcome without adverse event in patients with chronic stable heart failure[15,22,23], suggesting that EMS during the chronic phase is safe and feasible even in cardiac patients. Conversely, immediately after cardiovascular surgery, patients are usually in need of intensive care to maintain their hemodynamic status and the incidence of specific cardiac complications such as postoperative arrhythmia and low cardiac output syndrome is high. Present study provides the fundamental data about the safety and feasibility of EMS during the acute stage, immediately after cardiovascular surgery.

In this study, EMS was implemented without excessive change in systolic BP or marked increase in HR and none of the patients met the criteria for stopping EMS. Majority of the patients immediately after cardiovascular surgery are in need of inotropic or vasopressor support to keep their hemodynamic stabilities. One of the major concerns with applying EMS intervention to these patients is, therefore, the impact on their hemodynamic status. As a result, there was no clinically relevant change in BP and HR in all patients. Although we found marginal increases in systolic BP and HR from rest to EMS (Table 3), these changes are in accord with a previous study. Table 5 summarizes key features of previous and present studies. Gervasili and his colleague reported the changes in systolic BP (from 127 to 133 mmHg) and HR (from 94 to 99 beats/min) during EMS in hospital ICU patients[24]. In their study, current intensity of EMS was set to cause “visible contractions”. In our preliminary experiment, we have already confirmed that this intensity was equivalent to <10% of MVC. In contrast, our study demonstrates that EMS inducing stronger muscle contraction at 10% and 20% of MVC is feasible and safe in patients immediately after cardiovascular surgery in terms of cardiovascular response or events to EMS. It has been reported that, in patients with stable chronic heart failure, EMS did not cause any marked change in cardiac output[22], BP and HR[15,23]. Our study added the evidence that, even in acute phase of postsurgical patients, EMS did not cause excessive cardiovascular response. Indeed, in this study, thirty of the patients (49%) were receiving inotropic agents such as dobutamine, dopamine, or milrinone, and 10 patients (16.4%) were in need of continuous vasopressor support at the first EMS session, yet none of these patients presented with excessive cardiovascular responses to EMS.

Among the patients who received EMS, 10 patients (16.3%) required temporary cardiac pacing at the first session of EMS. Heart rate monitoring in these patients revealed no abnormalities in this study. The application of EMS to patients with cardiac pacemaker has not reached a consensus because of concerns about potential electromagnetic field interference and subsequent pacing failure. Previous studies investigating the functional effect of EMS have excluded the patients with pacemaker[13,15,23]. In patients immediately after cardiovascular surgery, however, temporary epicardial pacing is commonly used in the management of their cardiac functions. Thus, it is necessary to determine whether EMS causes temporary pacemaker dysfunction in these patients for assessing the feasibility. Previous case series studies reported that EMS of knee extensor muscle did not cause any abnormalities of implanted pacemakers[28,29]. The results of present study were in line with these previous reports and added the evidence that EMS of lower extremities was safe even in patients with temporary epicardial pacing. A detailed observation of the impact of EMS in patients with postoperative therapeutic devices, such as epicardial pacing or mechanical circulatory supports, will be important issue in further studies.

Risk of inducing cardiac arrhythmias is also one of major concerns with applying EMS immediately after cardiovascular surgery. AF is the most common arrhythmia encountered postoperatively. Although postoperative AF is not a life-threatening event, it associates with hemodynamic compromise and may lead to longer hospital stay. We, therefore, established the feasibility criteria regarding postoperative AF based on the previous reports[26,27]. In this study, the incidence of postoperative AF in each surgery group was below the criteria values. Increased sympathetic activation during the postoperative period increases susceptibility to postoperative AF[26]. Indeed, several clinical trials have shown that the beta-blocking agents reduced the incidence of postoperative AF[31, 32, 33]. Despite the fact that only three of 61 patients received beta-blocking drugs at the first EMS session, the increase in HR was small (1.5 ± 3.5 beats/min on average), demonstrating the evidence that EMS prescribed in our study does not provide a harmful effect even in the patients without beta-blocking agents. Added to this, we found neither sustained ventricular arrhythmias nor ventricular fibrillation during study period. These findings suggest that EMS can be implemented without cardiac complications even immediately after cardiovascular surgery.

Adherence of EMS is another considerable factor because treatment effects depend on the dose[34]. We, therefore, set the compliance rate of EMS as feasibility outcome. Good compliance of EMS (89.6%) in this study showed the applicability of EMS to usual clinical practice. Among 7 patients who dropped out, only one patient (1.5%) could not tolerate EMS because of muscle soreness. Moreover, among patients who completed EMS intervention, we did not observe any remarkable symptoms such as dyspnea, fatigue and muscle soreness during EMS. It is noteworthy that the incidence of dropout due to muscle soreness was low even with EMS inducing 20% of MVC. Previous study reported that dropout due to muscle pain during EMS was 11% in chronic heart failure patients[35]. In our opinion, low incidence of dropout due to pain is of particular important when applying EMS immediately after cardiovascular surgery in terms of avoiding the elevation in sympathetic activity leading to postoperative cardiac arrhythmias.

Quadriceps muscle strength significantly decreased after surgery but the amount of reduction was small. Previous study has reported that a 51.7% decrease in isometric quadriceps strength occurred at POD7 in patients after cardiac surgery[7]. Conversely, in this study, the reduction in isometric quadriceps strength was 2.7-7.5%. Although present study was not designed to examine the preventive effect of EMS on postoperative muscle weakness, this result suggests that EMS immediately after cardiovascular surgery has a favorable effect in preventing postoperative muscle weakness. The abnormality of skeletal muscle, not the degree of cardiac weakness, is directly related to functional capacity in cardiac patients[36]. In addition, functional capacity is an independent predictor of all-cause mortality in patients after cardiac surgery[37]. Preservation of postoperative muscle strength by EMS, therefore, can lead to improvement of long-term outcome after cardiovascular surgery. Further study will be needed to investigate the effect of EMS intervention on muscle strength, functional capacity, and long-term outcome after cardiovascular surgery.

Present study may have several limitations. First, the results in this study might be limited in generalizability because patients with severe chronic renal failure and prolonged postoperative mechanical ventilation were excluded. These conditions were not contraindications to EMS, but they were excluded because of a possibility to affect the main outcome of our ongoing study, the concentration of amino acids in urine. The effects of EMS on clinical status of these patients should be carefully examined in future study. Second, since this study did not have a control group, we could not fully understand the impact of EMS on the BP, HR, temporary pacemaker and the incidence of postoperative arrhythmia compared to control group.

Nonetheless, the observation that these outcomes were within clinically acceptable range when applying EMS indicates the safety of EMS immediately after cardiovascular surgery.

Summary of this study

The main findings of this study were as follows: 1) EMS immediately after cardiovascular surgery did not cause abnormal cardiovascular responses or pacemaker malfunction, 2) EMS did not increase the incidence of postoperative cardiac arrhythmias, 3) EMS was acceptable to patients immediately after cardiovascular surgery.

Table 1. Demographics of the patients

Demographics	(n=68)
Age, yrs	67.3±10.4
Male, %	75.0%
Body mass index, kg/m^2	23.6±3.3
LVEF, %	62.2±9.9
eGFR, ml/min./1.73m^2	68.7±16.5
Operative procedure	
Coronary artery bypass, n (%)	26 (38.2%)
Valvular, n (%)	22 (32.3%)
Aortic, n (%)	13 (19.1%)
Combined, n (%)	7 (10.2%)
CPB time, min	148.0±86.2
Patients with temporary external cardiac pacing at 1st EMS session, n (%)	10 (16.3%)
Intravenous drugs at 1st session (n=61)	
Norepinephrine, n (%)	10 (16.4%)
Dobutamine, n (%)	20 (32.8%)
Dopamine, n (%)	12 (19.7%)
Milrinone, n (%)	5 (8.2%)
Furosemide, n (%)	5 (8.2%)
Carperitide , n (%)	7 (11.5%)
Nicardipine, n (%)	12 (19.7%)
Nicorandil, n (%)	33 (54.1%)
Landiolol, n (%)	3 (4.9%)

Abbreviations: LVEF=left ventricular ejection fraction, eGFR=estimated glomerular filtration rate, CPB=cardiopulmonary bypass, EMS=electrical muscle stimulation

Table 2. Feasibility Outcomes

Variables	Study outcome
Compliance	61 of 68 (89.7%)
Cardiovascular response to EMS	
Change in systolic BP >20 mmHg	0%
Increase in HR >20 beats/min	0%
Cardiac events	
Pacing failure of external cardiac pacing	0%
New onset of AF	
Coronary artery bypass surgery	7 of 26 (26.9%)
Valvular surgery	4 of 22 (18.2%)
Aortic or combined surgery	4 of 20 (20.0%)
Sustained ventricular arrhythmia / ventricular fibrillation	0%

Abbreviations: EMS=electrical muscle stimulation, BP=blood pressure, HR=heart rate, AF=atrial fibrillation

Table 3. Cardiovascular response at 1st session

		EMS					
	Rest	10min	20min	30min	40min	50min	60min
SBP	106.6 ±13.6	106.7±14.1	108.7±15.0	106.8±14.6	107.4±13.4	107.3±14.2	107.0±13.7
⊿SBP		0.1±5.7	2.1±6.8	0.2±6.8	1.2±6.8	0.9±7.5	0.4±7.0
HR	84.8±11.1	85.0±11.0	85.6±12.1	86.0±10.9	86.3±11.3	86.9±11.3	87.2±11.2
⊿HR		0.2±3.1	0.8±4.3	1.1±3.4	1.4±3.3	1.4±3.3	1.7±3.8

Abbreviations: SBP=systolic blood pressure. HR=heart rate. EMS=electrical muscle stimulation, ⊿=The amount of change from the mean value at rest to each value during EMS.

Data are presented as mean ± standard deviation.

Table 4. Changes in muscle strength after surgery

	baseline	POD7	*P*	% change
Right leg, Nm	82.5±30.8	79.3±28.8	<0.01	2.7±15.0
Left leg, Nm	79.7±31.0	73.0±28.0	<0.01	7.5±12.3

Abbreviations: POD7=postoperative day 7

Data are presented as mean ± standard deviation.

Table 5. Comparison with previous studies investigating cardiovascular response to EMS

Author	Population	Muscle	Current intensity	Outsomes	Results
Gervasili V, et al.	Patients in the ICU	Vastus lateralis Vastus medialis Perneus longs	Visible contraction	HR Systolic BP	+5 bpm +6 mmHg
This study	Patients immediately after cardiovascular surgery	Vastus lateralis Vastus medialis Triceps surae	10% and 20% MVC	HR Systolic BP	+1.5±3.5 bpm +0.9±5.7 mmHg

Abbreviations: EMS=electrical muscle stimulation, MVC=maximal voluntary contraction, ICU=intensive care unit, BP=blood pressure, HR=heart rate

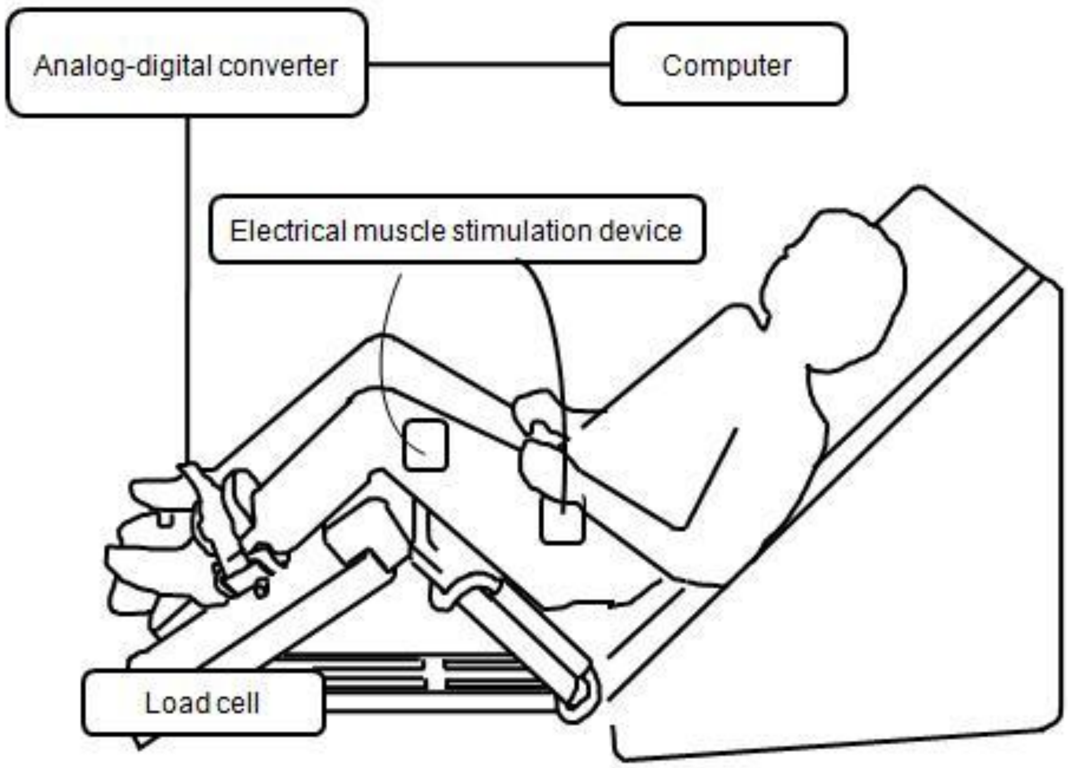

Figure 1. Measurement system of maximal voluntary contraction

During measurement the patient was in Fowler's position with their hips at 90° and knees at a 60° flexed position; their ankles were strapped into an ankle rest with a high-sensitivity load cell.

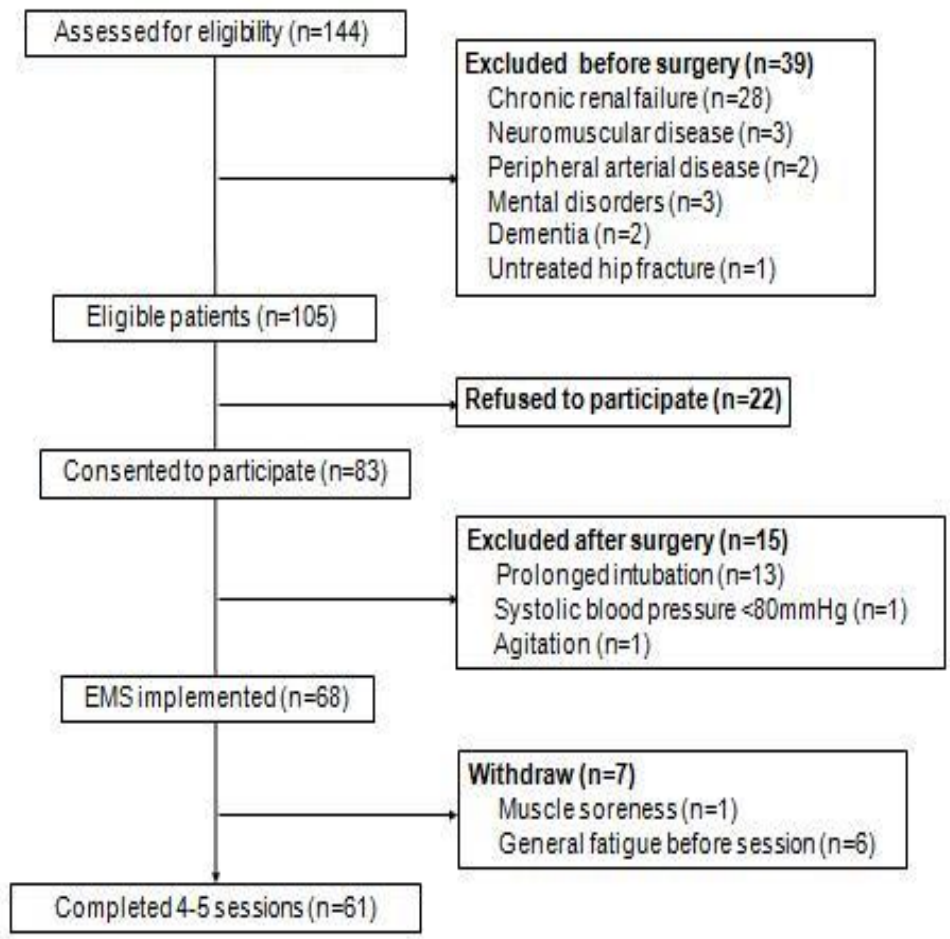

Figure 2. Flow diagram of study participants

Ⅲ. Conclusions

This study provides the first evidence that EMS after cardiovascular surgery is feasible and safely implemented even in hemodynamically unstable phase. With increasing number of elderly patients who are intended for cardiovascular surgery, there will be a growing number of patients at risk of developing postoperative muscle weakness. To counter this, EMS has a possibility to be a novel early intervention directed at muscular function in patients after cardiovascular surgery. Further randomized controlled study is required to confirm the preventive effect of EMS on postoperative muscle wasting and weakness.

Ⅳ. Acknowledgments

This study was supported by Grant-in-Aid for Scientific Research (B) from the Japanese Society for the Promotion of Science (Grant No: 22300186. Clinical principal investigator: Sumio Yamada). We thank Dr. Yuji Kono, Mr. Hideyuki Sampei, Mr. Yuta Hagiwara, Mr. Shimpei Ishida, and Mr. Naoki Iritani for participating in data acquisition and EMS intervention. In addition, we are grateful for the enthusiastic support of the doctors, physical therapists, nurses, clinical engineers, and assistant nurses of the surgical ICU and cardiovascular surgery ward at Nagoya University Hospital.

Ⅴ. Referrences

1. Bloch SA, Lee JY, Wort SJ, Polkey MI, Kemp PR, Griffiths MJD. Sustained elevation of circulating growth and differentiation factor-15 and a dynamic imbalance in mediators of muscle homeostasis are associated with the development of acute muscle wasting following cardiac surgery. *Crit Care Med*. 2013;41(4):982–9.

2. Biolo G, Toigo G, Ciocchi B, et al. Metabolic response to injury and sepsis: changes in protein metabolism. *Nutrition*. 1997;13(9 Suppl):52S–57S.

3. Chioléro R, Revelly JP, Tappy L. Energy metabolism in sepsis and injury. *Nutrition*. 1997;13(9 Suppl):45S–51S.

4. Chambers MA, Moylan JS, Reid MB. Physical inactivity and muscle weakness in the critically ill. *Crit Care Med*. 2009;37(10 Suppl):S337–46.

5. Ferrando AA, Lane HW, Stuart CA, Davis-Street J, Wolfe RR. Prolonged bed rest decreases skeletal muscle and whole body protein synthesis. *Am J Physiol*. 1996;270(4 Pt 1):E627–33.

6. Chaloupecký V, Hucín B, Tláskal T, et al. Nitrogen balance, 3-methylhistidine excretion, and plasma amino acid profile in infants after cardiac operations for congenital heart defects: the effect of early nutritional support. *J Thorac Cardiovasc Surg*. 1997;114(6):1053–60.

7. Iida Y, Yamazaki T, Kawabe T, Usui A, Yamada S. Postoperative muscle proteolysis affects systemic muscle weakness in patients undergoing cardiac surgery. *Int J Cardiol*. 2014.172(3):595–7.

8. LeBlanc AD, Schneider VS, Evans HJ, Pientok C, Rowe R, Spector E. Regional changes in muscle mass following 17 weeks of bed rest. *J Appl Physiol*. 1992;73(5):2172–8.

9. Pohlman MC, Schweickert WD, Pohlman AS, et al. Feasibility of physical and occupational therapy beginning from initiation of mechanical ventilation. *Crit Care Med*. 2010;38(11):2089–94.

10. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009;373(9678):1874–82.

11. Doucet BM, Lam A, Griffin L. Neuromuscular electrical stimulation for skeletal muscle function. *Yale J Biol Med*. 2012;85(2):201–15.

12. Sillen MJ, Speksnijder CM, Eterman RM, et al. Effects of neuromuscular electrical stimulation of muscles of ambulation in patients with chronic heart failure or COPD: a systematic review of the English-language literature. *Chest*. 2009;136(1):44–61.

13. Nuhr MJ, Pette D, Berger R, et al. Beneficial effects of chronic low-frequency stimulation of thigh muscles in patients with advanced chronic heart failure. *Eur Heart J*. 2004;25(2):136–43.

14. Vivodtzev I, Pépin JL, Vottero G, et al. Improvement in quadriceps strength and dyspnea in daily tasks after 1 month of electrical stimulation in severely deconditioned and malnourished COPD. *Chest*. 2006;129(6):1540–8.

15. Quittan M, Sochor A, Wiesinger GF, et al. Strength improvement of knee extensor muscles in patients with chronic heart failure by neuromuscular electrical stimulation. *Artif Organs*. 1999;23(5):432–5.

16. Dobsák P, Nováková M, Siegelová J, et al. Low-frequency electrical stimulation increases muscle strength and improves blood supply in patients with chronic heart failure. *Circ J*. 2006;70(1):75–82.

17. Maddocks M, Gao W, Higginson IJ, Wilcock A. Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease. *Cochrane database Syst Rev*. 2013;1:CD009419.

18. Vinge O, Edvardsen L, Jensen F, Jensen FG, Wernerman J, Kehlet H. Effect of transcutaneous electrical muscle stimulation on postoperative muscle mass and protein synthesis. *Br J Surg*. 1996;83(3):360–3.

19. Strasser EM, Stättner S, Karner J, et al. Neuromuscular electrical stimulation reduces skeletal muscle protein degradation and stimulates insulin-like growth factors in an age- and current-dependent manner: a randomized, controlled clinical trial in major abdominal surgical patients. *Ann Surg*. 2009;249(5):738–43.

20. Gerovasili V, Stefanidis K, Vitzilaios K, et al. Electrical muscle stimulation preserves the muscle mass of critically ill patients: a randomized study. *Crit Care*. 2009;13(5):R161.

21. Maffiuletti NA, Roig M, Karatzanos E, Nanas S. Neuromuscular electrical stimulation for preventing skeletal-muscle weakness and wasting in critically ill patients: a systematic review. *BMC Med*. 2013;11:137.

22. Maillefert JF, Eicher JC, Walker P, et al. Effects of low-frequency electrical stimulation of quadriceps and calf muscles in patients with chronic heart failure. *J Cardiopulm Rehabil*. 1998;18(4):277–82.

23. Dobsák P, Nováková M, Fiser B, et al. Electrical stimulation of skeletal muscles. An alternative to aerobic exercise training in patients with chronic heart failure? *Int Heart J*. 2006;47(3):441–53.

24. Gerovasili V, Tripodaki E, Karatzanos E, et al. Short-term systemic effect of electrical muscle stimulation in critically ill patients. *Chest*. 2009;136(5):1249–56.

25. Thabane L, Ma J, Chu R, et al. A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol*. 2010;10:1.

26. Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. *J Am Coll Cardiol*. 2008;51(8):793–801.

27. Matsuura K, Ogino H, Matsuda H, et al. Prediction and incidence of atrial fibrillation after aortic arch repair. *Ann Thorac Surg*. 2006;81(2):514–8.

28. Wiesinger GF, Crevenna R, Nuhr MJ, Huelsmann M, Fialka-Moser V, Quittan M. Neuromuscular electric stimulation in heart transplantation candidates with cardiac pacemakers. *Arch Phys Med Rehabil*. 2001;82(10):1476–7.

29. Crevenna R, Mayr W, Keilani M, et al. Safety of a combined strength and endurance training using neuromuscular electrical stimulation of thigh muscles in patients with heart failure and bipolar sensing cardiac pacemakers. *Wien Klin Wochenschr*. 2003;115(19-20):710–4.

30. Chung M. Cardiac surgery: postoperative arrhythmias. *Crit Care Med*. 2000;28(10 Suppl):N136–N144.

31. Connolly SJ, Cybulsky I, Lamy A, et al. Double-blind, placebo-controlled, randomized trial of prophylactic metoprolol for reduction of hospital length of stay after heart surgery: the beta-Blocker Length Of Stay (BLOS) study. *Am Heart J*. 2003;145(2):226–32.

32. Sezai A, Minami K, Nakai T, et al. Landiolol hydrochloride for prevention of atrial fibrillation after coronary artery bypass grafting: new evidence from the PASCAL trial. *J Thorac Cardiovasc Surg*. 2011;141(6):1478–87.

33. Ferguson TB, Coombs LP, Peterson ED. Preoperative beta-blocker use and mortality and morbidity following CABG surgery in North America. *JAMA*. 2002;287(17):2221–7.

34. Drummond MJ, Dreyer HC, Pennings B, et al. Skeletal muscle protein anabolic response to resistance exercise and essential amino acids is delayed with aging. *J Appl Physiol*. 2008;104(5):1452–61.

35. Banerjee P, Caulfield B, Crowe L, Clark AL. Prolonged electrical muscle stimulation exercise improves strength, peak VO2, and exercise capacity in patients with stable chronic heart failure. *J Card Fail*. 2009;15(4):319–26.

36. Middlekauff HR. Making the case for skeletal myopathy as the major limitation of exercise capacity in heart failure. *Circ Heart Fail*. 2010;3(4):537–46.

37. Cacciatore F, Abete P, Mazzella F, et al. Six-minute walking test but not ejection fraction predicts mortality in elderly patients undergoing cardiac rehabilitation following coronary artery bypass grafting. *Eur J Prev Cardiol*. 2012;19(6):1401–9.