

博士論文

論文題目 Site specificity of acute disuse muscle atrophy in
critically ill patients and construction of early rehabilitation
programs targeting lower-limb muscles in intensive care units

(ICU 入室患者の廃用性筋萎縮の部位別特異性と
下肢筋群に重点をおいた急性期リハビリテーションの構築)

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	Abbreviation
ADL	Activities of daily living
ANOVA	Analysis of variance
AT	Anaerobic threshold
ARH	Acute rehabilitation
AROM	Active range of motion
BGA	Blood gas analysis
BMI	Body mass index
CaO ₂	Arterial oxygen content
CHDF	Continuous hemodiafiltration
CI	Cardiac index
CO	Cardiac output
CPA	Cardiopulmonary arrest
CRP	C-reactive protein
CSA	Cross sectional area
CT	Computed tomography
DPC	Diagnosis procedure combination
DO ₂	Oxygen delivery
EMS	Electric muscle stimulation
GCS	Glasgow Coma Scale
Hb	Hemoglobin
HR	Heart rate
IABP	Intra-aortic balloon pumping

ICC	Inter or intra correlation coefficient
ICU	Intensive care unit
Lt	Left
MRI	Magnetic resonance imaging
PROM	Passive range of motion
PCPS	Percutaneous cardiopulmonary support
PT	Physical therapist
RN	Registered Nurse
ROM	Range of motion
Rt	Right
SaO ₂	Arterial blood oxygen saturation
ScvO ₂	Central venous blood oxygen saturation
SD	Standard deviation
SLR	Straight leg raising
SpO ₂	Percutaneous arterial blood oxygen saturation
SOFA	Sequential organ failure assessment
SV	Stroke volume
SvO ₂	Mixed venous oxygen saturation
TP	Total protein
VF	Ventricular fibrillation
VO ₂	Oxygen consumption
VT	Ventricular tachycardia
WBC	White blood cell

Abstract

Critically ill patients admitted to the intensive care unit (ICU) are placed on long-term bed rest during treatment because of the severity of their disease or postoperative condition after major surgeries. Excessive bed rest and immobilization have been shown to cause ICU-acquired weaknesses, such as disuse muscle atrophy, which contribute to prolonged hospitalizations and decreased activity of daily living (ADL) levels after discharge. However, the degree and the site specificity of acute disuse muscle atrophy in critically ill patients during a relatively short ICU stays have not been fully elucidated.

In this study, I evaluated the chronological change in the acute disuse muscle atrophy of these patients using the anthropometric method, and found that disuse muscle atrophy developed rapidly, specifically in the lower limbs in ADL-independent patients during their 6-day ICU stay. This result emphasized the necessity of intensive early rehabilitation programs targeting the lower-limb muscles. I then constructed an acute rehabilitation (ARH) program from the viewpoint of ICU nurses which consisted of a feasible daily rehabilitation plan, including lower-limb resistance exercises that would prevent lower-limb muscle atrophy, and introduced it to the clinical field. The reduction in the lower-limb circumference in the intervention group was smaller than

that in the control group. This result suggested that an ARH program initiated soon after ICU admission could prevent acute disuse muscle atrophy in critically ill patients, especially that in the lower limbs. Furthermore, this rehabilitation program may shorten the hospital stay and help critically ill patients return to the ADL level before ICU admission.

Introduction

Many critically ill patients in the intensive care unit (ICU) have been placed on long-term bed rest during treatment because of the severity of their disease or their postoperative condition after major surgeries. Excessive bed rest and immobilization have been shown to cause ICU-acquired weakness ^{1, 2, 3, 4)}, which contributes to prolonged hospitalization and decreased activity of daily living (ADL) levels after discharge ^{5,6,7)}. Many patients who have suffered from ICU-acquired weakness do not fully recover their pre-admission physical function levels, and residual physical limitations persist in 69% patients after ICU discharge ⁸⁾. ICU patients often develop disuse skeletal muscle atrophy because they are often immobilized during their ICU stays. It has been reported that skeletal muscle volume may decline by 1%–1.5% per day of strict bed rest ⁹⁾ and by 4%–5% for each week of bed rest ¹⁰⁾; this leads to a 10% reduction in skeletal muscle strength after 1 week of bed rest ¹¹⁾. Patients over 60 years old who are admitted to ICU are expected to suffer a 20% skeletal muscle loss because of sarcopenia, which is a higher amount than that in younger patients ¹²⁾. Even though their ADL levels before ICU admission were normal, even a moderate progression of muscle atrophy could affect their ability to perform ADLs after discharge ¹³⁾.

Furthermore, the decline of skeletal muscle strength due to immobilization may be associated with substantial morbidity and the delay of ADL recovery to former levels^{6, 14)}.

In the previous study, Kondo *et al* described the relationship between disuse muscle atrophy and its recovery process, and showed that after a period of immobilization, it took 3 times longer than the immobilization period to bring it back to former levels once disuse muscle atrophy developed¹⁵⁾. Thus, it is very important for all patients admitted to ICU to initiate interventions that can prevent disuse muscle atrophy as early as possible. In another study, Fujii *et al* reported 6 patients who developed muscle atrophy after joint replacement operations for hip osteoarthritis¹⁶⁾. They evaluated the change in cardiovascular response and muscle atrophy for 2–3 weeks (12–22 days; average 17.6 days) using 3 parameters: change of muscle strength, muscle endurance, and capacity of cardiopulmonary activity. Furthermore, Ferrando *et al* described that muscle atrophy accompanying bed rest with high inflammatory response progressed 3-fold faster than that in bed rest alone¹⁷⁾. Although these previous studies examined the degree and the importance of disuse muscle atrophy after long-term bed rest, there have been few studies that have evaluated the effect of short-term bed rest on

the degree of disuse muscle atrophy in critically ill patients, who often present with high inflammatory response, as well as hemodynamic and respiratory instabilities.

The aim of this study was to evaluate the degree of skeletal muscle atrophy and to elucidate the region of skeletal muscle that would be susceptible to disuse muscle atrophy in critically ill patients who were on bed rest because of severity of their disease or postoperative condition during their 6-day ICU stay (Chapter 1). Considering the results of Chapter 1, I constructed a feasible early rehabilitation program to prevent disuse muscle atrophy (Chapter 2). Furthermore, I examined the efficacy of the early rehabilitation program in Chapter 3.

Chapter 1: Site specificity of acute disuse muscle atrophy in critically ill patients

Introduction

The effect of short-term bed rest on the degree of disuse muscle atrophy in critically ill patients, who often present with high inflammatory response as well as hemodynamic and respiratory instabilities, has not been fully elucidated in previous studies. The aim of the study in Chapter 1 was to compare the degree of skeletal muscle atrophy between ADL-independent and ADL-dependent patients before the ICU admission, and clarify the region of skeletal muscle that was susceptible to disuse muscle atrophy in critically ill patients on bed rest due to the severity of their disease or postoperative condition during their 6-day ICU stay.

Materials and Methods

Setting

This observational study was conducted in ICU of Keio University Hospital, which is a teaching hospital that includes 1044 beds, from October 2012 to October 2013. This study was approved by the hospital's ethics committee before any

participants were enrolled (approval number of the hospital's ethics committee: 20130181), and informed consent was obtained from participants or their authorized representatives according to the code of ethics when needed.

Patients

Patients over 20 years old and who were expected to stay in ICU for over 6 days and required bed rest as the initial rest level at ICU admission were eligible for this study. The exclusion criteria were as follows: patients who had received either upper-limb or lower-limb amputation, patients with refractory shock after large numbers of transfusions and high-dose catecholamine therapy, deep-vein thrombosis, either upper-limb or lower-limb burns, and also limb-bone fractures. Obese patients, with a body mass index (BMI) of over 35 (morbid obesity), who had more adipose tissue at the peripheral sites, such as the upper and lower limbs ¹⁸⁾, were also excluded to eliminate the effects of the fat layer. Subjects were divided into 2 groups depending on the ADL level before ICU admission: ADL-independent group and ADL-dependent group. Although the ADL-independent group included patients who could spend their daily lives without assistance (no support for eating, transferring to a chair, cosmetic cleaning,

taking a bath, toileting assistance, ambulation, or changing clothes), the ADL-dependent group consisted of patients who required partial or total assistance in their daily lives. The ADL dependency level before ICU admission was classified for either group on the basis of the diagnosis procedure combination (DPC). The demographic information and baseline characteristics of the subjects, such as age, sex, BMI, sequential organ failure assessment (SOFA) score, blood chemical analysis data, and ICU primary admission diagnosis, were also recorded.

Outcome

The primary outcome of this study was the degree of skeletal muscle atrophy in the upper and lower limbs measured by the chronological change of muscle thickness in the critically ill patients in ICU. For the evaluation of muscle thickness, I measured the limb circumference using the same soft tape. The measurement sites were selected on the basis of previous studies regarding anthropometric measurements. There were 5 sites: the midpoint of the upper limb between the acromion and olecranon for the biceps brachii evaluation ^{19, 20, 21)}, the maximum point of the lower leg for the triceps surae evaluation ^{22, 23, 24)}, and 3 different points of 5 cm, 10 cm, and 15 cm above the superior

pole of the patella for the quadriceps femoris evaluation ^{25, 26, 27, 28, 29, 30, 31, 32}. The respective measurement sites for limb circumference are shown in Figure 1. Limb circumferences were measured to the nearest 5 mm. The measurements were taken at the day of ICU admission, and at 72 hours (hrs), and 144 hrs after ICU admission. Subjects were maintained in the supine position with each limb being at extension position during the measurement of the circumference, and respective measurement points were marked by red marker for the initial measurement to avoid inter-measurement errors. Inter-class and intra-class correlation coefficients (ICC) were calculated to evaluate the anthropometrical artificial error (ICC (1, 1) = 0.997, ICC (2, 1) = 0.996). To exclude the effect of fluid therapy on the limb circumference ³³, I also recorded the daily fluid balance for each day.

Statistics

Demographic data and fluid balance were compared with Student *t*-test or chi-square test between the ADL-independent group and the ADL-dependent group, and presented as mean \pm standard deviation (SD). The length of limb circumference was described as the percentage compared with the value at ICU admission, and results were

presented as median (interquartile range). The change of limb circumference during the ICU stay at each site and the difference in the limb circumference change at 72 and 144 hrs after ICU admission among the 5 different sites were compared with 1-way analysis of variance (ANOVA) followed by a *post hoc* analysis. All statistical analyses were performed with IBM SPSS Statistics, version 22 (SPSS, Inc., Chicago, IL). A *p* value of <0.05 was considered as statistically significant.

Results

After eliminating participants on the basis of exclusion criteria, forty-one patients were enrolled in this study during the study period, including 31 patients in the ADL-independent group and 10 patients in the ADL-dependent group. Demographic information and baseline characteristics at the admission to ICU in both the ADL-independent group and the ADL-dependent group are shown in Table 1. Except for age, there were no significant differences in the demographic information and baseline characteristics between the ADL-independent group and the ADL-dependent group.

The results of the changes of limb circumference at each site at 72 and 144 hrs after ICU admission are presented in Table 2. In the ADL-dependent group, at 72 hrs after

ICU admission, the limb circumferences were not significantly decreased compared with the baseline except in the left thigh at 15 cm above the patella. However, limb circumferences at all sites were decreased significantly at 144 hrs after ICU admission compared with the baseline. On the other hand, the limb circumferences at all sites except for the left upper limb decreased significantly at 72 hrs after admission in the ADL-independent group, and limb circumferences at all sites were all decreased significantly compared with the baseline at 144 hrs after admission.

The comparisons between the 5 different sites at the same time point in both the ADL-independent group and the ADL-dependent group are shown in Figure 2. There were no significant differences in the change of limb circumference among all 5 sites at 72 and 144 hrs after ICU admission in the ADL-dependent group (Figure 2 a-d). Whereas, in the ADL-independent group, the change of limb circumference at the 4 different lower-limb sites was larger than that in the upper limb in both the right and left sides at 72 and 144 hrs after ICU admission (Figure 2 e-h). The change at the site 15 cm above the superior pole of patella was particularly noticeable. The fluid balance during the first 72 hrs and the next 72 hrs after ICU admission in the ADL-independent group was +1260 mL and -74 mL, respectively. The fluid balance of the ADL-dependent

group was +2511 mL and +479 mL, respectively. There were no significant differences in the chronological changes in the fluid balance between the ADL-independent group and the ADL-dependent group (Table 3). To eliminate the bias caused by fluid balance, I classified the patients in the ADL-independent group into 3 groups according to the fluid balance 144 hrs after ICU admission, and compared the limb circumferences between these 3 groups. As shown in Table 4, there were no significant differences in the change of limb circumferences between the 3 groups.

Because there was a significant difference in age in the demographic information between the ADL-independent group and the ADL-dependent group, I examined whether aging affected the progress of muscle atrophy by classifying the patients of the ADL-independent group into 4 groups by age, and comparing the limb circumferences between these 4 groups. As shown in Table 5, there were no significant differences in the change of limb circumferences between the 4 groups.

Discussion

The major finding of this study was that the acute muscle atrophy progressed during only 6 days in ICU, and advanced faster in the ADL-independent patients than in

the ADL-dependent patients. Furthermore, the degree of muscle atrophy was more severe in the lower limbs, which are used as antigravity muscles for maintaining sitting and standing positions, than in the upper limbs in the ADL-independent group during a short-term ICU stay. It has been reported that age-related sarcopenia progressed greater in lower-limb muscles in the elderly ³⁴⁾. Another studies demonstrated that in healthy people, the muscle atrophy caused by prolonged bed rest for 5–17 weeks was more severe in the lower-limb muscles than in the upper-limb muscles ^{35, 36, 37)}. However, there have been few studies, which compared the degree of muscle atrophy between the upper and lower limbs during this relatively short period in critically ill patients. In this study, I focused on the acute disuse muscle atrophy during the acute stage of critically ill patients admitted to ICU who often presented with both hemodynamic and respiratory instabilities, a high inflammatory response, and malnutrition; I also demonstrated that muscle atrophy progressed more in the lower-limb muscles than in the upper limb muscles, which was consistent with sarcopenia associated with aging in elderly patients. Furthermore, compared with the state before ICU admission, the muscle atrophy progressed greater and faster during the short period of 6 days in the ADL-independent patients. These results strongly emphasized that a rehabilitation program to prevent

acute muscle atrophy targeting the lower-limb muscles should be initiated as early as possible after ICU admission, especially for the ADL-independent patients.

In this study, I demonstrated that the degree of muscle atrophy reflected by the reduction of limb circumference was more severe in critically ill patients who managed their own daily lives before ICU admission than in those who needed some support for their daily lives or spent most of their time in the bed despite a relatively short stay in ICU. It is very natural that the effects of acute disuse muscle atrophy during an ICU stay would be remarkable in patients who may spend their lives without limitation because chronic disuse muscle atrophy was likely to have progressed before ICU admission in the ADL-dependent patients ³⁸⁾. Moreover, the development of muscle atrophy in the lower limbs was more noticeable than that in the upper limbs, suggesting that the effect of bed rest for more than 72 hrs on the lower-limb muscles was more intensive than that on the upper-limb muscles. In the ADL-independent group, ICU staff performed everyday care, such as bed-baths, teeth-brushing, clothing changes, and postural changes, with the smallest amount of support, and allowed patients to use their upper limbs as much as possible. Therefore, the progression of muscle atrophy in the upper limbs may be attenuated, compared with lower limbs of which usage was restricted by

bed rest. The lower-limb muscles, whose strength has a strong relationship with the patient's activity level in their daily life ³⁹⁾, have also a very important role as the muscle pump to assist venous return and stabilize hemodynamics ⁴⁰⁾. Thus, the initiation of the intervention to prevent acute muscle atrophy as early as possible in critically ill patients is very important not only to attenuate the reduction of their ADL but also to maintain stable hemodynamic conditions.

I used the limb circumference to evaluate muscle thickness changes in this study. Anatomically, human limbs are composed of bone, muscle layers, and fat layers in order from the center. Furthermore, the existence of edema caused by poor nutritional status and inflammatory conditions hinders evaluation of muscle thickness changes using anthropometrical measurements ⁴¹⁾. For that reason, the cross-sectional area (CSA) calculated from computed tomography (CT) and magnetic resonance imaging (MRI) can be used as a mainstream method to evaluate muscle thickness changes in many studies ^{42, 43, 44, 45, 46)}. However, frequent CTs or MRIs are not clinically practicable because of the unstable physical condition of ICU patients, high cost, and lack of manpower in ICU staff. An ultrasound technique to measure the muscle volume can also be a reliable method to evaluate muscle atrophy ⁴⁷⁾, even though technical

difficulties may prevent ICU nurses from using the ultrasound as a routine practice.

There have been previous studies describing the high reliability and strong relationship among measurement sites, limb circumference, and CSA. Willan *et al* reported that limb circumferences measured at both 10 cm and 15 cm above the superior pole of the patella proved to be a good predictor of the total CSA of the quadriceps muscle ⁴⁸⁾. In another study, it was reported that serial measurements at the 5-cm and 10-cm levels could be of value as an index of the quadriceps power ⁴⁹⁾. Chen *et al* demonstrated that the MRI-measured thigh volume was positively correlated with anthropometric data, such as thigh circumference measured at the point 15 cm proximal from the superior pole of the patella, and developed the prediction equation: thigh muscle volume (cm³) = 4226.3 – 42.5 × age (year) – 955.7 × gender (male = 1, female = 2) + 45.9 × body weight (kg) + 60.0 × thigh circumference (cm); this provided evidence of a strong relationship between thigh muscle volume and physical function ²⁸⁾. Furthermore, thigh circumference at the point 15 cm proximal from the superior pole of the patella was frequently used to assess the muscle volume of quadriceps in many clinical studies ^{28, 29, 50, 51, 52)}. I adopted 3 measurement sites (at 5 cm, 10 cm, and 15 cm proximal to the superior pole of the patella) for all patients with wide ranges in height. Miura *et al*

reported that the percentage of CSA of quadriceps femoris to the whole CSA of the femur measured by MRI in patients with various heights (155–174 cm) was similar at the 3 different points at 5 cm, 10 cm, and 15 cm proximal to the superior pole of the patella ⁵³⁾. For that reason, I determined that the serial measurements at these 3 sites were adequate enough for quadriceps femoris evaluation in all patients. Considering the usefulness and the validity of the limb circumference for the evaluation of muscle atrophy reported in many previous studies, the anthropometrical measurement of muscle thickness change has been regarded as the justifiable method in this study.

There were several limitations to interpreting the study data. First, the quantity and the frequency of mobilization therapy and physical therapy as usual care were not programmed to be unified during the study period, which could have affected the results of this study. However, ICU nurses mainly provided mobilization therapy, such as range of motion (ROM) exercises, but did not provide physical therapy, such as muscle resistance exercise, during the study period. There were no routine exercise programs that ICU nurses performed daily. Instead, the equivalent physical therapy was performed by the same physical therapists who belong to ICU exclusively. Thus, it was unlikely that the difference in levels of physical therapy during the study period could

modulate the results of the limb circumference. Second, the degree of limb edema, which was not evaluated in this study, could have affected the results of the limb circumference. The evaluation of muscle atrophy by the measurement of limb circumference was likely to be underestimated by the presence of increased edema, especially in the ADL-dependent group. However, as shown in Table 3, the fluid balance during the study period was not different significantly between the ADL-independent group and the ADL-dependent group although SD was greater than the mean values. Moreover, the difference in the fluid balance had no effect on the values of the limb circumferences as described in Table 4. These results implied that the degree of edema had little effect on the results. Furthermore, the validity of this method of using the limb circumference for the evaluation of muscle atrophy has been certified in previous studies ^{28, 48, 49)}. Third, the difference in ages between the ADL-independent group and the ADL-dependent group could affect the results although it was quite inevitable that ADL dependence would progress with aging ³⁴⁾. However, as shown in Table 5, there were no significant differences in the change of limb circumferences between the 4 groups of age. It implied that the change of muscle atrophy was not affected by aging. Moreover, the differences in ages could not change the finding that

the muscle atrophy in the lower limbs developed during the early course of the ICU stay in relatively young patients with independent ADLs before their admission to ICU. Considering the small sample size in the ADL-dependent group, this could have resulted in no significant differences in limb circumferences between the upper and the lower limbs in the ADL-dependent group. Fourth, there was a patient with pelvic fracture admitted to the ICU in the ADL-independent group. The severe unstable pelvic fracture patient who had an external fixator should have been excluded because the swelling and the edema could have influenced the limb circumference. However, this patient received conservative therapy without an external fixator during the ICU stay. Thus, this patient was enrolled in this study. Fifth, in order to elucidate the site specificity of acute muscle atrophy, the forearm should be measured for the upper-limb evaluation. However, there was anthropometric difficulty in measuring the forearm due to the existence of the frequent placement of the infusion lines. Finally, there was some heterogeneity in the disease condition between the ADL-independent group and the ADL-dependent group, and the severity and the clinical course of disease during the ICU stay in each patient were not evaluated; however, the severity at admission reflected by SOFA score and the maximum value of C-reactive protein (CRP) during

the study period did not differ between the ADL-independent group and the ADL-dependent group. Because various critically ill patients, including not only surgical but also medical patients, are admitted to ICU, it may be very difficult to make the conditions homogeneous between the ADL-independent group and the ADL-dependent group.

In this observational study, the disuse muscle atrophy in critically ill patients developed rapidly, especially in the lower limbs in the ADL-independent patients before ICU admission. This result emphasized the necessity of the intensive early rehabilitation program focusing on the lower-limb muscles to prevent muscle atrophy, which could affect the prognosis of critically ill patients. Then, I constructed an acute rehabilitation (ARH) program as the early rehabilitation program targeting lower-limb muscle atrophy; this program is likely to be practicable and adaptable to ICU patients in acute stage of a critical illness. These details are shown in the next chapter.

Chapter 2: Construction and introduction of ARH program in a clinical field

Introduction

In Chapter 1, I elucidated the site specificity of the acute muscle atrophy, which progressed predominantly in the lower limbs during only 6 days in ICU, especially in the ADL-independent patients. The quadriceps femoris and triceps surae muscles, which are the major components of the lower-limb muscles, have a strong relationship with the patient's activities in their daily life, such as sitting and standing ³⁹⁾. The weakness of these muscles is associated with the decrement of the ADL performance ^{54,} ⁵⁵⁾. Furthermore, these muscles have the very important role of muscle pump to assist venous return and to stabilize hemodynamics ⁴⁰⁾. This function is needed to support ICU patients implement the stepwise mobilization safely and effectively. For that reason, I found that early rehabilitation should focus on the lower-limb muscles (the quadriceps femoris and triceps surae muscles as the targeted muscles) in the acute stage of critical illness in ICU.

Patients admitted to ICU are usually critically ill with systemic instability. These critically ill patients receive medical treatment and life support systems, such as

mechanical ventilation, as a first priority. Because the increase of oxygen consumption caused by the initiation of rehabilitation in acute phase might impose the risk of deterioration in the cardiopulmonary or respiratory condition of critically ill patients, early initiation of the rehabilitation program is usually difficult to perform during this acute stage. However, a recent study has shown the safeness and feasibility of early rehabilitation ^{5, 56, 57)}. In these studies, only Morris *et al* showed the contents of a mobility protocol and described the effectiveness of the protocol on the patients with acute respiratory failure ⁵⁾. However, none of them emphasized the importance of the physical therapies focused on the lower-limb muscles in the acute stage of critically ill patients in ICU, nor described the details regarding the introduction, assessment, step-up/step-down of the rehabilitation level, discontinuation criteria, and contraindications.

Thus, I modified the mobility protocol reported by Morris *et al* ⁵⁾, and developed an ARH program, which described the detailed daily rehabilitation plan to optimize the contents of rehabilitation. This ARH program included many steps to effectively prompt rehabilitation according to the patient condition, regarding the introduction, frequent assessment, step-up/step-down of the rehabilitation level, discontinuation criteria, and contraindications. This ARH program also included intensive lower-limb intervention to

prevent acute disuse lower-limb muscle atrophy that had been elucidated in the previous chapter. In this chapter, I have introduced the detailed process and contents of the ARH program that I established, and described the purpose and the background of the development of the ARH program, including the selection of the countermeasures for the lower-limb muscle atrophy, on the basis of systematic reviews.

Search strategy and selection of the countermeasure

In the previous studies, there have been several countermeasures to prevent lower-limb muscle atrophy, which can be performed during the period of bed rest. I searched the database PubMed (Issue 21st Feb 2015) to identify these studies, which reported the efficacy of countermeasures to prevent lower-limb muscle atrophy, written in English and published between 1995 and 2014. The search terms included these keywords; “muscle atrophy,” either “bed rest” or “critically ill,” and either with or without “lower limb.” As shown in Figure 3, there were 228 studies identified. I then screened the titles and the abstracts to exclude studies, which had no relevance to any intervention to prevent lower-limb muscle atrophy. There were 28 studies after the screening. Then, I excluded the studies with countermeasures to prevent lower-limb muscle atrophy that

were performed out of bed and with nutrition countermeasure because they were impracticable for an ICU. Furthermore, I excluded the studies which were not intensive interventions for lower-limb muscles because the lower-limb muscles were the targeted muscles for intervention. Finally, there were 19 studies with 4 types of countermeasures to prevent lower-limb muscle atrophy: passive stretching (n = 1)⁵⁸⁾, electric muscle stimulation (EMS) (n = 5)^{59 60 61 62 63)}, resistive vibration exercise (n = 5)^{64 65 66 67 68)}, and resistance exercises (n = 8)^{69 70 71 72 73 74 75 76)}. All these studies have shown the efficacy of the countermeasures to prevent lower-limb muscle atrophy. Because the subjects in this study were critically ill patients in ICU, who were bedridden because of hemodynamic or respiratory instabilities and were likely to have less exercise tolerance, I determined that the passive stretch could be the primary choice. However, even though it has been reported that the passive stretch prevented the progress of muscle atrophy in critically ill patients⁵⁸⁾, the exact mechanism of its effect was not completely understood. For that reason, I excluded this method. The previous studies demonstrated that EMS, which is a noninvasive method to induce the muscle contraction directly without a patient's effort⁷⁷⁾, can prevent muscle atrophy⁷⁸⁾. The effect of muscle contraction by EMS is equivalent to that of the patient's voluntary muscle contraction by the resistance

exercise when it is performed at the same intensity ⁷⁹⁾. However, EMS was not available in the ICU of the Keio University Hospital. The previous studies had demonstrated the efficacy of the resistive vibration as well as EMS. However, I excluded the resistive vibration exercise for the same reason as EMS. It was not available in the ICU of the Keio University Hospital. Considering the feasibility and the adoptability of the each countermeasure to the clinical field, I decided to adapt these resistance exercises for lower-limb muscle atrophy. There were several types of resistance exercises in the previous studies, which were divided into 2 categories. One is the resistance exercise, which uses special machines, such as the flywheel ^{71 72)} and calf press machine ⁷¹⁾, and the others that can be performed without special machines ^{80 81)}. I finally decided to adapt the lower-limb resistance exercises that do not use the special machine at every level of the ARH program to prevent lower-limb muscle atrophy, because the special machines for resistance exercises were not available in the ICU of the Keio University Hospital; the conscious patients could perform the resistance exercises spontaneously with the limited level of ROM in the bed without special machines.

According to the search strategy and the selection of the countermeasure based on the systemic reviews, the detail contents of the ARH program are described below.

The content of ARH program

ARH program

The ARH program that was constructed with the anesthesiologists that belonged to ICU, ICU nurses, and physical therapists, is shown in Figure 4. There were 7 rehabilitation levels in this program, and patients were assigned to 1 of these levels on the basis of the individual bed rest level from complete bed rest level to the ambulation level. The detailed plan for the patient's active and passive exercises given by ICU nurses was also included in each rehabilitation level.

Lower-limb resistance exercise

As the lower-limb resistance exercises, both straight leg raising (SLR) (Figure 5) and quadriceps setting (quad-set) (Figure 6) were selected for the isometric contraction exercise of the quadriceps femoris muscle, and was also contained in the standard nursing plan at Keio University Hospital. The efficacy of those exercises on the respective muscles composing the quadriceps femoris muscle are not exactly the same between SLR and quad-set ⁸²⁾ and may also be partially different depending on the

performing posture⁸³⁾. It has been reported that SLR stimulated not only the quadriceps femoris muscle but the iliopsoas muscle and abdominal muscles⁸³⁾, which were targeted muscles for stepwise rehabilitations, such as standing and ambulation. For that reason, I selected these 2 exercises for isometric contraction exercises of the quadriceps femoris muscle. The plantar flexion exercise⁸⁴⁾ (ankle-pump) (Figure 7) was selected for the contraction of the triceps surae muscle, and was also contained in the standard nursing plan at Keio University Hospital. Either SLR or quad-set was introduced to train the quadriceps femoris muscle. The ankle-pump was introduced to train the triceps surae muscle. Each resistance exercise was adjusted to the individual subject's physical condition and their muscle strength. SLR plus ankle-pump was considered the first choice, and the quad-set plus ankle-pump was considered the second choice. In order to perform this lower-limb resistance exercise with an effective and efficient plan under limited manpower in ICU staff, ICU nurses aimed to teach the methods of these exercises to patients so that patients could perform them spontaneously in bed if possible. Each resistance exercise was scheduled to be performed 10 times per set and 3 sets per day⁸⁵⁾. The stepwise rehabilitation approach for each subject, such as the bed rest position to 30 degrees head-up position, sitting position, sitting on edge of bed,

wheelchair, standing position, and ambulation, were performed with high priority during ICU stay. For the rest of the time other than these rehabilitations, the patients performed either SLR or Quad-set plus ankle-pump for the lower-limb muscles.

Respective mobilization level

Level 0

Patients assigned to Level 0 were those with unstable cardiopulmonary conditions who needed extracorporeal circulation, such as percutaneous cardiopulmonary support (PCPS), intra-aortic balloon pumping (IABP), and continuous hemodiafiltration (CHDF), and they were placed on complete bed rest. At this mobilization level, patients did not receive passive rehabilitation and mobilization. However, patients were maintained in a functional and safe position.

Level I-

Patients assigned to Level I- were those with Glasgow Coma Scale (GCS) M5 or lower, cognitive impairment, and whose bed rest level in ICU was the 45 degrees head-up position. At this mobilization level, active exercises of daily cosmetic cleaning, such

as bed-bath, teeth-brushing, and changing clothes, were not expected due to the patient's cognitive level. Because active ROM exercises and lower-limb resistance exercises were not adaptable, patients mainly accepted at least 3 sets a day of the passive ROM exercises for both the upper and lower limbs to prevent joint contracture.

Level I+

Patients assigned to Level I+ were those with GCS M6 and basically no cognitive impairment, and whose bed rest level in ICU was up to 45 degrees head-up position. At this mobilization level, the patients were prompted to participate in as many active exercises as possible, such as bed-baths, teeth-brushing, and changing clothes, with medical staff support during the ICU stay. Patients implemented active ROM exercises of both the upper and lower limbs for at least 3 sets a day to prevent joint contracture. Passive ROM exercise was performed with assistance by the medical staff as necessary. Patients also implemented lower-limb resistance exercises 10 times per set and 3 sets a day to prevent acute disuse lower-limb muscle atrophy.

Level II-

Patients assigned to Level II- were those with GCS M5 or lower, cognitive impairment, and whose bed rest level in ICU was up to 90 degrees head-up position. At this mobilization level, the active exercises in daily cosmetic cleaning, such as bed-bath, teeth-brushing, and changing clothes, were not expected due to the patient's cognitive level. Because active ROM exercises and lower-limb resistance exercises were not adapted, patients mainly accepted the passive ROM exercises of both the upper and lower limbs for at least 3 sets a day for the prevention of joint contracture. In the daytime and during the tube feeding, patients were maintained in a sitting position on the bed, using positioning pillows as necessary to effectively maintain the posture and extend the time in the sitting position as long as possible according to individual activity tolerance.

Level II+

Patients assigned to Level II+ were those with GCS M6 and basically no cognitive impairment and whose bed rest level in ICU was up to 90 degrees head-up position. At this mobilization level, patients were prompted to perform as many active exercises as possible for daily cosmetic cleaning, such as bed-bath, teeth-brushing, and changing

clothes, with medical staff support during the ICU stay. Patients implemented the active ROM exercise of both the upper and lower limbs for at least 3 sets a day to prevent joint contracture. The passive ROM exercises were given by medical staff as necessary.

Patients also implemented the lower-limb resistance exercises 10 times per set and 3 sets a day to prevent the acute disuse lower-limb muscle atrophy. In the daytime, patients assumed a sitting position on the bed, using positioning pillows as necessary to effectively maintain the posture and extend the time in sitting position as long as possible in proportion to the individual activity tolerance.

Level III

Patients on Level III were those with GCS M6 and basically no cognitive impairment and whose bed rest level in ICU was up to sitting on the edge of bed. At this mobilization level, patients were prompted to perform as many active exercises as possible, such as bed-bath, teeth-brushing, and changing clothes, with medical staff support during ICU hospitalization. Patients implemented active ROM exercises for both the upper and lower limbs for at least 3 sets a day to prevent joint contractures. Patients also implemented lower-limb resistance exercises 10 times per set and 3 sets a

day to prevent the acute disuse lower-limb muscle atrophy. In the daytime, patients are challenged to sit on the edge of bed with medical staff support as long as possible in proportion to individual activity tolerance. During the daytime, patients took a sitting position on bed using positioning pillows as necessary to effectively maintain posture. The patient's adequate upper-limb active exercise (patients can move arms against gravity) was a requisite condition for this mobilization level. Patients performed the intensive lower-limb active exercise to step up to the next mobilization level.

Level IV

Patients assigned to Level IV were those with GCS M6 and basically no cognitive impairment and whose bed rest level in ICU was up to a wheelchair. At this mobilization level, patients were prompted to complete as many active exercises as possible in daily cosmetic cleaning, such as bed-bath, teeth-brushing, and changing clothes, with medical staff support during the ICU stay. Patients implemented active ROM exercises for both the upper and lower limbs for at least 3 sets a day to prevent joint contractures. Patients also implemented lower-limb resistance exercises 10 times per set and 3 sets a day to prevent the acute disuse lower-limb muscle atrophy. In the

daytime, patients were challenged to transfer from the sitting position on the edge of bed to wheelchair with medical staff support and to stay on the wheelchair as long as possible in proportion to individual activity tolerance. In addition to the adequate upper-limb active exercise, adequate the lower-limb exercise (patients can move legs against gravity) was a requisite condition at this mobilization level. Patients continued practicing the lower-limb active exercises to proceed to the next mobilization level.

Level V

Patients assigned to Level V were those with GCS M6 and basically no cognitive impairment and whose bed rest level in ICU was up to standing and stepping. At this mobilization level, patients were prompted to perform as many active exercises as possible in daily cosmetic cleaning, such as bed-bath, teeth-brushing, and changing clothes, with medical staff support during the ICU stay. Patients performed active ROM exercises for both the upper and lower limbs for at least 3 sets a day to prevent joint contracture. Patients also implemented lower-limb resistance exercises 10 times per set and 3 sets a day to prevent acute disuse lower-limb muscle atrophy. During the daytime, patients were challenged with standing and stepping with medical staff support and

extended this time as long as possible in proportion to individual activity. Adequate upper and lower-limb power for maintaining the sitting position on the edge of bed and transferring to a wheelchair was requisite condition in this mobilization level. Patients continued practicing especially lower-limb active exercise to step up to next mobilization level.

Level VI

Patients assigned to Level VI were those with GCS M6 and basically no cognitive impairment and whose bed rest level in ICU was up to ambulation. At this mobilization level, patients were prompted to perform as many active exercises as possible in daily cosmetic cleaning, such as bed-bath, teeth-brushing, and changing clothes, under medical staff support during the ICU stay. Patients implemented active ROM exercises for both the upper and lower limbs for at least 3 sets a day to prevent joint contractures. Patients also implemented lower-limb resistance exercises 10 times per set and 3 sets a day to prevent acute disuse lower-limb muscle atrophy. During the daytime, patients were challenged with ambulation after a standing position, and step training was given with medical staff support. The distance of ambulation was extended as long as possible

in proportion to individual activity tolerance. Adequate upper and lower active exercise for maintaining a standing position was a requisite condition for this mobilization level. Patients continued practicing ambulation to improve their own ADL.

The difference of how to increase mobilization level between conscious patient and unconscious patient

Both Level I and Level II were divided into 2 stages: Level I+ and Level I-, Level II+ and Level II-, respectively. When patients in Level 0 recovered and stepped up to the next mobilization level, they stepped up to either Level I+ or Level I- depending on their level of consciousness and cognition. If the patients were conscious, they stepped up from Level 0 to Level I+, Level II+, Level III, and Level VI in that order. Conversely, if patients were unconscious, they stepped up from Level 0 to Level I- and then to Level II- as the final mobilization level as long as patient's consciousness level did not recover. In this ARH program, I defined patients with GCS M6 as conscious, whereas patients with GCS M5 or lower, including cognitive impairment, were considered as unconscious. The reason why I established this step up criteria for unconscious patients was that these patients could not be expected to perform active

exercises, but had to mainly accept passive exercises. Furthermore, it has been reported that these unconscious patients have a high risk of falling because of the cognitive impairment, especially in the older adult ⁸⁶⁾. It implied that these patients could not maintain their posture by themselves when they were challenged to sit on the edge of bed or to further rehabilitation. For that reason, these patients were not able to step up to further mobilization levels.

Initiation of ARH

All patients admitted to ICU were automatically enrolled in this ARH program. Anesthetists, who belong to ICU and work as intensivists, held conferences with other medical staff, including attending physicians and ICU nurses, at the beginning of the day. They discussed and shared the patients' short-term and long-term goals, and which mobilization level to initiate first for the ARH intervention.

How to perform ARH program and step up a mobilization level

ARH was performed on the basis of the patient's mobilization level. ICU nurses monitored vital signs before and after rehabilitation and also during the rehabilitation. If

the vital signs gradually reached the discontinuation criteria, ICU nurses reported to the anesthetists to evaluate whether this rehabilitation level should be continued or not. If the vital signs met the contraindication criteria, such as ventricular tachycardia (VT) or ventricular fibrillation (VF) during the rehabilitation, rehabilitation was instantaneously discontinued, and ICU nurses reported to the anesthetists and the attending physicians. When ICU nurses assessed the patients during the rehabilitation, they monitored not only the changes in vital signs but also the subjective symptoms shown in detail in later sections. When the vital signs of the patients were either stable or within the continuation criteria through the rehabilitation procedure, patients could step up to the next mobilization level after the doctor's decision. The first trial of rehabilitation in every mobilization level was implemented with ICU nurses plus either anesthetists or attending physicians. After the first successful trial, ICU nurses could generally support a patient's rehabilitation without a doctor.

Discontinuation criteria

As physical and pathological conditions were varied in each patient admitted to ICU, it may not be practicable to establish common discontinuation criteria uniformly

for all patients. While it may be very preferable to monitor the anaerobic threshold (AT) for each patient during the rehabilitation procedure ⁸⁷⁾, it can be very difficult to establish accurate AT criteria that can cover all patients in the clinical situation. Then, either anesthetists or the attending physicians can establish the discontinuation criteria adjusted to the individual patient's condition and share these with ICU nurses before rehabilitation.

Systemic assessment during rehabilitation based on oxygen delivery-consumption balance *in vivo*

Because oxygen consumption is increased during the rehabilitation procedure, it has been very important to assess whether oxygen delivery-consumption balance was disrupted during the exercise or not. In order to complete this ARH program safely and effectively, exercise overload should be prevented while supplying optimal exercise training. In this ARH program, I assessed the optimal exercise tolerance for each patient considering AT and oxygen delivery-consumption balance *in vivo* ⁸⁸⁾. As patients stepped up to the next exercise tolerance level during rehabilitation, patients augmented oxygen delivery following their increased oxygen consumption. This was a normal

physical compensation mechanism. However, once the exercise tolerance was overloaded, patients could not deliver adequate oxygen, leading to the delivery-consumption imbalance. Delayed discontinuation of the rehabilitation can be very dangerous for significantly ill patients admitted to ICU, who have little residual organ capacity. Thus, ICU nurses assessed the exercise tolerance for rehabilitation by monitoring vital signs and the change of the patient's subjective/objective symptoms, which reflected the oxygen delivery-consumption balance and AT.

AT was the maximum exercise intensity provided by aerobic energy pathway (Figure 8). If patients exceeded this exercise tolerance, the pathway of energy metabolism shifted from aerobic to anaerobic, and lactate started to accumulate in the blood stream ⁸⁷⁾. Therefore, AT and AT-related subjective symptoms should be used as discontinuation criteria and these parameters can give very important information about the patient's optimal exercise tolerance. In ICU, ICU nurses monitored the various parameters described below, which could reflect the AT status, to optimize the efficacy of the rehabilitation program.

Then oxygen delivery (DO_2) equation is shown in Figure 9. DO_2 is determined by the production of arterial oxygen content (CaO_2) and cardiac output (CO) ⁸⁹⁾. CaO_2 is

calculated by hemoglobin (Hb) concentration and arterial blood oxygen saturation (SaO_2). ICU nurses can check the value of the Hb concentration in the arterial blood by the mean of the blood gas analysis (BGA) before the initiation of rehabilitation. It was important to check this value because if the Hb concentration was decreased by 30% due to hemodilution, hemorrhage, or the other causes compared with the previous values, the patient's DO_2 can be decreased by 30% without compensation due to other parameters.

There is another main parameter that determines DO_2 : the SaO_2 , which is substituted by percutaneous arterial blood oxygen saturation (SpO_2) in the clinical situation. ICU nurses are required to monitor the SpO_2 change and transition during rehabilitation. When oxygen consumption was augmented, patients elevated their respiratory rates and the minute volume of ventilation to meet the increased oxygen consumption. However, if exercise tolerance was overloaded, respiratory muscle fatigue might develop the use of the accessory muscle and paradoxical motion of the abdomen followed by subjective symptoms. Therefore, ICU nurses need to monitor the patient's respiratory pattern and the appearance of dyspnea in addition to SpO_2 value.

CO is the product of stroke volume (SV) and heart rate (HR), which is another parameter that can determine the value of DO_2 . Although SV of each patient is different due to the patient's physical baseline, such as cardiac function, body type, sex, and age, it is not likely that the value of SV changed dramatically during rehabilitation. As the oxygen consumption increased, patients elevated their HR to augment CO to increase the oxygen delivery⁹⁰⁾. Therefore it was important to monitor the HR transition continuously. Overloaded rehabilitation especially in patients with poor cardiac function could induce arrhythmia, which might cause further CO decrease and heart failure. For these reasons, ICU nurses were required to monitor not only the HR transition but also the subjective cardiac symptoms, such as palpitation, chest pain, lassitude, facial expression, and malaise. It was preferable for ICU nurses to monitor the invasive hemodynamic parameters if available, such as the cardiac index (CI), CO, mixed venous oxygen saturation (SvO_2), and central venous oxygen saturation (ScvO_2), and to use these parameters correctly as effective factors to assess the balance between oxygen delivery and consumption.

The staff in ICU has to be trained to perform the ARH program safely and effectively by monitoring the various parameters described above validly and correctly,

which could contribute to the improvement of ICU care and the prognosis of the critically ill patients.

Chapter 3: The efficacy of ARH program

Introduction

ARH program constructed in Chapter 2 was introduced into ICU practice. Then, I evaluated the efficacy of the ARH program. In order to evaluate the efficacy of the ARH program, a randomized control trial needed to be performed because of the high reliability of the study. However, because it was the first time for the initiation of the ARH program in ICU and it was uncertain whether this ARH program could work, an observational study was conducted to evaluate of the efficacy of the program as a preliminary study. The data before the initiation of ARH program described in Chapter 1 was used as the control, because the study setting was almost exactly the same except for the ARH intervention. The evaluation of muscle atrophy was performed in the same way as in Chapter 1.

Materials and Methods

Setting

The observational study was conducted in ICU of the Keio University Hospital, which is a teaching hospital that includes 1044 beds, from October 2012 to September 2014. This study was approved by the hospital's ethics committee before any participants were enrolled (approval number of hospital's ethics committee: 20130181), and informed consent was obtained from participants or their authorized representatives according to the code of ethics when needed.

Patients

Patients over 20 years old and who were expected to stay in ICU for more than 6 days and required bed rest as the initial rest level at ICU admission were eligible for this study. The exclusion criteria were as follows: patients who received either upper-limb or lower-limb amputations, patients with refractory shock after a significant amount of transfusions and high-dose catecholamine therapy, deep-vein thrombosis, either upper-limb or lower-limb burns, and limb-bone fractures. Obese patients with a BMI over 35 (morbid obesity), who had more adipose tissue at peripheral sites, such as the upper and lower limbs¹⁸⁾, were also excluded to eliminate the effects of the fat layer.

Subjects consisted of 2 groups: the control and intervention groups. Thirty-one ADL-independent patients from before the ARH program introduction that were enrolled in Chapter 1 were treated as the control group. Another 31 ADL-independent patients after the ARH program introduction in November 2013 were treated as the ARH intervention group.

Outcome

The primary outcome of this study was the degree of skeletal muscle atrophy in the upper and lower limbs measured by the chronological change of muscle thickness in the critically-ill patients in ICU in the same way as in the study from Chapter 1.

Statistics

Demographic data and fluid balance were compared with Student *t*-test or chi-square test between the control and intervention groups when appropriate, and presented as mean \pm SD. The length of limb circumference was described as the percentage compared with the value at ICU admission, and results were presented as the median (interquartile range). The chronological change of the respective limb circumferences

between the control and intervention groups during ICU stay were compared with ANOVA repeated measures. All statistical analyses were performed with IBM SPSS Statistics version 22 (SPSS, Inc., Chicago, IL). A *p* value of <0.05 was considered as statistically significant.

Results

Sixty-two patients were enrolled in this study during the study period, including 31 patients in the control group and 31 patients in the intervention group. Demographic information and baseline characteristics at the admission to ICU in both the control and intervention groups are shown in Table 6. There were no significant differences in the demographic information and baseline characteristics between the control and intervention groups. Fluid balance during the first 72 hrs and the next 72 hrs after ICU admission in both the control and intervention groups is also shown in Table 7. There were no significant differences in fluid balance between the control and intervention groups. The results of the changes in limb circumference at each site during the 144 hrs of ICU admission are presented in Table 8. The reduction of the limb circumference at the 4 different lower-limb sites in the intervention group was smaller than these in the

control group in both right and left sides during the 144 hrs of ICU admission, while that of the upper limbs were not different significantly between the control and intervention groups.

Discussion

This study demonstrated that ARH program initiated soon after ICU admission could prevent acute disuse muscle atrophy in critically ill patients, especially in the lower limbs. The results of this study suggested that it should be mandatory to initiate an ARH program as early as possible. Furthermore, this rehabilitation program may be expected to shorten the hospital stay and help critically ill patients recover to their prior ADL level faster, which should be clarified in the future study. Although the efficacy of the ARH program in critically ill patients was shown in this study, there were various diagnoses of the critically ill patients, and the sample size was small. Therefore, in order to increase the reliability, a large, multicenter, randomized controlled trial will be warranted to evaluate the efficacy of this program, in which not only the muscle atrophy but the length of hospital stay and the ADL levels after discharge should be evaluated. I

have to work so that the ARH program in the acute phase of critically illness becomes widespread in the field of ICU.

Conclusion and perspectives

In conclusion, I evaluated the chronological changes in the acute disuse muscle atrophy of ICU patients using the anthropometric method, and found that the disuse muscle atrophy developed rapidly, specifically in the lower limbs of the ADL-independent patients after 6 days in ICU. These results strongly emphasized that the rehabilitation program to prevent acute muscle atrophy that targeted the lower-limb muscles should be initiated as early as possible after ICU admission, especially for the ADL-independent patients.

I then constructed an ARH program from the viewpoint of ICU nurses which consisted of a feasible daily rehabilitation plan, including lower-limb resistance exercises to prevent lower-limb muscle atrophy, and introduced it to the clinical field, as described in Chapter 2. As shown in the study of Chapter 3, the reduction of the lower-limb circumference in the intervention group was significantly smaller than that in the control group after the ARH intervention. These results suggested that it may be necessary to initiate an ARH program as early as possible. Furthermore, this rehabilitation program may shorten the hospital stay and help critically ill patients recover to their prior ADL level faster, which should be elucidated in the future study.

Although the efficacy of the ARH program in critically ill patients was shown in this study, there were various diagnoses for the critically ill patients, and the sample size was small. Therefore, in order to increase the reliability, a large, multicenter, randomized, controlled trial will be warranted to evaluate the efficacy of this program, in which not only the muscle atrophy but the length of hospital stay and the ADL level after discharge would be evaluated.

Table 1: Demographic information and baseline characteristics in both the ADL-independent group and the ADL-dependent group

	ADL-independent (n = 31)	ADL-dependent (n = 10)	<i>p</i>
Age	60.1 ± 15.5	74.7 ± 13.4	.012
Sex- male (no. and %)	22 (70 %)	6 (60 %)	.517
BMI	21.4 ± 3.57	19.9 ± 4.14	.364
Surgical patient (no. and %)	11 (35 %)	3 (30 %)	.750
Mechanical ventilation (no. and %)	27 (87 %)	10 (100 %)	.232
SOFA SCORE	7.42 ± 4.05	8.9 ± 4.81	.164
CRP max (mg / dL)	13.8 ± 10	10.3 ± 6.63	.320
WBC max (10 ³ / µL)	14.1 ± 6.33	12.3 ± 4.84	.428
TP min (g / dL)	4.95 ± 0.75	4.73 ± 1.06	.458
Diagnoses (no.)			.743
Pneumonia	4	1	
Respiratory failure	3	2	
CPA recover	6	1	
Sepsis	1	0	
Heart failure	2	1	
Subarachnoid hemorrhage	2	0	
Traumatic subarachnoid hemorrhage	1	0	
Angina pectoris	1	0	
Myasthenia gravis	2	1	
Fulminant hepatitis	1	1	
Duodenal perforation	0	1	
Living donor liver transplantation	1	0	
Myocarditis	1	0	
Strangulated ileus	0	1	
Inhalation injury	1	0	
Atrial tumor	1	0	
Hypothermia	0	1	
Pelvic fracture (conservative therapy)	1	0	
Brain stem hemorrhage	1	0	
Drug overdose	1	0	
Pancreatic cancer	1	0	

BMI: body mass index, SOFA: sequential organ failure assessment, WBC: white blood cell, TP: total protein, ICU: intensive care unit, CPA: cardiopulmonary arrest.

Table 2: Site-specific chronological change of muscle circumference in both the ADL-independent group and the ADL-dependent group

		baseline(%)	72 hrs change Median (interquartile)		144 hrs change Median (interquartile)	
ADL- independent n = 31	Upper limb	100	100 (99.1-100)	*	100 (97.5-100)	*
	Thigh 15 cm	100	95.1 (91.9-95.9)	*	90.2 (87.7-93.6)	*
	Rt Thigh 10 cm	100	96.0 (94.2-97.6)	*	93.1 (90.0-95.4)	*
	Thigh 5 cm	100	97.3 (94.2-98.1)	*	92.6 (91.1-95.3)	*
	Lower leg	100	97.2 (95.9-98.4)	*	94.7 (92.4-96.2)	*
	Upper limb	100	100 (100-100)		100 (98.0-100)	*
	Thigh 15 cm	100	95.5 (92.7-96.9)	*	89.7 (88.6-92.2)	*
	Lt Thigh 10 cm	100	95.6 (94.7-97.8)	*	92.4 (89.5-95.6)	*
	Thigh 5 cm	100	97.1 (94.9-97.6)	*	93.0 (90.2-95.2)	*
	Lower leg	100	97.0 (95.9-98.4)	*	94.5 (92.9-96.8)	*
ADL- dependent n = 10	Upper limb	100	100 (100-100)		98.9 (96.6-100)	*
	Thigh 15 cm	100	98.1 (97.3-100)		97.6 (96.4-99.4)	*
	Rt Thigh 10 cm	100	98.7 (98.4-100)		98.4 (96.5-100)	*
	Thigh 5 cm	100	99.3 (96.9-100)		97.0 (96.2-100)	*
	Lower leg	100	100 (96.7-100)		97.1 (95.9-100)	*
	Upper limb	100	100 (100-100)		100 (96.3-100)	*
	Thigh 15 cm	100	97.3 (95.6-100)	*	96.5 (94.8-98.5)	*
	Lt Thigh 10 cm	100	100 (97.7-100)		97.8 (96.8-100)	*
	Thigh 5 cm	100	100 (99.0-100)		99.1 (96.9-100)	*
	Lower leg	100	100 (96.8-100)		97.2 (96.0-100)	*

*: $p < 0.05$ versus baseline

Upper limb: upper limb circumference at the midpoint of the upper limb between the acromion and olecranon

Thigh 5 cm: thigh circumference at point 5 cm proximal to the superior pole of the patella

Thigh 10 cm: thigh circumference at point 10 cm proximal to the superior pole of the patella

Thigh 15 cm: thigh circumference at point 15 cm proximal to the superior pole of the patella

Lower leg: maximal circumference in lower leg

Rt: right, Lt: left

Table 3: Fluid balance in both the ADL-independent group and the ADL-dependent group

	ADL- independent n = 31	ADL- dependent n = 10	<i>p</i>
0-72 hours (mL)	1260 ± 4039	2511 ± 2517	.364
72-144 hours (mL)	-74 ± 2797	479 ± 1954	.565

Table 4: The influence of fluid balance on the chronological change of the limb circumferences in the ADL-independent group

		144 hours fluid balance in ICU (mean \pm SD) (%)			between groups
		minus balance n = 11	0-5000 mL n = 13	over 5000 mL n = 7	
right	Upper limb	98.4 \pm 1.75	99.1 \pm 1.60	98.6 \pm 1.77	n.s
	Thigh 15 cm	89.4 \pm 3.32	91.2 \pm 3.32	90.5 \pm 4.34	n.s
	Thigh 10 cm	91.8 \pm 4.18	93.1 \pm 3.81	91.3 \pm 4.73	n.s
	Thigh 5 cm	91.8 \pm 3.83	94.4 \pm 3.05	91.5 \pm 3.71	n.s
	Lower leg	93.0 \pm 3.75	94.6 \pm 3.50	94.9 \pm 3.18	n.s
left	Upper limb	98.5 \pm 1.82	98.8 \pm 1.59	99.5 \pm 1.30	n.s
	Thigh 15 cm	90.2 \pm 2.76	90.3 \pm 3.63	91.6 \pm 3.58	n.s
	Thigh 10 cm	91.3 \pm 3.35	93.0 \pm 3.64	91.8 \pm 6.25	n.s
	Thigh 5 cm	92.4 \pm 3.52	94.0 \pm 3.70	92.0 \pm 3.48	n.s
	Lower leg	94.2 \pm 2.87	94.1 \pm 3.58	93.6 \pm 3.61	n.s

n.s: not significant

Upper limb: upper limb circumference at the midpoint of the upper limb between the acromion and olecranon

Thigh 5 cm: thigh circumference at point 5 cm proximal to the superior pole of the patella

Thigh 10 cm: thigh circumference at point 10 cm proximal to the superior pole of the patella

Thigh 15 cm: thigh circumference at point 15 cm proximal to the superior pole of the patella

Lower leg: maximal circumference in lower leg

Table 5: The influence of age on the chronological change of the limb circumferences in the ADL-independent group

		group of age (mean \pm SD) (years)				between groups
		under 51 n = 9	51–64 n = 7	65–74 n = 9	over 74 n = 6	
right	Upper limb	99.2 \pm 1.22	99.2 \pm 1.26	98.0 \pm 1.95	98.6 \pm 2.15	n.s
	Thigh 15 cm	91.4 \pm 4.06	90.1 \pm 3.86	90.4 \pm 3.78	89.3 \pm 2.10	n.s
	Thigh 10 cm	92.7 \pm 4.53	93.2 \pm 5.06	91.6 \pm 4.00	91.3 \pm 2.72	n.s
	Thigh 5 cm	93.0 \pm 4.18	94.6 \pm 4.30	91.6 \pm 3.02	92.2 \pm 2.65	n.s
	Lower leg	95.2 \pm 3.12	93.5 \pm 4.81	94.3 \pm 3.10	92.9 \pm 3.34	n.s
left	Upper limb	99.4 \pm 1.20	99.2 \pm 1.29	98.0 \pm 1.95	98.9 \pm 1.79	n.s
	Thigh 15 cm	91.3 \pm 3.73	91.6 \pm 2.69	89.9 \pm 2.67	89.2 \pm 4.03	n.s
	Thigh 10 cm	93.8 \pm 3.19	91.9 \pm 5.84	91.5 \pm 3.63	90.6 \pm 4.27	n.s
	Thigh 5 cm	93.8 \pm 2.20	94.0 \pm 4.73	92.7 \pm 3.93	90.8 \pm 2.95	n.s
	Lower leg	95.1 \pm 2.53	93.6 \pm 3.63	93.9 \pm 2.93	93.1 \pm 4.51	n.s

n.s: not significant

Upper limb: upper limb circumference at the midpoint of the upper limb between the acromion and olecranon

Thigh 5 cm: thigh circumference at point 5 cm proximal to the superior pole of the patella

Thigh 10 cm: thigh circumference at point 10 cm proximal to the superior pole of the patella

Thigh 15 cm: thigh circumference at point 15 cm proximal to the superior pole of the patella

Lower leg: maximal circumference in lower leg

Table 6: Demographic information and baseline characteristics at the admission to ICU in both the control group and the ARH intervention group

	control (n = 31)	intervention (n = 31)	<i>P</i>
Age	60.1 ± 15.5	65.4 ± 17.5	.215
Sex- male (no. and %)	22 (70 %)	17 (54 %)	.189
SOFA SCORE	7.42 ± 4.05	6.03 ± 3.6	.413
BMI	21.4 ± 3.57	22.6 ± 3.78	.178
Surgical patient (no. and %)	11 (35 %)	15 (52 %)	.303
Mechanical ventilation (no. and %)	27 (87 %)	21 (67 %)	.068
Diagnoses (no.)			.254
Heart failure	2	4	
Pneumonia	4	1	
CPA recover	6	1	
Sepsis	1	3	
Living donor liver transplantation	1	3	
Subarachnoid hemorrhage	2	1	
Myasthenia gravis	2	1	
Respiratory failure	3	0	
Angina pectoris	1	1	
Fulminant hepatitis	1	1	
Gastrointestinal hemorrhage	0	2	
Aortic dissection Stanford A	0	2	
Myocarditis	1	0	
Inhalation injury	1	0	
Atrial tumor	1	0	
Traumatic subarachnoid hemorrhage	1	0	
Pelvic fracture (conservative therapy)	1	0	
Brain stem hemorrhage	1	0	
Drug overdose	1	0	
Pancreatic cancer	1	0	
Subdural hematoma	0	1	
Colon cancer	0	1	
Aortic valve stenosis	0	1	
Infective endocarditis	0	1	
Cerebral infarction	0	1	
Descending aortic aneurysm rupture	0	1	
Consciousness disorder	0	1	
Hemoptysis	0	1	
Endometrial sarcoma	0	1	
Cholecystolithiasis	0	1	
Renal hemangioma rupture	0	1	

BMI: body mass index, SOFA: sequential organ failure assessment, ICU: intensive care unit, CPA: cardiopulmonary arrest.

Table 7: Fluid balance in both the control and the intervention group

n = 31	control (mL)	intervention (mL)	<i>p</i>
0-72 hours	1260 ± 4039	2077 ± 3772	.414
72-144 hours	-74 ± 2797	-508 ± 881	.074

Table 8: The relative value of the limb circumference compared with that of baseline at 72 and 144 hours after ICU admission between the control and the ARH intervention group

			0 hour	72 hours	144 hours	
right	Upper limb	control	100 (100-100)	100 (99.1-100)	100 (97.5-100)	n.s
		intervention	100 (100-100)	100 (100-100)	100 (100-100)	
	Thigh 15 cm	control	100 (100-100)	95.1 (91.9-95.9)	90.2 (87.7-93.6)	*
		intervention	100 (100-100)	97.7 (97.5-98.7)	97.5 (95.6-97.7)	
	Thigh 10 cm	control	100 (100-100)	96.0 (94.2-97.6)	93.1 (90.0-95.4)	*
		intervention	100 (100-100)	97.5 (97.3-97.9)	97.2 (95.0-97.6)	
	Thigh 5 cm	control	100 (100-100)	97.3 (94.2-98.1)	92.6 (91.1-95.3)	*
		intervention	100 (100-100)	97.6 (97.2-99.4)	97.3 (94.8-97.7)	
	Lower leg	control	100 (100-100)	97.2 (95.9-98.4)	94.7 (92.4-96.2)	*
		intervention	100 (100-100)	97.0 (96.6-99.2)	96.9 (95.7-97.9)	
left	Upper limb	control	100 (100-100)	100 (100-100)	100 (98.0-100)	n.s
		intervention	100 (100-100)	100 (97.9-100)	100 (96.7-100)	
	Thigh 15 cm	control	100 (100-100)	95.5 (92.7-96.9)	89.7 (88.6-92.2)	*
		intervention	100 (100-100)	97.7 (97.5-98.7)	97.5 (95.5-97.7)	
	Thigh 10 cm	control	100 (100-100)	95.6 (94.7-97.8)	92.4 (89.5-95.6)	*
		intervention	100 (100-100)	97.5 (96.5-99)	97.0 (95.0-97.7)	
	Thigh 5 cm	control	100 (100-100)	97.1 (94.9-97.6)	93.0 (90.2-95.2)	*
		intervention	100 (100-100)	97.6 (97.2-99.4)	97.3 (94.8-99.3)	
	Lower leg	control	100 (100-100)	97.0 (95.9-98.4)	94.5 (92.9-96.8)	*
		intervention	100 (100-100)	97.0 (96.7-98.5)	96.9 (95.9-97.3)	

*: $p < 0.01$ n.s: not significant

Upper limb: upper limb circumference at the midpoint of the upper limb between the acromion and olecranon

Thigh 5 cm: thigh circumference at point 5 cm proximal to the superior pole of the patella

Thigh 10 cm: thigh circumference at point 10 cm proximal to the superior pole of the patella

Thigh 15 cm: thigh circumference at point 15 cm proximal to the superior pole of the patella

Lower leg: maximal circumference in the lower leg

Figure 1: Measurement sites

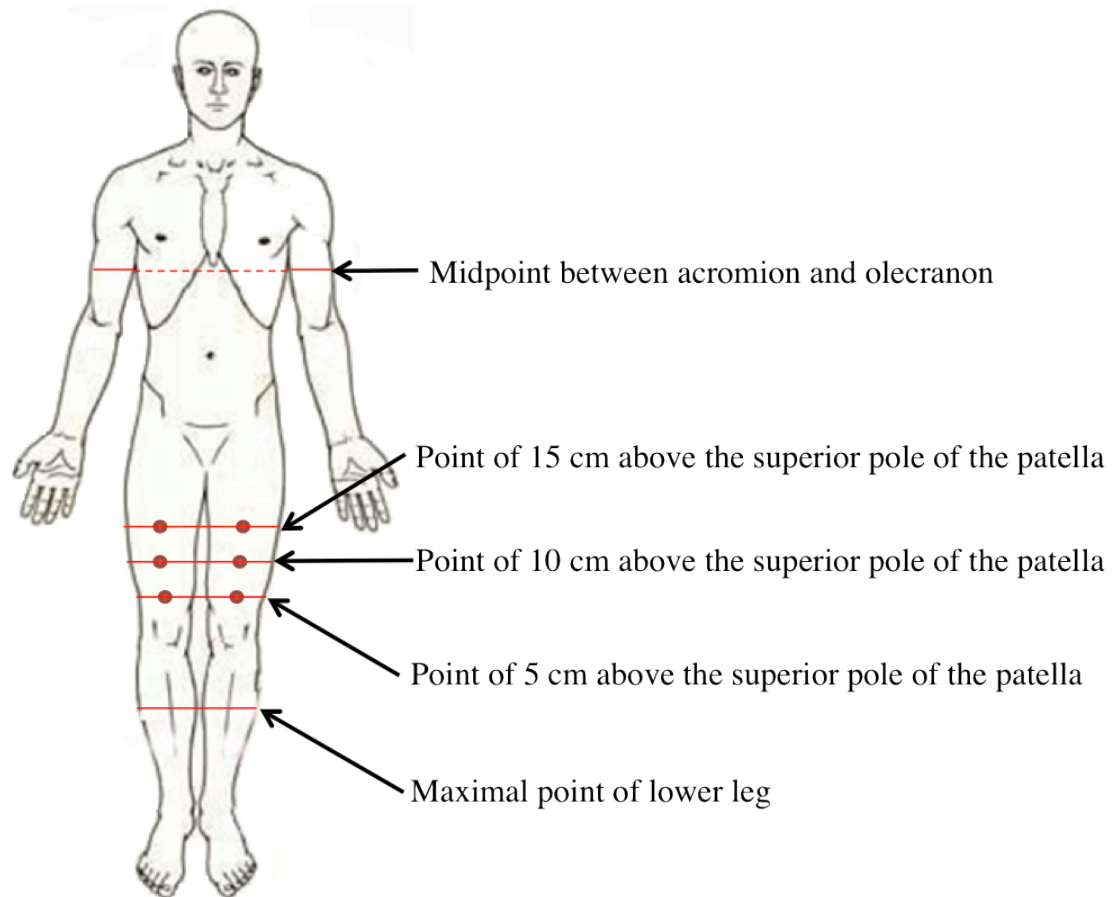


Figure 2-a: The relative value of the limb circumference in right sides in the ADL-dependent group after 72 hours ICU admission

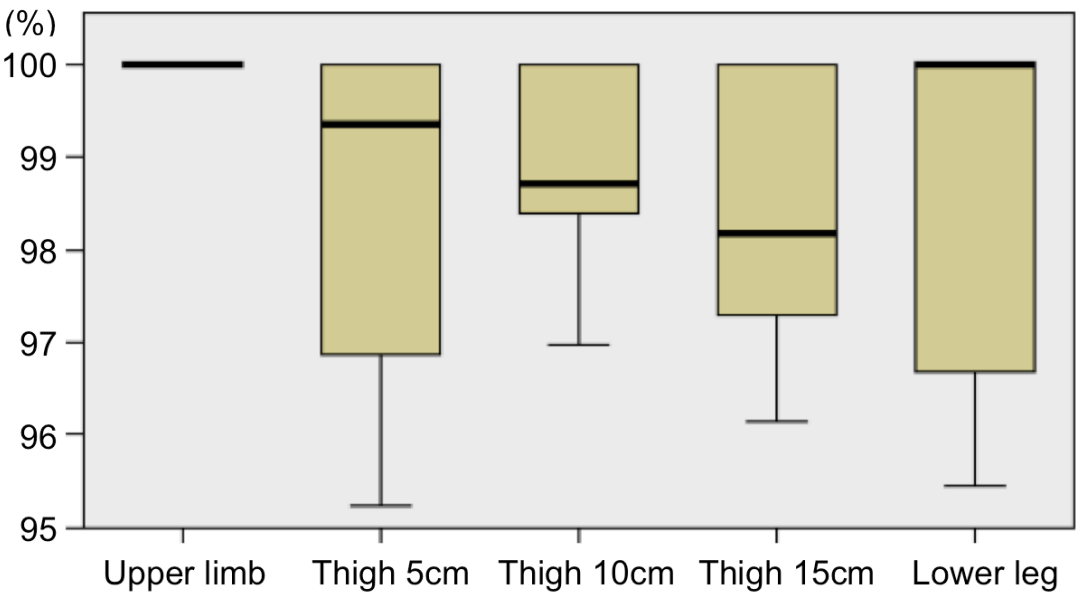


Figure 2-b: The relative value of the limb circumference in right sides in the ADL-dependent group after 144 hours ICU admission

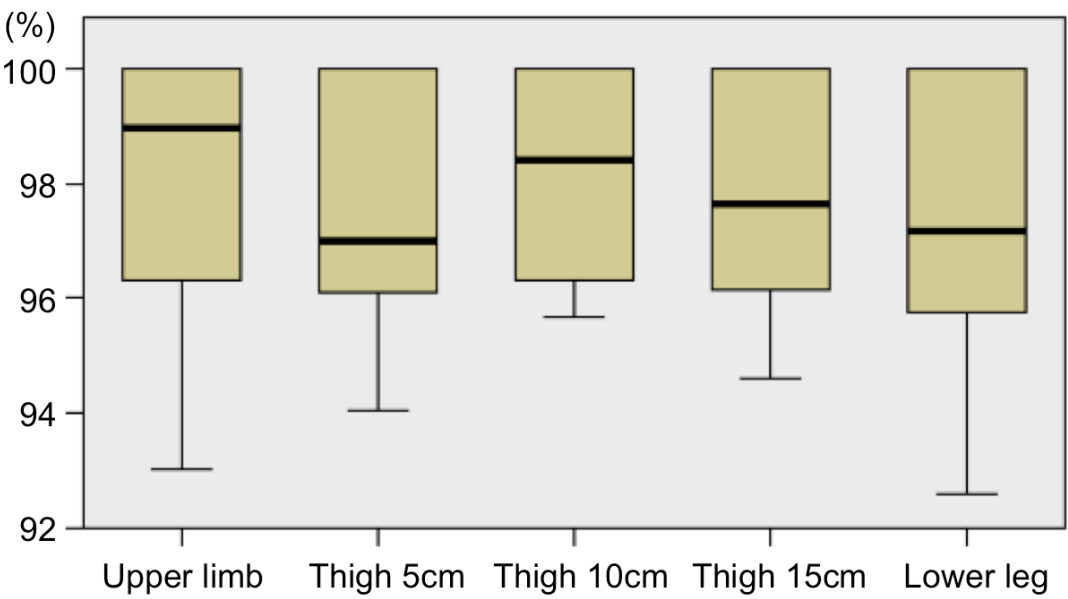


Figure 2-c: The relative value of the limb circumference in left sides in the ADL-dependent group after 72 hours ICU admission

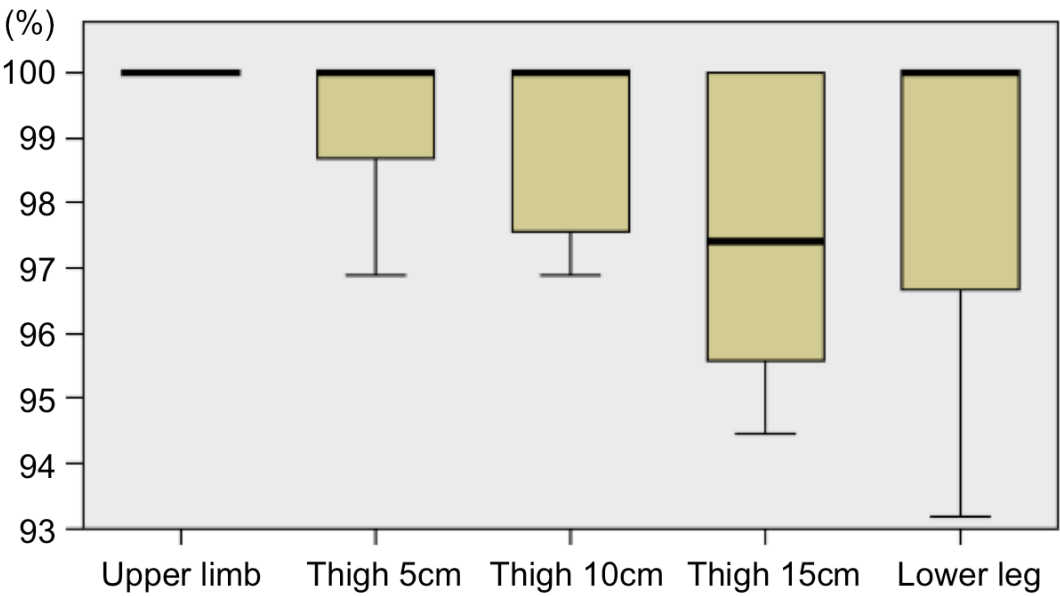


Figure 2-d: The relative value of the limb circumference in left sides in the ADL-dependent group after 144 hours ICU admission

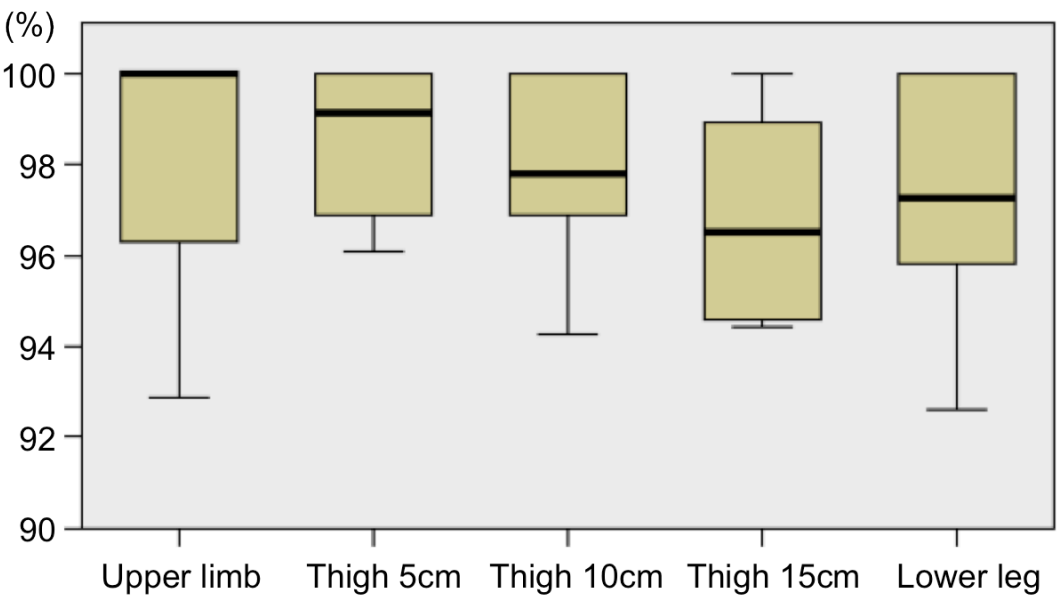


Figure 2-e: The relative value of the limb circumference in right sides in the ADL-independent group after 72 hours ICU admission

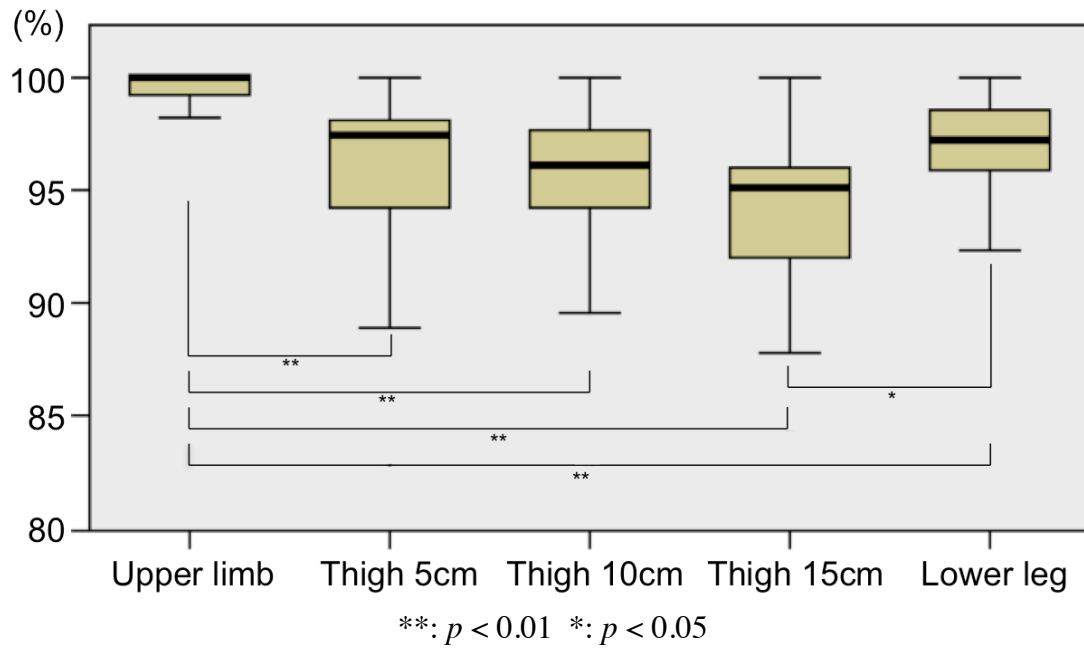


Figure 2-f: The relative value of the limb circumference in right sides in the ADL-independent group after 144 hours ICU admission

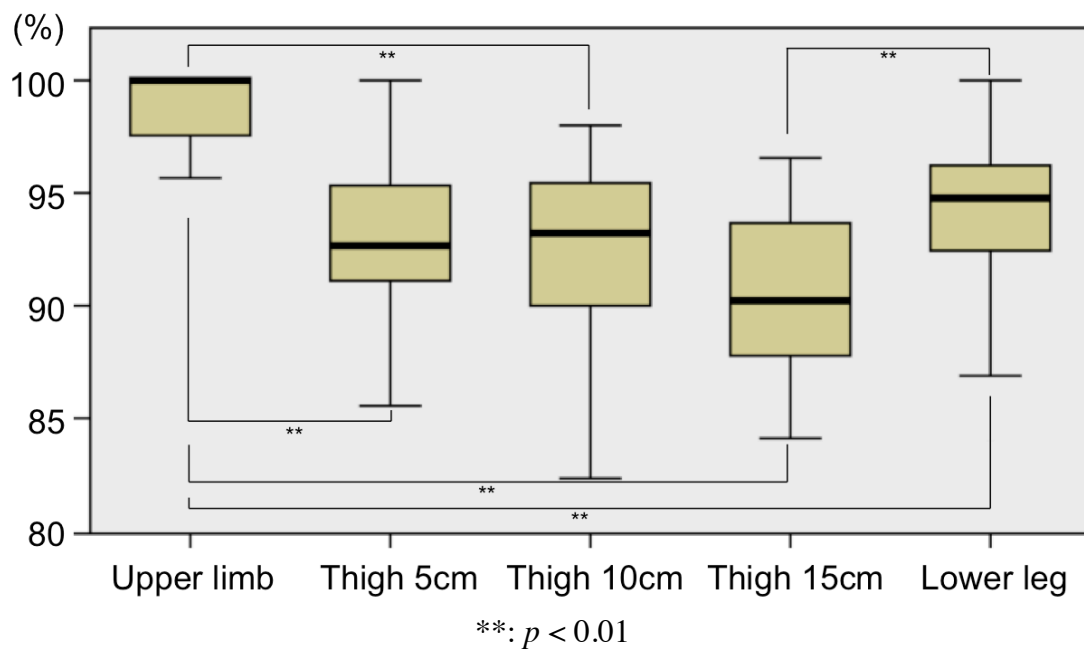


Figure 2-g: The relative value of the limb circumference in left sides in the ADL-independent group after 72 hours ICU admission

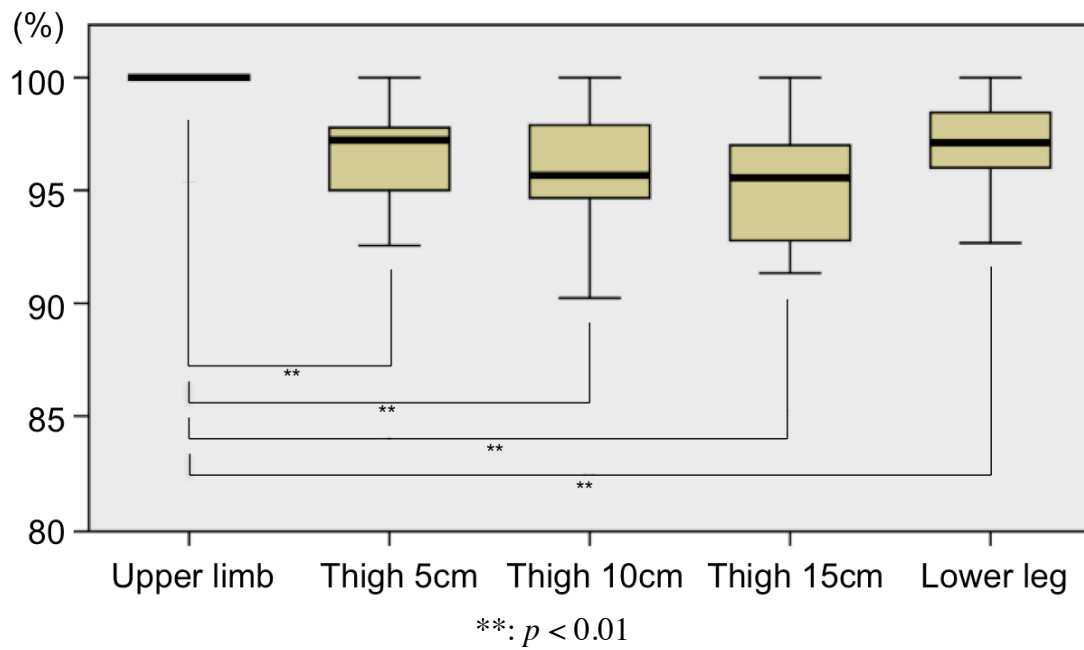
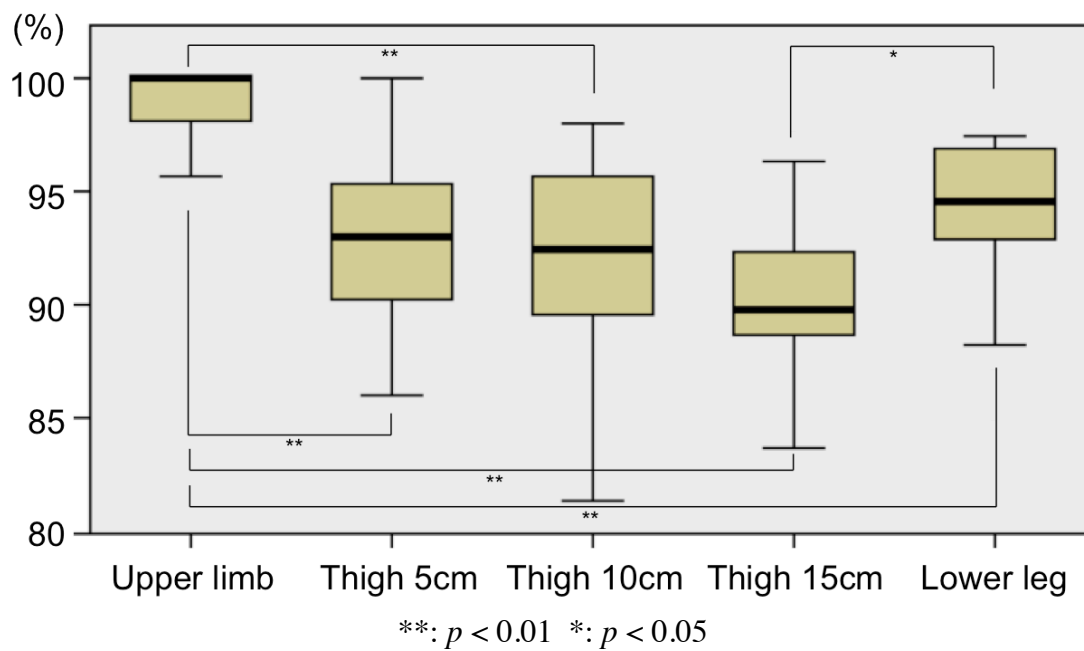


Figure 2-h: The relative value of the limb circumference in left sides in the ADL-independent group after 144 hours ICU admission



The relative value of the limb circumference to the baseline at 72 and 144 hours after ICU admission were compared between each 5 different sites in both right and left sides in the ADL-dependent group (a-d) and the ADL-independent group (e-h); a, e: right side at 72 hours, b, f: right side at 144 hours, c, g: left side at 72 hours, d, h: left side at 144 hours. The relative value to the baseline was described as the percentage regarding the baseline as 100%. While the relative values of the limb circumference in 4 sites of lower limbs were decreased significantly compared to that of upper limb both at 72 and 144 hours in the ADL-independent group, there were no significant differences between 5 different sites both at 72 and 144 hours in the ADL-dependent group. The decrease was noticeable in the thigh 15 cm above the superior pole of the patella in the ADL-independent group.

Upper limb: upper limb circumference at the midpoint of the upper limb between the acromion and olecranon

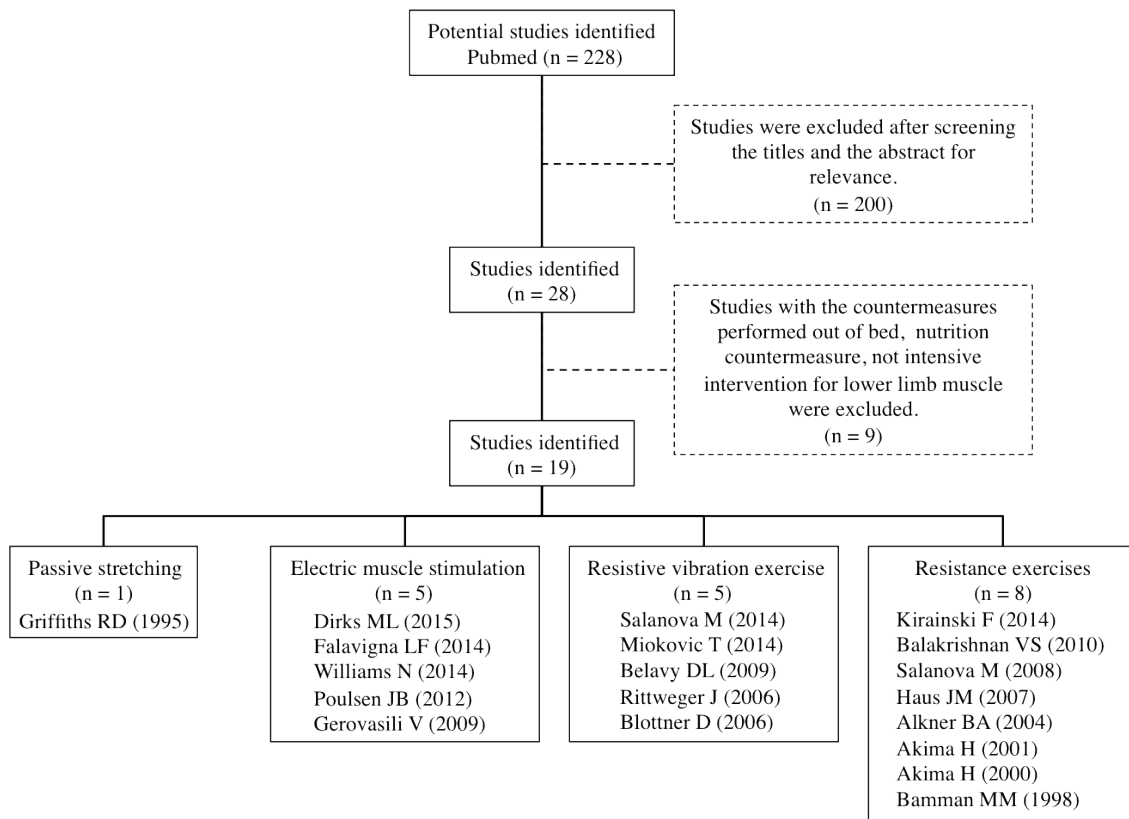
Thigh 5 cm: thigh circumference at point 5 cm proximal to the superior pole of the patella

Thigh 10 cm: thigh circumference at point 10 cm proximal to the superior pole of the patella

Thigh 15 cm: thigh circumference at point 15 cm proximal to the superior pole of the patella

Lower leg: maximal circumference in the lower leg

Figure 3: Flow chart of the study identification for the countermeasure selection



Two hundred and twenty eight studies were identified in PubMed (Issue 21st Feb 2015). Twenty-eight studies were examined for the eligibility after screening of titles and abstracts. Finally, 19 studies were identified to be relevant to the intervention to prevent the lower-limb muscle atrophy in the ICU with 4 types of the countermeasures; passive stretching (n = 1), electric muscle stimulation (n = 5), resistive vibration exercise (n = 5) and resistance exercises (n = 8).

The flowchart illustrates the progression of a patient from ICU admission to the General ward. The levels are defined as follows:

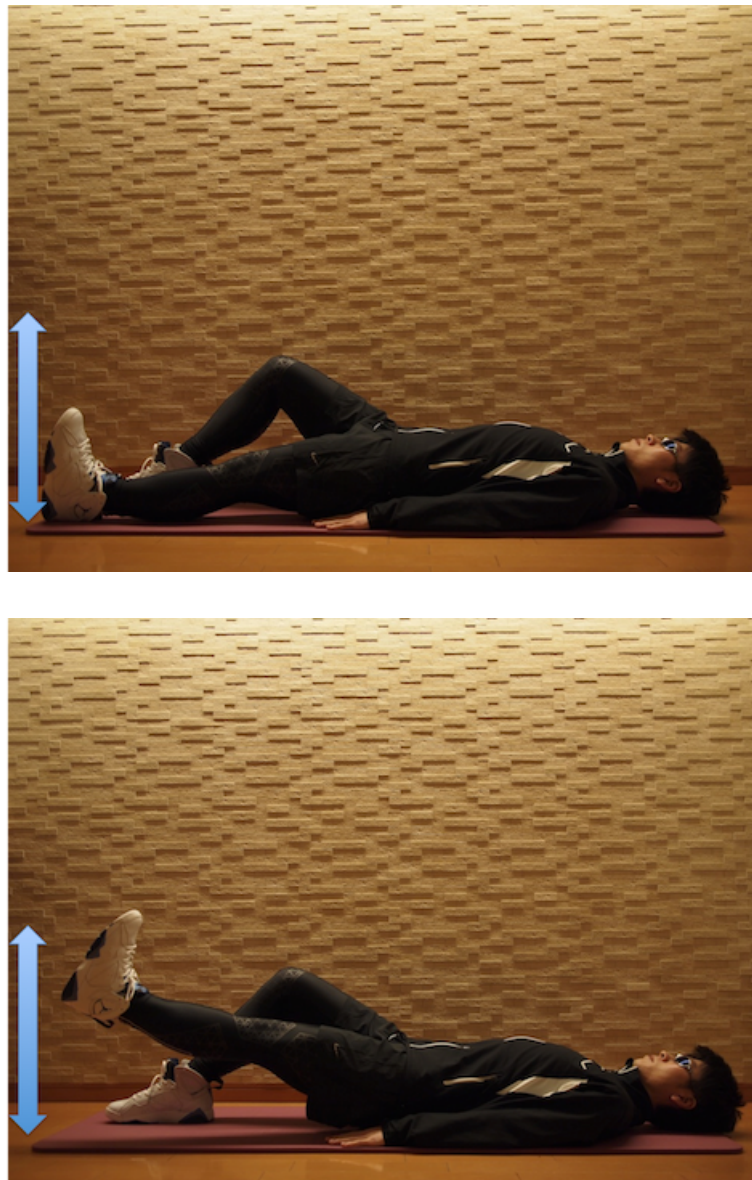
Level	Consciousness	Head Position	Resistance Exercise	ROM	Other
Level 0	Unconscious	Head up 0°		Functional position	
Level I+	Conscious	Head up 45°	Resistance exercise	AROM, PROM	
Level II+	Conscious	Sitting position	Resistance exercise	AROM, PROM	Can move arm against gravity
Level III	Conscious	Sitting on edge	Resistance exercise	AROM	Can move leg against gravity
Level IV	Conscious	Wheelchair	Resistance exercise	AROM	
Level V	Conscious	stand & step	Resistance exercise	AROM	Can keep standing and stepping
Level VI	Conscious	Ambulation	Resistance exercise	AROM	
Level I-	Unconscious	Head up 45°		PROM	
Level II-	Unconscious	Sitting position		PROM	

Progression: Level 0 → Level I+; Level I- and Level II- → Level I+; Level I+ → Level II+ → Level III → Level IV → Level V → Level VI. A large arrow at the bottom points to 'General ward'.

AROM: active range of motion exercise

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Figure 5: SLR



This exercise targets on quadriceps. To perform this exercise, patients attempt to straighten their knee by tightening their thigh. Once patients have the thigh muscle tighten, patients raise the entire leg slowly up to their foot 10 inches. Then patients lower the leg and relax the thigh muscle. It is important to relax the thigh between repetitions so that patients get good at illuming their thigh muscle on and off. Preferably patients repeat this exercise 10 times per set and 3 sets per day in both right and left side. patients do not have to be like this posture in the figure above for this exercise. patients can also head-up and perform this exercise.

Figure 6: quad-set



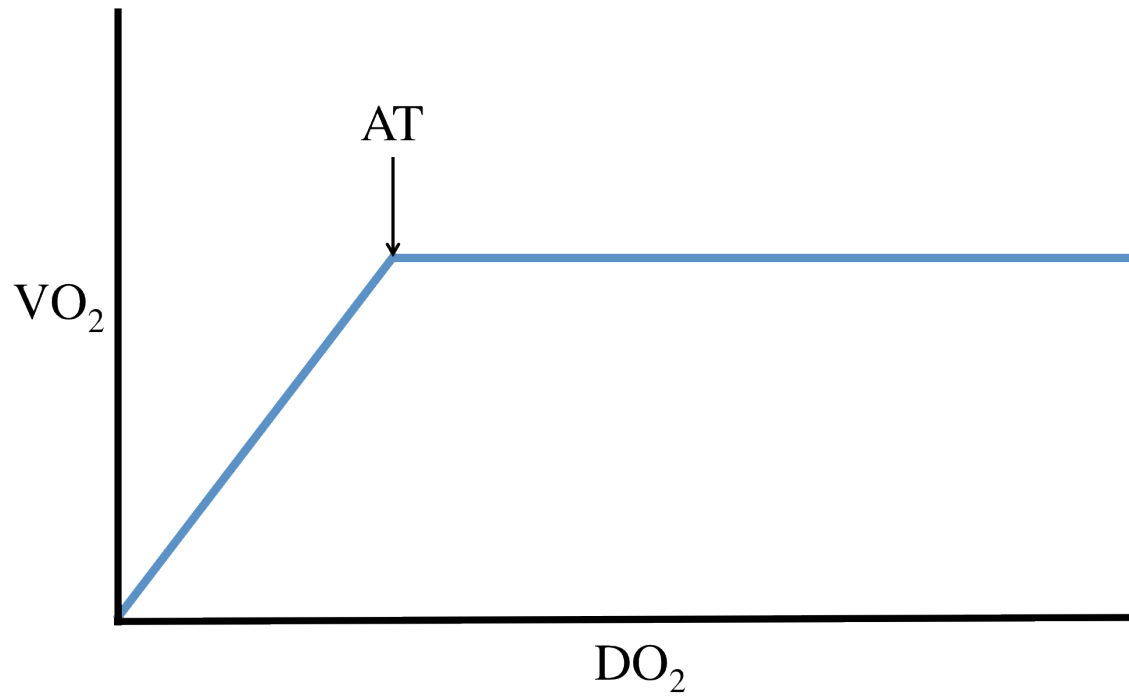
This exercise targets on quadriceps. To perform this exercise, patients place a towel roll under their knee, attempt to straighten their knee and push down the towel roll by tightening their thigh. Once patients have the thigh muscle tighten, patients tighten as hard as they can and hold for 10 seconds. Then patients relax the thigh muscle. It is important to relax the thigh between repetitions so that patients get good at illuming their thigh muscle on and off. Preferably patients repeat this exercise 10 times per set and 3 sets per day in both right and left side if patients cannot perform SLR with any reasons. patients do not have to be like this posture in the figure above for this exercise. patients can also lie down and perform this exercise.

Figure 7: ankle-pump



This exercise targets on triceps surae. To perform this exercise, patients have to keep their leg flat on the bed as shown in the figure. Patients usually use the low bounding pillow or positioning pillow set against their foot soles, and push down the pillow when they perform the plantar flexion to stimulate the triceps surae. Once patients have the triceps surae contracted, patients hold their foot position for 1 second. Then, patients dorsiflex their foot joints. Preferably patients repeat this exercise 10 times per set and 3 sets per day in both right and left side. Patients do not have to keep their posture as shown in the figure during their exercise. Patients can also lie down and perform this exercise.

Figure 8: Oxygen delivery-consumption balance and AT

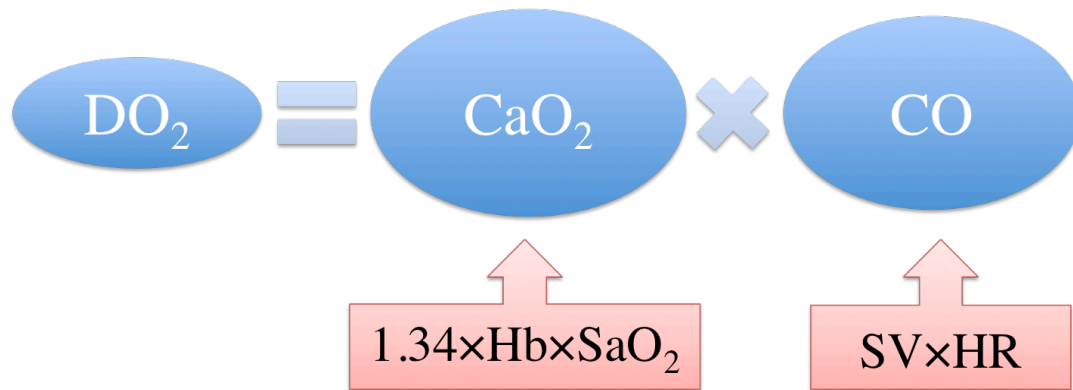


DO_2 : oxygen delivery

VO_2 : oxygen consumption

AT: anaerobic threshold

Figure 9: Oxygen delivery equation



DO_2 : oxygen delivery

CaO_2 : arterial oxygen content

Hb: hemoglobin

SaO_2 : arterial blood oxygen saturation

CO: cardiac output

SV: stroke volume

HR: heart rate

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