ADEQUATE CALORIES REDUCE SARCOPERIA

(AdCaloReS)

DR. GAITHRIDEVI V.SINGAM

DISSERTATION SUBMITTED IN FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF ANAESTHESIOLOGY

FACULTY OF MEDICINE

UNIVERSITY OF MALAYA

KUALA LUMPUR

2017

UNIVERSITY OF MALAYA

ORIGINAL LITERARY WORK DECLARATION

Name of Candidate: GAITHRIDEVI V.SINGAM

(I.C/Passport Number: [redacted])

Registration/Matriculation Number: MGE130030

Name of Degree: Master of Anaesthesiology

Title of Project Paper/Research Report/Dissertation/Thesis ("this Work"):

Adequate Calories Reduce Sarcopenia (AdCaloReS)

Field of Study:

I do solemnly and sincerely declare that:

(1) I am the sole author/writer of this Work;
(2) This Work is original;
(3) Any use of any work in which copyright exists was done by way of fair dealing and for permitted purposes and any excerpt or extract from, or reference to or reproduction of any copyright work has been disclosed expressly and sufficiently and the title of the work and its authorship have been acknowledged in this Work;
(4) I do not have any actual knowledge nor do I ought reasonably to know that the making of this work constitutes an infringement of any copyright Work;
(5) I hereby assign all and every rights in the copyright to this Work to the University ofMalaya ("UM"), who henceforth shall be owner of the copyright in this Work and that any reproduction or use in any form or by any means whatsoever is prohibited without the written consent of UM having been first had and obtained;
(6) I am fully aware that if in the course of making this Work I have infringed any copyright whether intentionally or otherwise, I may be subject to legal action or any other action as may be determined by UM.

Candidate's Signature [redacted] Date 28/3/17

Subscribed and solemnly declared before,

Witness's Signature [redacted] Date 28/3/17

Name:

Designation: Associate Professor Vinaya Rai A/L Mohanmet Rai

ABSTRACT

Objective: To evaluate the effect of using daily indirect calorimetry (IC) in determination of the resting energy expenditure (REE) of the patient and achieving the required calories versus standard protocol. To determine the energy balance achieved using IC versus standard protocol. To evaluate the correlation between energy balance and the quadriceps muscle layer thickness (QMLT) between both groups. To determine the protein balance vs the QMLT. To evaluate the correlation between the protein balance and QMLT.

Methods: A total of 30 mechanically ventilated patients who were within 48 hours of ICU stay with an expected stay of more than 10 days and had no contraindication to enteral nutrition were included in this study. This was a prospective randomized study with one group receiving standard enteral nutrition protocol and one group receiving enteral nutrition as per guided by IC REE. Both these groups of patients had a 10 day study protocol which included the measurement of REE using IC and the QMLT measurement on day one, day five and day ten.

Results: There appeared to be no significant difference between both the control and the interventional arm in terms of caloric and protein prescription and delivery, caloric and protein balance and a correlation between caloric and protein balance with measurement of QMLT.

Conclusion: Feeding using standard protocol appears to be as effective in caloric delivery compared to IC but a larger sample size might be necessary to be able to achieve a significant result.

Key words: Indirect Calorimetry (IC), Resting Energy Expenditure (REE), Quadriceps Muscle Layer Thickness (QMLT).

ACKNOWLEDGEMENT

I extend my heartfelt gratitude to Associate Professor Vineya Rai, consultant Anaesthetist who is also my supervisor for all his time, effort and guidance. I would also like to extend my gratitude to Associate Professor Shahnaz,Consultant Anaesthetist for all his timely guidance in my thesis preparation.

I also thank patients and their families who participated in this study, as well as my friends, colleagues and staff who provided assistance during the completion of this study.

My sincere appreciation to Ms Tah Pei Chien from the department of dietetics, University Malaya for all her invaluable help in diligently performing the indirect calorimetry in my patients. Special mention to Mr. Mohammad Irfan, Research Assisstant at University Malaya for helping out with the statistical analysis of my raw data and also to Mdm Mazuin Kamarul Zaman who helped out with data collection and ancillary help throughout this journey.

Finally, I am indebted to my family for their constant support and encouragement throughout my pursuit of this research.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS AND ABBREVIATION

REE	Resting energy expenditure
IC	Indirect calorimetry
QMLT	Quadriceps muscle layer thickness
EN	Enteral nutrition
PN	Parenteral nutrition
RF	Rectus femoris
CSA	Cross sectional area
RCT	Randomised control trial
ICU	Intensive care unit
BW	Body weight
VO2	Maximum oxygen consumption
VCO2	Maximum carbon dioxide production

CHAPTER 1.0

INTRODUCTION

The difficulty to reach the prescribed calorie intake in the ICU can be attributed to cautious decision making in the early phase of stress or early postoperative state, gastroparesis, lack of normal gastric emptying process related to sepsis, treatment with noradrenaline or morphine derivatives, absence of protocols and trend for a decrease in parenteral nutrition prescription. This may induce an energy deficit that can cause an increase in number of ventilator days, mortality and morbidity in the ICU as many previous studies have shown.

No general amount can be recommended as Enteral Nutrition (EN) therapy has to be adjusted according to the progression/course of the disease and to gut tolerance. During the acute and initial phase of critical illness an exogenous energy supply in excess of 20–25kcal/kg BW/day may be associated with a less favorable outcome. During recovery (anabolic flow phase), the aim should be to provide 25–30 total kcal/kg BW/day.

There is general agreement that hyper-alimentation (provision of more energy than actually expended) should be avoided in the critically ill, although this has not yet been confirmed by randomized controlled trials. Even generally reported target values of 25–30 total kcal/kg BW/day for men and 20–25 total kcal/kg BW/day for women may be too much during the first 72–96 h of critical illness. A prospective observational cohort study on patients with an ICU length of stay of at least 96 h showed that patients who received only 33%–66% of the target energy intake had a significantly greater likelihood of being discharged from hospital alive than those who received 66%–100% of the targeted intake. The results are difficult to interpret as the severity of illness, the

incidence of undernutrition, and the length of stay in relation to the level of caloric feeding were not reported. Although this was not a randomised clinical trial, the results raise the same concern as those reported by Ibrahim et al and support the idea that, during the acute phase of critical illness, the provision of higher amounts of nutrients is associated with a less advantageous outcome. However, this is an area which is in particular need of prospective studies, since hypocaloric feeding in the initial phase of ICU-stay may or may not be a disadvantage for the patient. In particular, caution is warranted in patients with prior undernutrition. A recent trial has put emphasis on the relation between growing energy deficit and the number of complications. There seems to be a cut off of cumulated energy deficit (10,000 kcal) beyond which the complications increase (infections, wound healing). During stabilisation and recovery (anabolic flow phase) larger amounts of energy (25–30 total kcal/kg) are required to support the anabolic reconstitution.

With regards to determining energy needs in the critically ill patients, indirect calorimetry (IC) has been recommended to be used when available in the absence of variables that affect the efficacy of nutrition. Most clinicians use the simplistic weight-based equation (25-30 kcl/kg/d) to determine energy requirements limited by availability and cost. More than 200 predictive equations have been published in the literature, with accuracy rates ranging from 40% - 75% when compared to IC, and no single equation emerges as being more accurate in the ICU. The poor accuracy of predictive equations is related to many nonstatic variables affecting energy expenditure in the critically ill patient, such as weight, medications, treatments and body temperature. Achieving energy balance as guided by IC measurements compared with predictive equations may lead to more appropriate nutrition intake. While 2 RCTs with data from 161 patents showed that higher mean intake of energy and protein was provided in IC-directed protocol compared with controls whose nutrition therapy

directed by predictive equations, those studies had issues with study designs. In a study with burn patients, use of IC-directed nutrition therapy helped provide the minimal effective intake, avoiding the excesses of overfeeding seen in controls based on the Curreri formula. A second study in general ICU patients used both EN and parenteral nutrition (PN) to meet target energy goals determined by IC measurement or a weight based predictive equation. While the IC directed energy goal was no different from the value obtained from the predictive equation, the amount of energy and protein delivered to the IC group was higher and this led to a reduction in mortality and length of ventilator days (LOV). But this begs to a study to further reevaluate the importance of IC in terms of higher delivery of calories and thus leading to a reduction in LOV, length of ICU stay (LOS) and mortality in ICU.

Sarcopenia has currently been recognized as the new pandemic affecting critically ill patients. Sarcopenia can be defined as a condition characterized by loss of muscle mass and muscle strength. Although sarcopenia is a primarily a disease of the elderly, its development can be associated with conditions that are not exclusively seen in old adults, like starvation, malnutrition, bed rest, prolonged physical inactivity, denervation and critical illness. During metabolic stress, muscle protein is rapidly mobilized in order to provide the immune system, liver and gut with amino acids, especially glutamine.

The quadriceps muscle group is generally regarded as the site to be imaged as it is commonly associated with muscle atrophy in immobilization models, various disease states and critically ill patients. Thigh muscles also have excellent associations with measures of whole body muscle mass in healthy populations. The quadriceps muscle is an accessible landmark in immobile patients and have well-defined fascial borders for identification during analysis. The quadriceps group may also have greater implications compared with other muscle groups on clinical and functional outcomes for patients,

such as ICU length of stay and physical function at ICU discharge. Thickness of the quadriceps was chosen over the cross sectional area (CSA) in this study because of the ease of measurement on the ultrasound screen, and as the structure of the muscle begins to deteriorate, thickness may be more readily identifiable in comparison with cross sectional area.

The aim of our study is to perform a prospective, randomized, controlled, blinded study in critically patients to assess the necessity for measuring daily resting energy expenditure as a guide for nutritional support. Our hypothesis is that a targeted nutritional therapy using indirect calorimetry will reduce the incidence of the reduction of the quadriceps femoris muscle layer thickness in critically ill patients.

CHAPTER 2.0

LITERATURE REVIEW

Critical illness survivors state that muscle wasting and weakness are the greatest problems that they face. Both quality of life questionnaires and 6 minute walk tests have been used to objectively demonstrate that muscle weakness is the primary contributor to functional disability (Cheung, 2006; Cuthbertson, Roughton, Jenkinson, Maclennan, & Vale, 2010; Diaz-granados et al., 2011; Herridge et al., 2003; Myhren, Ekeberg, & Stokland, 2010; Roch et al., 2011). In fact, all patients with functional disability in Herridge *et al.'s* cohort reported muscle weakness as the primary cause of their disability (Diaz-granados et al., 2011; Herridge et al., 2003), a finding confirmed by other studies (Poulsen, Moller, Kehlet, & Perner, 2009). Rather than having a primary psychological or cardio-respiratory cause, increasing evidence suggests that skeletal muscle dysfunction plays an important role in the pathogenesis of post-critical care debility. Functional disability was objectively demonstrated in the Herridge *et al.'s* study, where 6 minute walk test distances rose to a maximum of 66% predicted at 1 year(Herridge et al., 2003). These patients had lost 18% of their base line body weight by discharge (more accurately, perhaps, they were at 82% of their baseline weight, with fluctuations after ICU discharge and before hospital discharge being unmeasured), with only 71% of patients recovering their baseline weight at 1 year. Investigators have examined the association between muscle weakness and clinical outcome measures, and have found muscle weakness to be an independent predictor of mortality associated with increased ventilator dependent time and length of stay (Ali et al., 2008; De Jonghe et al., 2007; Sharshar et al., 2009; van

der Schaaf, Beelen, Dongelmans, Vroom, & Nollet, 2009). Macfarlane *et al.*'s case report is often quoted as the first case of critical care myopathy (at that stage variably known as acute quadriplegic myopathy) (MacFarlane & Rosenthal, 1977).

The National Institute of Clinical Excellence (NICE) has recently issued guidance regarding critical illness rehabilitation (NICE, 2009). A major weakness in its evidence based guidance is the lack of basic understanding of the pathophysiology of muscle wasting (which the NICE authors acknowledge). NICE strongly recommends that research in this area should be prioritized. Very little work has been performed in the critical care setting examining the nutritional contribution to muscle mass maintenance as a primary aim, the focus has always been on survival, hampered yet again by the lack of objective tool to measure ICU-AW. But based on the evidence pointing towards a large discrepancy in the predictive equations available to calculate the energy requirements, in this study IC will be used as a tool to calculate REE in patients to tailor the patient's caloric intake and measurement of the QMLT using the ultrasound will help us correlate the energy supplementation with the muscle loss.

Many modalities of muscle mass testing have been utilized in the critically ill, but few have been validated. The most frequently used for the reasons of ease of use would be the non-invasive measurement modalities. Whilst these modalities are considered to be the gold standard for measurements of muscle mass, their use is limited in the critical care setting. Patient transfer (and its accompanying risks), expense and technical issues (radiation dose in the case of CT; problems with monitoring equipment and ventilator circuits for MRI) preclude their use in larger trials. One study has used computer tomography but the limited number involved (n=8) preclude meaningful interpretation (Poulsen et

al., 2011). Recent paper published in 2016 aimed to showcase that the measurement of quadriceps muscle layer thickness (QMLT) via ultrasound was able to identify critically ill patients with low muscularity (Paris et al., 2016). The study will also be then able to evaluate the validity and reliability of ultrasound protocol that can be used to estimate muscle mass in the ICU population and be able to demonstrate a critical comparison between ultrasound and CT analysis for muscle quantification in the ICU. The study found that there was modest correlation between CT measurements and QMLT analysis using ultrasound. It also found that there was significant absolute difference in muscle thickness observed between 2 observers using the ultrasound, thus recommending that a sole person performing ultrasound guided muscle layer thickness more reliable but less feasible. The study concluded with saying that ultrasound has great potential for identifying patients with low muscularity in the ICU but further protocols are required to validate its usage. Using ultrasound in the intensive care setting is appealing as it is cheap, portable and readily available. Rectus Femoris cross sectional area and muscle limb thickness (MLT) have both been used in the past (campbell iain, 1995; Gruther et al., 2008; Reid, Campbell, & Little, 2004; Seymour et al., 2009; Sipila & Suominen, 1991). RF_{CSA} correlates well with strength and Rectus Femoris muscle volume , and has good inter-rater reliability, meaning that data derived from cross-sectional area measurements are highly likely to have functional relevance (de Bruin, Ueki, Watson, & Pride, 1997; Mathur, Takai, Macintyre, & Reid, 2008; Seymour et al., 2009; Sipila & Suominen, 1991; Walton, Roberts, & Whitehouse, 1997).

More than 200 equations have been developed to predict resting energy expenditure (REE) of critically ill patients. These equations are generally based on weight, height, age and sex. In addition body temperature and minute volume are taken into consideration when the patient is ventilated. The resulting over or underestimation have been demonstrated at 40% leading to large errors in the evaluation of energy requirements. The energy expenditure during an ICU stay are dynamic and influenced by body temperature, level of nutritional support, presence of sepsis, level of sedation and therapies including physiotherapy and other invasive therapies. The Penn State University equation is the most accurate and precise predictor of REE in the critically ill patient and should be used on all ventilated patients when IC testing is not feasible. There are currently no recommendations for predicting REE in acutely ill, spontaneously breathing patients. Predictive equations can be used in conjunction with the A.S.P.E.N. guidelines of 20–35 kcal/kg/d in adults. In the obese patient, 11–14 kcal/kg actual body weight per day or 22–25 kcal/kg IBW is recommended (Singer & Singer, 2016).

Indirect calorimetry (IC) remains the gold standard for determination of caloric needs. IC calculates REE by measuring whole body oxygen consumption (VO2) and CO2 production (VCO2) [26,27]. It is estimated that approximately 80% of energy expenditure was due to oxygen consumption and 20% was due to carbon dioxide production (Singer & Singer, 2016). However, IC testing may not be practical for clinicians, because of associated time, costs, resources, personnel, and technical training. Even the ideal candidate may not be appropriate in view of air leaks or other technical factors that affect IC testing accuracy (Oshima et al., 2016). My study uses IC as a tool for REE estimation and feeding as per obtained REE and thus aims to compare standard feeding protocols applied in my local setting to IC in terms of caloric delivery and muscle mass correlation.

CHAPTER 3.0

METHODOLOGY

3.1 STUDY PARTICIPANTS AND STUDY DESIGN

This was a prospective randomized single-blinded study with a target sample size of 30 patients. The hospital ethics committee approval was obtained. There was a standard inclusion and exclusion criteria set for the study.

Inclusion criteria

1. Mechanically-ventilated adults (Male or Female) admitted to general ICU within the first 48 hours of ICU admission.
2. Expected to be mechanically ventilated for at least 3 days.
3. Age ≥ 18 years; no upper age limit
4. Expected stay in ICU> 5 days
5. Medical and abdomino/thoracic surgery patients, as well as multiple trauma patients with Glasgow Coma Score ≥ 10.

Exclusion criteria

1. Pregnancy.
2. DNR order.
3. Readmission in the ICU during the same hospitalization/ transfer from other ICU.
4. Admission for postoperative monitoring.
5. Aerosolization with nitric oxide or heliox, tracheal insufflations or visible leaks in chest drainage system.
6. FiO2 > 80% or patients requiring prone position
7. Chronic/ acute liver failure: Child-Pugh class C
8. Brain injury for various reasons with Glasgow Coma Scale below 10.

9. Contra indication to use enteral nutrition.

Withdrawal criteria

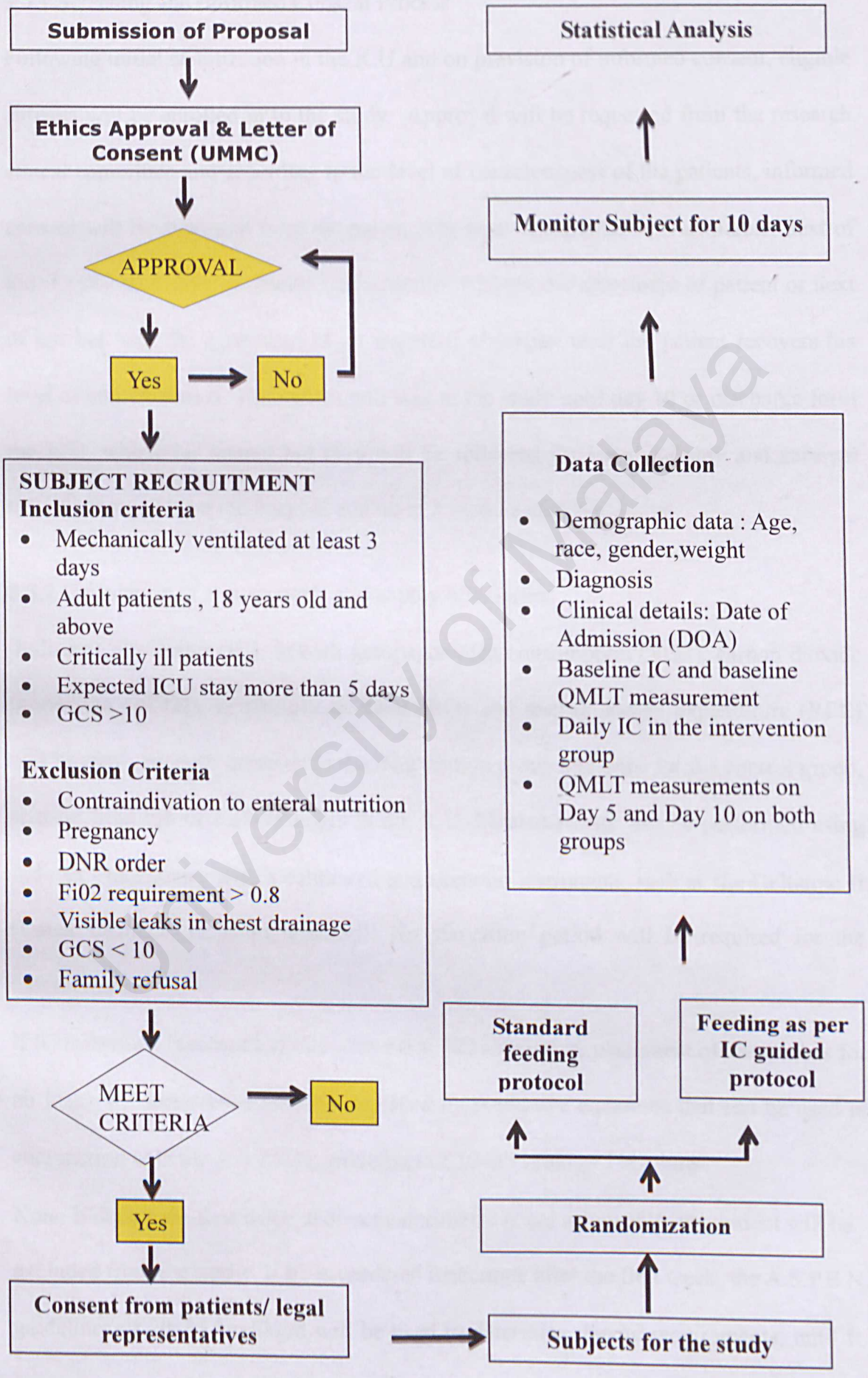
1. Daily energy requirements over 4500kcal.

2. If during the first week, indirect calorimetry is not achievable.

3. Subject withdraws consent.

3.2 RANDOMIZATION AND BLINDING

Figure 3.1: Study flowchart



3.3 STUDY PROTOCOL

Procedures

3.3.1 Screening and Informed Consent Process

Following initial stabilization in the ICU and on prevision of informed consent, eligible patients will be enrolled in to the study. Approval will be requested from the research ethical committee and according to the level of consciousness of the patients, informed consent will be requested from the patient, the legal representative if available, next of kin if valid according to country legislation or without the agreement of patient or next of kin but with the agreement of an impartial physician until the patient recovers his level of consciousness. The patient will stay in the study until day 10 or discharge form the ICU, whichever sooner but they will be followed for length of stay and survival until discharged from the hospital and up to 3 months after admission.

3.3.2 Calculation of requirements and supply of calories:

Indirect Calorimetry (IC): In both groups, oxygen consumption (VO2), carbon dioxide production (VCO2), respiratory quotient (RQ) and resting energy expenditure (REE) will be assessed, each morning in the intervention group and once for the control group, starting from the first 24-48 hours in the ICU. Measurements will be performed using Indirect Calorimetry with a calibrated and accurate instrument, such as the Deltatrac II (Datex Ohmeda, Helsinki, Finland). No starvation period will be required for the measurement.

If IC is deemed inaccurate (FIO2 above 0.8, NO inhalation, placement of chest tubes for air leak), IC measurement will be replaced by predictive equations that can be used in conjunction with the A.S.P.E.N. guidelines of 20–35 kcal/kg/d in adults.

Note: If during the first week, indirect calorimetry is not achievable, the patient will be excluded from the study. If IC is rendered inaccurate after the first week, the A.S.P.E.N. guidelines of 20–35 kcal/kg/d will be used to determine energy requirements, until IC

can be resumed, and such patients will be included in final analysis.

3.3.3 Administration of caloric requirements

In the intervention group, ICU staff will strive to supply 100% of a patient's energy requirements (i.e. REE kcal/day) through artificial nutrition, preferably utilizing EN and including non nutritional calories.

Patients' caloric requirements will be defined as:

⇒ intervention group: IC REE

⇒ control group: "liberal ", i.e. according to local practice

Our local practice subscribes to the A.S.P.E.N. guidelines of 20–35 kcal/kg/d.

PN will be added if EN caloric supply is < 90% caloric requirements from day 2-3 onwards, as well as in other scenarios (discussed below). PN will be added in an amount to cover the difference between the measured energy expenditure and the amount of calories given enterally.

3.3.3.1 Via enteral route

In patients with a functional gastrointestinal tract, enteral feeding via a nasogastic tube will be started at 20 ml/hr and increased progressively every 4 hours to reach daily caloric requirements. A nutritional formula will be prescribed according to the unit routine, with a preference for polymeric formulas. However, high density nutrients will be preferred if high level of calories is required according to the measured energy expenditure or the predicted formulas.

The nutrition formula that will be used will be osmolite as a standard. If the patient is having difficult glycemic control, sugar > 15 for 3 consecutive reading while on insulin, to change feeds to glucerna.The nutritional formula will be delivered continuously, providing patient tolerance. The gastric residual volume should be measured every 6 hours (according to local normal practice) and the mode of feeding should be modified accordingly, if necessary:

⇒ Gastric residual volume > 500 mL, vomiting, diarrhea more than 3 times/day: Enteral feeding will be stopped and replaced by parenteral nutrition.

⇒ Gastric residual volume between 150 and 300 mL: Enteral feeding rate will be reduced and/or prokinetic therapy (metoclopramine 10 mg x 3/day)will be initiated. If the residual volume remains below 500 ml and > 90% of caloric needs are met by EN alone, this regimen

should be maintained. Protein supplementation was determined at 1.5g /kg/day for the patients in both arms of the study.

3.3.3.2 Via parenteral route Parenteral nutrition will be commenced, either as alone or supplementary nutritional support, if:

• A contraindication for EN is present on admission

• A contraindication for EN evolves during trial

• Gastric residual volume consecutively > 300 mL

• EN delivers (or is expected to deliver) ≤ 90% daily caloric requirements

Parenteral nutrition will be delivered continuously preferentially as an all in one bag Fresenius Kabiven. This bag contains: Alanine 6.48g,Arginine 5.5g, Glycine 5.1g, Histidine 1.3g, Isoleucine 2.3g, Leucine 3.3g, Lysine 3g as acetate, Sodium Acetate 1.6g, Methionine 1.9g, Phenylalanie 2.3g, Proline 5.1g, Serine 3g, Taurine 0.46g, Sodium glycero phosphate 1.9g, Tyrosine 0.17g, Threonine 2g, Tryptophan 0.91g, Calcium chloride 0.26g, Potassium chloride 2g,Zinc sulphate 0.006 g, Olive oil refined 10.1g, Soy bean oil refined 12.2g, Fish oil omega 3 6.1g, MCT 12.3 g, Amino acid 96g, Nitrogen 7.8g, Glucose 103g, Lipids 41g.

The control group will be managed by the patient's physician without intervention, according to "local" practice with the addition of protein at 1.5g/kg/day. The study group will be managed by the research team using indirect calorimetry. The use of PN will be at the physician discretion in the control group. In the study group, PN will be

prescribed to cover the needs, when enteral nutrition <90% of the measured requirements. Only in a minority of cases when IC is not achievable, the 25-30 ml/kcal/d energy calculation method will be used as a target for energy requirements. The route of feeding as well as its site will be recorded using a computerized system or a written order system for both enteral (NG, ND, NJ, PEG, or surgical gastrostomy or jejunostomy) and parenteral (central, PICC line or peripheral)

3.3.4 Daily monitoring

3.3.4.1 Daily energy expenditure and protein intake:

Energy expenditure will be measured/calculated, and recorded, as described above.

Energy intake (kCalories delivered) will be calculated and recorded on the CRF

And this will include energy supplemented from solutions such as colloids, and in sedation (propofol) in addition to the enteral and parenteral support if available. Protein intake will be recorded daily (prescribed and administered.)

3.3.5 Measurement of quadriceps muscle layer thickness

The sonosite ultrasound will be used to measure the quadriceps muscle layer thickness (QMLT). The ultrasound protocol used in this study was previously published and is feasible for application in critically ill patients.The thickness of the quadriceps musculature was quantified with a portable B-mode ultrasound device with a multifrequency linear transducer.

With the patient lying supine, knees extended and relaxed, the landmarks on each quadriceps were identified and marked with an indelible pen. The landmarks are on the anterior surface of the quadriceps from the midpoint between the anterior superior iliac spine and the upper pole of the patella.A water soluble transmission gel was applied to the probe, which was held perpendicular to the skin with the depth adjusted to image the femur.For the muscle thickness to be quantified, the use of calipers to be taken as the distance between the upper margin of the femur and the lower boundary of the rectus

femoris, incorporating both the rectus femoris and the vastus intermedialis. The imaging will be done twice and averaged across each leg and then between legs.

The imaging will be done on recruitment into the study (day 1), on day 5 and day 10.

The data will be recorded into the CRF.

3.3.6 At day 10/discharge from ICU

The average calories received by the patients in both the intervention group and control group will be tabulated and the energy balance quantified.

Ultrasound of the QMLT.

Updating of the CRF with the relevant information and proceed with data analysis.

3.4 DATA ANALYSIS

The primary outcomes of this study were to assess the feasibility of using indirect calorimetry (IC) and a direct comparison between IC and standard protocol in nutrition prescription and energy balance, a correlation between energy balance and the average measurement of quadriceps muscle layer thickness (QMLT) and a correlation between protein balance and the average measurement of QMLT. Descriptive statistics was presented as absolute numbers, percentages, median or mean ± standard deviation from data extracted from patients demographics. Statistical analysis were performed using SPSS version 24.0. T-test comparison of both groups were done and futher, correlation analysis were carried out using Pearson's chi-squared test and Fischer's exact test which were two-tailed and p-values less 0.05 were considered significant.

CHAPTER 4.0

RESULTS

The number of patients successfully included in this study was 30 in total, over a period of 6 months (June 2016 to December 2016). Patients were included in the study as per the inclusion and exclusion criteria. The included patients were subjected to a 10 day study where the intervention group had daily IC measurements done and the control group had baseline IC measurement but the standard feeding protocol was carried out. They also had ultrasound measurement of the QMLT done on day 1,5 and 10.

Out of 83 patients assessed for eligibility, only 38 patients were randomized using a computer generated randomization table. 40 patients were excluded as per the exclusion criteria and 5 patients had declined to participate. Out of the 38 patients randomized, 4 patients had to be excluded from participation in the study due to dying after randomization. 34 patients were then subjected to the study, but had a further 4 patients dropping out during the follow up, as 4 patients had discharged from the ICU prior to completion of the study.

The data collected from the patients included the patients' weight on day of admission and a subsequent follow up of the weight, daily IC measurement from the intervention group, baseline IC measurement from the control group, the amount of calories prescribed and actual calorie intake for both groups, the caloric balance for both groups, the amount of protein prescribed and the amount of protein intake with the protein balance for both groups and ultrasound measurement of the QMLT on day 1,5 and 10 of both groups.

Figure 4.1: Consort diagram depicting study process

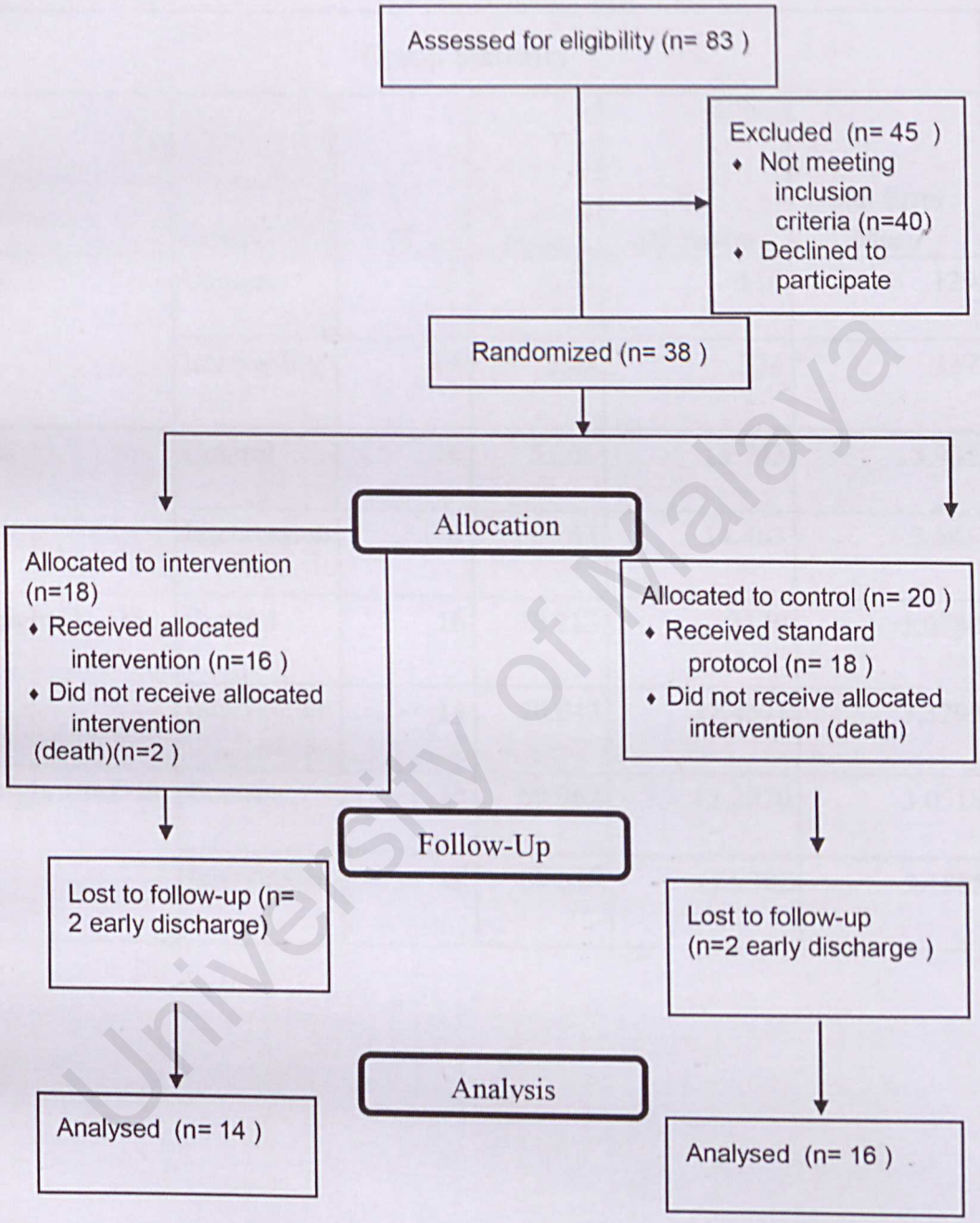


Table 4.1: Showing the descriptive statistics of the age, sex and weight of the patient

Group Statistics					
	Group	N	Mean	Std. Deviation	Std. Error Mean
Sex	Control	16	1.50	.516	.129
	Intervention	14	1.43	.514	.137
Age	Control	16	51.06	15.742	3.935
	Intervention	14	61.43	14.463	3.865
Weight D1-D5	Control	16	70.213	12.3120	3.0780
	Intervention	14	70.043	12.4571	3.3293
Weight D6-D10	Control	16	69.963	12.2070	3.0518
	Intervention	14	69.557	11.9302	3.1885

Table 4.2: Showing the study population difference between both the control and intervention group

Independent Samples Test									
	Levene's Test for Equality of Variances		t-test for Equality of Means						
								95% Confidence Interval of the Difference	
	f	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Sex	.311	.581	.379	28	.708	.071	.188	-.315	.458
			.379	27.51	.708	.071	.188	-.315	.458
Age	.879	.356	-1.868	28	.072	-10.366	5.549	-21.73	1.000
			-1.879	27.92	.071	-10.366	5.516	-21.66	.935
Weight D1-D5	.103	.751	.037	28	.970	.1696	4.5305	-9.110	9.449
			.037	27.38	.970	.1696	4.5341	-9.127	9.466
Weight D6-D10	.039	.844	.092	28	.928	.4054	4.4206	-8.649	9.460
			.092	27.63	.927	.4054	4.4136	-8.640	9.451

The table shows that there is no significant difference between both, the group using standard protocol and the intervention group in terms of age, gender and baseline weight. This makes it easier to analyze further as there is no confounding data between both groups.

Table 4.3: The mean difference of energy balance between Group A (standard protocol) and Group B (Intervention)

Group	Control (A)			Intervention (B)		
	N	Std Error (SEM)	Std Deviation	N	Std Error (SEM)	Std Deviation
Energy Prescribed D1-D5	16	47.895	191.581	14	42.879	160.439
Energy Prescribed D6-D10	9	56.703	160.379	10	54.783	173.238
Energy Intake D1-D5	16	132.98	531.921	14	108.71	406.754
Energy Intake D6-D10	9	88.262	264.787	10	69.673	220.324
REE IC D1-D5	16	64.991	259.964	14	77.321	289.309
REE IC D6-D10	9	171.19	513.570	10	67.073	212.104
Protein Prescribed D1-D5	16	2.1274	8.5095	14	3.5645	13.3373
Protein Prescribed D6-D10	9	2.3329	6.9986	10	3.0131	9.5283
Protein Intake D1-D5	16	5.2196	20.8785	14	4.8394	18.1075
Protein Intake D6-D10	9	2.9153	8.7458	10	3.2548	10.2925
Protein Balance D1-D5	16	5.2792	21.1169	14	4.7369	17.7239
Protein Balance D6-D10	9	2.1898	6.5694	10	3.5602	11.2582

This table outlines the standard deviation and standard error of mean (SEM) for both groups featuring the calculated variables: energy prescribed, energy intake, REE IC, protein prescribed, protein intake and protein balance from D1-D5 and from D6-D10.

Table 4.4: The descriptive statistics of the calculated REE vs REE obtained from predictive equations from D1-D5

Group		Mean	Std. Deviation	N
	REE IC D1-D5	.	.	0
	REE Calculated D1-D5	.	.	0
Control	REE IC D1-D5	1505.44	259.964	16
	REE Calculated D1-D5	1633.00	191.581	16
Intervention	REE IC D1-D5	1688.43	289.309	14
	REE Calculated D1-D5	1612.07	160.439	14

Table 4.5: The descriptive statistics of the calculated REE vs REE obtained from predictive equations from D6-D10

Group		Mean	Std. Deviation	N
	REE IC D6-D10	.	.	0
	REE Calculated D6-D10	.	.	0
Control	REE IC D6-D10	1653.94	412.251	16
	REE Calculated D6-D10	1633.00	191.581	16
Intervention	REE IC D6-D10	1737.29	257.592	14
	REE Calculated D6-D10	1612.07	160.439	14

Table 4.7: Correlations between REE IC and REE calculated between both arms of the study from D6-D10

Group			REE IC D6-D10	REE Calculated D6-D10
	REE IC D6-D10	Pearson Correlation	.[a]	.[a]
		Sig. (2-tailed)		.
		N	0	0
	REE Calculated D6-D10	Pearson Correlation	.[a]	.[a]
		Sig. (2-tailed)	.	
		N	0	0
Control	REE IC D6-D10	Pearson Correlation	1	.450
		Sig. (2-tailed)		.081
		N	16	16
	REE Calculated D6-D10	Pearson Correlation	.450	1
		Sig. (2-tailed)	.081	
		N	16	16
Intervention	REE IC D6-D10	Pearson Correlation	1	.189
		Sig. (2-tailed)		.517
		N	14	14
	REE Calculated D6-D10	Pearson Correlation	.189	1
		Sig. (2-tailed)	.517	
		N	14	14

The tables show us that generally there seems to be no significant correlations between the REE calculated using the predictive equations or REE based on IC. In my local setting, the REE was calculated using the predictive equation in conjunction with the A.S.P.E.N. guidelines of 20–35 kcal/kg/d. There does seem to be a significant

difference between the control and intervention group during D1-D5 in the control group, where the REE calculated using IC appeared to be significantly higher than the calculated REE. By this data analysis alone it does seem fair to say that the calculation of REE using the ASPEN guideline of 25-30 kcal/kg/d resembles the IC calculation of the REE in the real world scenario.

Table 4.8: The descriptive statistics of the energy prescribed and the energy intake of both the groups from D1-D5

Group		Mean	Std. Deviation	N
Control	Energy Prescribed D1-D5	1633.00	191.581	16
	Energy Intake D1-D5	1346.69	531.921	16
Intervention	Energy Prescribed D1-D5	1612.07	160.439	14
	Energy Intake D1-D5	1627.93	406.754	14

Table 4.9: The descriptive statistics of the energy prescribed and the energy intake of both the groups from D6-D10

Group		Mean	Std. Deviation	N
Control	Energy Presribed D6-D10	1633.00	191.581	16
	Energy Intake D6-D10	1653.56	261.513	9
Intervention	Energy Presribed D6-D10	1612.07	160.439	14
	Energy Intake D6-D10	1745.00	220.324	10

Table 4.10: Correlation between the energy prescribed and the energy intake between both the groups from D1-D5

Group			Energy Prescribed D1-D5	Energy Intake D1-D5
Control	Energy Prescribed D1-D5	Pearson Correlation	1	.168
		Sig. (2-tailed)		.533
		N	16	16
	Energy Intake D1-D5	Pearson Correlation	.168	1
		Sig. (2-tailed)	.533	
		N	16	16
Intervention	Energy Prescribed D1-D5	Pearson Correlation	1	-.253
		Sig. (2-tailed)		.383
		N	14	14
	Energy Intake D1-D5	Pearson Correlation	-.253	1
		Sig. (2-tailed)	.383	
		N	14	14

Table 4.11: The correlation between energy prescribed and energy intake between both the groups from D6-D10

Group			Energy Presribed D6-D10	Energy Intake D6-D10
Control	Energy Prescribed D6-D10	Pearson Correlation	1	.150
		Sig. (2-tailed)		.700
		N	16	9
	Energy Intake D6-D10	Pearson Correlation	.150	1
		Sig. (2-tailed)	.700	
		N	9	9
Intervention	Energy Prescribed D6-D10	Pearson Correlation	1	.236
		Sig. (2-tailed)		.511
		N	14	10
	Energy Intake D6-D10	Pearson Correlation	.236	1
		Sig. (2-tailed)	.511	
		N	10	10

The tables above outlined the difference in the energy prescribed and the actual energy delivered to the patient between both the groups. There appears to be no significant difference in the amount of energy prescribed and amount of energy that was delivered to the patients between both the control and the intervention group. This analysis goes to illustrate that using IC and having the patient adhere to a strict protocol did not make the amount of nutrition delivered significantly higher or with a better efficacy. Thus the question of using IC surfaces again, in our setting.

Now that we have established that there is no significant difference between the prescribed energy and the delivered energy between both the groups, the next set of analyses that were performed were to correlate the difference between the energy balance and the average ultrasound of the QMLT of both the lower limbs.

Table 4.12: The descriptive statistics of the energy balance of both the groups from D1-D5 and the average ultrasound measurement of both the lower limb

Group		Mean	Std. Deviation	N
	Energy Balance D1-D5	.	.	0
	Average Left QMLT D1-D5	.	.	0
	Average Right QMLT D1-D5	.	.	0
Control	Energy Balance D1-D5	-286.94	533.756	16
	Average Left QMLT D1-D5	1.8419	.39539	16
	Average Right QMLT D1-D5	1.8300	.38250	16
Intervention	Energy Balance D1-D5	6.57	473.718	14
	Average Left QMLT D1-D5	1.7021	.35089	14
	Average Right QMLT D1-D5	1.7636	.37912	14

Table 4.13: The correlation between the energy balance of both the groups and the average ultrasound measurement of the QMLT of both the lower limbs both the groups from D1-D5

Group			Weight D1-D5	Average QMLT D1-D5	Average QMLT D1-D5
	Weight D1-D5	Pearson Correlation	.[a]	.[a]	.[a]
		Sig. (2-tailed)		.	.
		N	0	0	0
	Average QMLT D1-D5	Pearson Correlation	.[a]	.[a]	.[a]
		Sig. (2-tailed)	.		.
		N	0	0	0
	Average QMLT D1-D5	Pearson Correlation	.[a]	.[a]	.[a]
		Sig. (2-tailed)	.	.	
		N	0	0	0
Control	Weight D1-D5	Pearson Correlation	1	.478	.490
		Sig. (2-tailed)		.061	.054
		N	16	16	16
	Average QMLT D1-D5	Pearson Correlation	.478	1	.961**
		Sig. (2-tailed)	.061		.000
		N	16	16	16
	Average QMLT D1-D5	Pearson Correlation	.490	.961**	1
		Sig. (2-tailed)	.054	.000	
		N	16	16	16
Intervention	Weight D1-D5	Pearson Correlation	1	.525	.554*
		Sig. (2-tailed)		.054	.040
		N	14	14	14
	Average QMLT D1-D5	Pearson Correlation	.525	1	.875**
		Sig. (2-tailed)	.054		.000
		N	14	14	14

Table 4.13 cont.

	Average_Ultrasound_Right_Quardicep_Femoris_D1_D5	Pearson Correlation	.554*	.875**	1
		Sig. (2-tailed)	.040	.000	
		N	14	14	14

Table 4.14: The descriptive statistics of the energy balance of both the groups from D6-D10 and the average ultrasound measurement of both the lower limbs

Group		Mean	Std. Deviation	N
	Energy_Balance_D6_D10	.	.	0
	Average Left QMLT D6-D10	.	.	0
	Average Right QMLT D6-D10	.	.	0
Control	Energy Balance D6-D10	48.00	284.835	9
	Average Left QMLT D6-D10	1.7806	.47310	16
	Average Right QMLT D6-D10	1.7688	.45210	16
Intervention	Energy Balance D6-D10	140.60	254.476	10
	Average Left QMLT D6-D10	1.6943	.31736	14
	Average Right QMLT D6-D10	1.7836	.32998	14

Table 4.15: The correlation between the energy balance of both the groups and the average ultrasound measurement of the QMLT of both the lower limbs both the groups from D6-D10

Group			Energy Balance D6-D10	Average Left QMLT D6-D10	Average Right QMLT D6-D10
	Energy Balance D6-D10	Pearson Correlation	.[a]	.[a]	.[a]
		Sig. (2-tailed)		.	.
		N	0	0	0
	Average Left QMLT D6-D10	Pearson Correlation	.[a]	.[a]	.[a]
		Sig. (2-tailed)	.		.
		N	0	0	0
	Average Right QMLT D6-D10	Pearson Correlation	.[a]	.[a]	.[a]
		Sig. (2-tailed)	.	.	

Table 4.15 cont.

		N	0	0	0
Control	Energy Balance D6-D10	Pearson Correlation	1	-.336	-.218
		Sig. (2-tailed)		.377	.572
		N	9	9	9
	Average Left QMLT D6-D10	Pearson Correlation	-.336	1	.962**
		Sig. (2-tailed)	.377		.000
		N	9	16	16
	Average Right QMLT D6-D10	Pearson Correlation	-.218	.962**	1
		Sig. (2-tailed)	.572	.000	
		N	9	16	16
Intervention	Energy Balance D6-D10	Pearson Correlation	1	.292	-.088
		Sig. (2-tailed)		.413	.808
		N	10	10	10
	Average Left QMLT D6-D10	Pearson Correlation	.292	1	.797**
		Sig. (2-tailed)	.413		.001
		N	10	14	14
	Average Right QMLT D6-D10	Pearson Correlation	-.088	.797**	1
		Sig. (2-tailed)	.808	.001	
		N	10	14	14

These analyses were done to ascertain if there was a significant difference between the energy balance between both the groups. The data analysis showed there that appeared to be no significant difference between the energy balance of both the groups, from day 1 to day 5 and also from day 6 to day 10. Furthermore, this study attempted to extrapolate the difference between the energy balance against the average QMLT of both the lower limbs. There was no significant difference between the energy balance of both the arms of the study and the average ultrasound measurement of the QMLT of both the lower limbs throughout the duration of the study, ie; day 1 to day 5 and from 6 to day 10. This could be attributed to the fact that there was no significant difference

between the energy balance of the control arm and the interventional arm.

Both the arms were given similar amount of protein during the duration of this study. This was in the lieu to not allow protein to be a confounding factor for the duration of this study as protein deficiency has been attributed to muscle mass loss. Further analysis was done to show the difference between protein intake and protein delivery.

Table 4.16: Descriptive statistics showing the differences between the protein prescribed and the protein intake from D1-D5

Group		Mean	Std. Deviation	N
Control	Protein Prescribed D1-D5	75.913	8.5095	16
	Protein Intake D1-D5	60.738	20.8785	16
Intervention	Protein Prescribed D1-D5	80.107	13.3373	14
	Protein Intake D1-D5	70.273	18.1075	14

Table 4.17: Table showing the correlation between the protein prescribed and the protein intake between both the groups from D1-D5

Group			Protein Prescribed D1-D5	Protein Intake D1-D5
Control	Protein Prescribed D1-D5	Pearson Correlation	1	.509*
		Sig. (2-tailed)		.044
		N	16	16
	Protein Intake D1-D5	Pearson Correlation	.509*	1
		Sig. (2-tailed)	.044	
		N	16	16
Intervention	Protein Prescribed D1-D5	Pearson Correlation	1	.397
		Sig. (2-tailed)		.160
		N	14	14
	Protein Intake D1-D5	Pearson Correlation	.397	1
		Sig. (2-tailed)	.160	
		N	14	14

Table 4.18: Descriptive statistics showing the difference between the protein intake and protein delivery between both the groups from D6-D10

Group		Mean	Std. Deviation	N
Control	Protein_Prescribed_D6_D10	75.913	8.5095	16
	Protein_Intake_D6_D10	67.888	19.6088	16
Intervention	Protein_Prescribed_D6_D10	80.621	13.6629	14
	Protein_Intake_D6_D10	76.450	13.5709	14

Table 4.19: Correlation between the protein prescribed and protein delivered between both the groups between D6-D10

Group			Protein Prescribed D6-D10	Protein Intake D6-D10
Control	Protein Prescribed D6-D10	Pearson Correlation	1	.425
		Sig. (2-tailed)		.101
		N	16	16
	Protein Intake D6-D10	Pearson Correlation	.425	1
		Sig. (2-tailed)	.101	
		N	16	16
Intervention	Protein_Prescribed D6-D10	Pearson Correlation	1	.684**
		Sig. (2-tailed)		.007
		N	14	14
	Protein Intake D6-D10	Pearson Correlation	.684**	1
		Sig. (2-tailed)	.007	
		N	14	14

In this set of data, there was a significant difference between the control group in terms of the amount of protein prescribed and the amount of protein delivered in the D1-D5 period with a p value of 0.044. The protein delivered seemed significantly less than the amount prescribed. In the intervention group there was no significant difference between the amount prescribed and delivered. However in the second half of the study, during the D6-D10 period, there seemed to be a significant difference between the protein delivered and the protein prescribed in the intervention group with a p value of 0.007. This could be attributed to the fact that a stringent feeding protocol that ensured the protein delivery made a difference in the protein delivered whereas a standard protocol that is not subjected to strict adherence to protocol might seem a bit lax with the addition of protein. The next set of data analyses was to show correlation between protein balance and the average measurement of QMLT of the lower limbs.

Table 4.20: Descriptive statistics showing the difference between the protein balance and the average QMLT measurement between both the groups from D1-D5

Group		Mean	Std. Deviation	N
	Protein Balance D1-D5	.	.	0
	Average Left QMLT D1-D5	.	.	0
	Average Right QMLT D1-D5	.	.	0
Control	Protein Balance D1-D5	-10.919	21.1169	16
	Average Left QMLT D1-D5	1.8419	.39539	16
	Average Right QMLT D1-D5	1.8300	.38250	16
Intervention	Protein Balance D1-D5	-9.836	17.7239	14
	Average Left QMLT D1-D5	1.7021	.35089	14
	Average Right QMLT D1-D5	1.7636	.37912	14

Table 4.21: Correlation between the protein balance and the average QMLT of both the lower limbs between both the groups from D1-D5

Group			Protein Balance D1-D5	Average Left QMLT D1-D5	Average Right QMLT D1-D5
	Protein Balance D1-D5	Pearson Correlation	.[a]	.[a]	.[a]
		Sig. (2-tailed)		.	.
		N	0	0	0
	Average Left QMLT D1-D5	Pearson Correlation	.[a]	.[a]	.[a]
		Sig. (2-tailed)	.		.
		N	0	0	0
	Average Right QMLT D1-D5	Pearson Correlation	.[a]	.[a]	.[a]
		Sig. (2-tailed)	.	.	
		N	0	0	0
Control	Protein Balance D1-D5	Pearson Correlation	1	.270	.270
		Sig. (2-tailed)		.311	.312
		N	16	16	16
	Average Left QMLT D1-D5	Pearson Correlation	.270	1	.961**
		Sig. (2-tailed)	.311		.000
		N	16	16	16
	Average Right QMLT D1-D5	Pearson Correlation	.270	.961**	1
		Sig. (2-tailed)	.312	.000	
		N	16	16	16
Intervention	Protein_Balance_ D1_D5	Pearson Correlation	1	-.220	-.500
		Sig. (2-tailed)		.451	.069
		N	14	14	14
	Average Left QMLT D1-D5	Pearson Correlation	-.220	1	.875**
		Sig. (2-tailed)	.451		.000
		N	14	14	14

Table 4.22: Descriptive statistics showing the difference between the protein balance and the average QMLT measurement between both the groups from D6-D10

Group		Mean	Std. Deviation	N
	Protein Balance D6-D10	.	.	0
	Average QMLT Left D6-D10	.	.	0
	Average Right QMLT D6-D10	.	.	0
Control	Protein Balance D6-D10	-6.769	18.3033	16
	Average QMLT Left D6-D10	1.7806	.47310	16
	Average Right QMLT D6-D10	1.7688	.45210	16
Intervention	Protein Balance D6-D10	-1.029	11.6038	14
	Average Left QMLT D6-D10	1.6943	.31736	14
	Average Right QMLT D6-D10	1.7836	.32998	14

Table 4.23: Correlation between the protein balance and the average QMLT of both the lower limbs between both the groups from D6-D10

Group			Protein Balance D6-D10	Average Left QMLT D6-D10	Average Right QMLT D6-D10
.	Protein Balance D6-D10	Pearson Correlation	.[a]	.[a]	.[a]
		Sig. (2-tailed)		.	.
		N	0	0	0
	Average Left QMLT D6-D10	Pearson Correlation	.[a]	.[a]	.[a]
		Sig. (2-tailed)	.		.
		N	0	0	0
	Average Right QMLT D6-D10	Pearson Correlation	.[a]	.[a]	.[a]
		Sig. (2-tailed)	.	.	
		N	0	0	0
Control	Protein Balance D6-D10	Pearson Correlation	1	.096	.093
		Sig. (2-tailed)		.724	.732
		N	16	16	16
	Average Left QMLT D6-D10	Pearson Correlation	.096	1	.962**
		Sig. (2-tailed)	.724		.000
		N	16	16	16
	Average Right QMLT D6-D10	Pearson Correlation	.093	.962**	1
		Sig. (2-tailed)	.732	.000	
		N	16	16	16
Interve-ntion	Protein Balance D6-D10	Pearson Correlation	1	.102	.429
		Sig. (2-tailed)		.728	.126
		N	14	14	14
	Average Left QMLT D6-D10	Pearson Correlation	.102	1	.797**
		Sig. (2-tailed)	.728		.001
		N	14	14	14
	Average Right QMLT D6-D10	Pearson Correlation	.429	.797**	1
		Sig. (2-tailed)	.126	.001	

These set of data attempted to analyze the protein balance with the average ultrasound measurement of the QMLT of both the groups and further compare these data between the two groups to find a significant correlation. There was no significant difference between the protein balance between both the groups. Further analysis failed to prove any significance with the QMLT measurement of the both the groups both for the duration of D1-D5 and D6-D10 with the protein balance.

CHAPTER 5.0

DISCUSSION

This is a pilot study done to ascertain the use of indirect calorimetry (IC) in the calculation of caloric needs and to compare and contrast an interventional protocol using IC vs a standard feeding protocol. This study further went on to then compare the difference in the average ultrasound of the quadratus muscle layer thickness (QMLT) with both the protocols, and if the feeding as guided by IC had any improvement in the QMLT of the patient. This study also prescribed protein to both the control and interventional arms similarly to avoid the bias of supplemental protein to interfere with the muscle bulk loss.

The results of the study were largely proven to be not significant. There was no significant difference between the amounts of energy prescribed with the amounts of energy delivered between both the groups for the duration of the study. An analysis of the REE calculated using predictive equations vs the REE calculated using IC showed significant difference in the interventional group in the D1-D5 duration but had no difference in the D6-D10 duration in the interventional group. Thus the calories prescribed to the interventional cohort on D1-D5 were significantly higher compared to the control group. The D6-D10 duration did not show any significant deference in the REE calculated using predictive equations vs IC for both the group. This shows that by large the predictive equations used by my centre which is in compliance with the ASPEN guideline of 25-30 kcal/kg/d practice seems to correlate with the REE calculated using IC. There could be a few factors influencing this result. The obvious one would be that the 25-30 kcal/kg/d is in fact closely related to the IC measurement of the REE and thus can be used in the real world scenario. The other factors that could influence this would be mainly the REE measurement using the metabolic cart. In general, inaccuracies occur when the patient is mechanically ventilated with a fraction

of inspired oxygen (FIO2) of more than 60 and with a positive end expiratory pressure (PEEP) of more than 12 cmH2O. Hyper/hypoventilation (acute changes altering body CO2 stores) also does cause significant errors. Sometimes there could be leaks and moisture in the sampling system that can affect the oxygen analyzer. Inability to collect all expiratory flow can cause measurement errors and these occur largely due to leaks in chest tube seals and bronchopleural fistulae to name a few. Hemodialysis, peritoneal dialysis, or continuous renal replacement therapy in progress can affect the calculation of REE using the metabolic cart although to what extent remains unclear. CRRT may increase CO2 elimination from the plasma. It is suggested that IC testing be repeated once CRRT is discontinued. This subject warrants further research. Errors in calibration of indirect calorimeter are a rookie mistake and can be overlooked but these can lead to gross error in measurement of the REE. In my center the Indirect Calorimeter used was the COSMED, Quark RMR 2.0,Indirect Calorimetry Lab, Italy. We obtained training in the use of the metabolic cart from the local and Italian COSMED team. We had 3 classes in total where we were thought how to use the turbine and flow REE systems of the metabolic cart. We then had trial runs on patients prior to embarking on this study. The IC was performed daily in the mornings by either the dietician or me. We tried to refrain from performing the IC during CRRT but that was not possible at all times as some of the patients we had recruited required CRRT during the course of their stay in the ICU. These factors could lead to a discrepancy in the IC reading although it has to be attested that there were no gross differences in the REE readings of each patient during the study period. These factors could in part explain the fact that there were no significant differences between the REE readings of the 2 groups.

There appeared to be no significant differences between the energy prescribed and the energy delivered between both the groups throughout the duration of this study. Here it is apparent that the standard feeding protocol while not having a stringent

protocol seemed sufficient to provide calories as per prescribed thus allowing a more liberal approach to feeding feasible without actually having a strict protocol. Subsequent analyses attempted to highlight the difference between the energy balances between both the groups. There was no significant difference between the energy balances between both the groups. This could be explained partly by the fact that the REE calculated via the metabolic cart and via the predictive equations had no significant differences except for the interventional arm for the D1-D5 duration. This also could be attributed to the fact that there was no significant difference in the prescribed and delivered nutrition between both the groups.

The next set of data that were analyzed was the correlation between the energy balance and the ultrasound measurement of the quadriceps muscle layer thickness (QMLT). There appeared to be no significant differences in the average measurement of the QMLT between both the groups. This comes as no surprise as there was no significant difference in the energy balance between both the groups.

Protein delivery has been a constant source of debate in terms of nutritional supplementation in critically ill patients. Septic auto cannibalism was a term used to describe the loss of muscle mass that does not benefit from increasing AA provision above minimum requirements. Therefore, through the 1970s, researchers focused on ensuring that energy intake exceeded expenditure, rather than on targets for adequate protein intake. Later, when enteral nutrition became a viable option in critically ill patients, nutritional interventions continued to focus on meeting energy requirements. When recommendations for protein or AA intake were given, they were generally expressed as a function of energy intake. For example, in the 1990s the American College of Chest Physicians recommended that, for patients in ICUs, `15-20% of the total calories administered per day can be given as protein or amino acids'. However,

the guidelines provided neither the rationale nor the scientific basis for this recommendation.

In stress situations, the priority of the metabolic response is to provide energy to both the brain and injured tissues to promote healing. In the absence of glucose intake, glucose is synthesized from gluconeogenic AA, lactate, and pyruvate. The pool of free essential AAs is very small, with most generated from net proteolysis, occurring particularly within muscles. In critically ill patients, in parallel with the severity of the injury, increases in proinflammatory cytokines, glucocorticoids, and oxidative stress reinforce the effect of catabolic hormones, and contribute to insulin resistance and muscle wasting. Insulin resistance is common in critically ill patients, and contributes to net muscle protein catabolism and liver gluconeogenesis.

In a stress situation, the catabolic loss of muscle can be avoided only if the uptake of AAs from the blood is increased either by intravenous infusion or the digestion of enterally administered proteins, peptides, or AAs. These sources of AA may then stimulate protein synthesis to offset the accelerated rate of protein breakdown and AA oxidation. In light of increasing evidence of protein being a major factor in muscle mass loss, after intense debates and discussions, the decision was made to supplement both arms with 1.5g/kg/d of protein. This would elimate the bias that protein might cause. But analyses were still performed using protein as a surrogate marker. First we aimed to see if there was a significant difference in the prescribed protein and the protein delivery. In this set of data, there was a significant difference between the control group in terms of the amount of protein prescribed and the amount of protein delivered in the D1-D5 period with a p value of 0.044. The protein delivered seemed significantly less than the amount prescribed. In the intervention group there was no significant difference between the amount prescribed and delivered. However in the second half of the study, during the D6-D10 period, there seemed to be a significant

difference between the protein delivered and the protein prescribed in the intervention group with a p value of 0.007. This could be attributed to the fact that a stringent feeding protocol that ensured the protein delivery made a difference in the protein delivered whereas a standard protocol that is not subjected to strict adherence to protocol might seem a bit more liberal with the addition of protein.

Subsequently we aimed to look at if there was a difference in the protein balance in both the groups. There was no significant difference in protein balance between both the groups. Although there appeared to be a significant difference in the protein prescription and protein delivery between both the groups, there appeared to be no significance in protein balance. Further comparison between the protein balance of both the groups and the average QMLT measurement also showed that there was no significant difference.

The usage of ultrasound will also require a mention in this discussion. The VALIDUM study (ASPEN 2016) found that there was significant absolute difference in muscle thickness observed between 2 observers using the ultrasound, thus recommending that a sole person performing ultrasound guided muscle layer thickness more reliable but less feasible. In this study, we wanted to limit the observer bias, thus I was the sole sonographer involved in this study. Prior to commencing with the study I had received training in ultrasound from a radiographer and performed practice ultrasound measurements in patients. I was helped during the study by clarification and confirmation from my Intensive care specialists.

5.1 LIMITATIONS

This study was not without its limitations. This was a single center study which is the main limitation of this study. The main short coming of single center studies is their limited external validity. Interventions tested in in a single clinical environment are not necessarily able to be extrapolated to a generalized population cohort, especially in intensive care. This can be determined by factors such as resources available, nurse/patient ratios, intensivist/patient ratios, and predictive mortality rates for each center that could possibly differ. Secondly, the allocation of resources might differ between centers. Single center studies like mine had dedication in ensuring the adherence to protocols and used resources like acquiring help from nursing and support staff. These would not be possible in other centers where resources are limited and time and effort might seem like something of a luxury. My study was a single blinded study whereby only the patient was blinded to the intervention and the doctors were not. This then inherently exposes the investigator to a bias of providing better care when appropriate. The clinical members of the staff will also be made aware of the goal of the study and possibly attempt to please the investigator. This is also known as the Hawthorne effect, and this can potentially affect patient care and the outcome.

The second factor limiting this study would be the ultrasound assessment of the quadriceps muscle layer thickness (QMLT). The usage of ultrasound was attempted to be validated by the VALIDUM study and that study concluded with saying that ultrasound has great potential for identifying patients with low muscularity in the ICU but further protocols are required to validate its usage(Paris et al., 2016). Thus a protocol hasn't in actuality been developed to correlate the QMLT with the overall muscle bulk measurement in a critically ill patient. Furthermore, critically ill patients tend to develop edema during their stay in the ICU and this compounds the measurement using ultrasound whereby some amount of indentation of the muscle is

required to get the fluid dispersed prior to accurate measurement of the ultrasound. The indentation pressure required for accurate measurement using the ultrasound hasn't been established, thus tissue edema is able to cause significant discrepancies to the result.

Lastly a comment on the sample size of this study has to be made. This study was able to recruit 30 patients and conducted as a pilot study. To be able to achieve a significant result, the results of this study should be powered to get a sample size. This would be then able to verify conclusively on the difference in nutritional prescription using IC or standard therapy vs muscle mass loss.

CHAPTER 6.0

CONCLUSION

This pilot study was done to ascertain if a targeted nutritional therapy using indirect calorimetry (IC) vs standard protocol does in fact have a significant difference between caloric and protein prescription, caloric and protein delivery, caloric and protein balance and finally if there is a correlation between caloric and protein balance and the average measurement of the quadriceps muscle layer thickness. The study went on to prove that there was in fact no significant difference between both caloric and protein delivery between both groups,caloric and protein balance between both the groups and the caloric and protein balance between ultrasound measurement between both the groups.

Thus the study was indicative that the standard feeding protocol seemed to be reasonably able to represent IC measurement in my setting. But it also begs for a bigger sample cohort to possibly show a significant difference between both the groups, and this can be done by powering the outcome of this study. IC being the gold standard of nutritional prescription in critically ill patients should still be considered when possible but it is certainly a modality that one can do without. Ultrasound measurement of the quadriceps muscle should remain in the loop as a surrogate marker of muscle mass measurement of critically ill patients indicative of muscle mass loss.

CHAPTER 7.0

REFERENCES

Ali, N. A., O'Brien, J. M., Hoffmann, S. P., Phillips, G., Garland, A., Finley, J. C. W., … Midwest Critical Care Consortium. (2008). Acquired weakness, handgrip strength, and mortality in critically ill patients. *American Journal of Respiratory and Critical Care Medicine*, *178*(3), 261–8. http://doi.org/10.1164/rccm.200712-1829OC

Campbell iain. (1995). muscle thickness , measured with ultrasound, indicator of lean tissue wasting in edema. *Therapy*. Retrieved from http://ajcn.nutrition.org/content/62/3/533.short

Cheung, A. et al. (2006). Two-Year Outcomes , Health Care Use , and Costs of Survivors of Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med*, *174*(2), 538 – 544. http://doi.org/10.1164/rccm.200505-693OC

Cuthbertson, B. H., Roughton, S., Jenkinson, D., Maclennan, G., & Vale, L. (2010). Quality of life in the five years after intensive care: a cohort study. *Critical Care (London, England)*, *14*(1), R6. http://doi.org/10.1186/cc8848

de Bruin, P. F., Ueki, J., Watson, A., & Pride, N. B. (1997). Size and strength of the respiratory and quadriceps muscles in patients with chronic asthma. *The European Respiratory Journal*, *10*(1), 59–64. http://doi.org/10.1183/09031936.97.10010059

De Jonghe, B., Bastuji-Garin, S., Durand, M.-C., Malissin, I., Rodrigues, P., Cerf, C., … Sharshar, T. (2007). Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. *Critical Care Medicine*, *35*(9), 2007–2015. http://doi.org/10.1097/01.ccm.0000281450.01881.d8

Diaz-granados, N., Sc, M., Cooper, A., Guest, C. B., Mazer, C. D., Mehta, S., … Ph, D. (2011). Functional Disability 5 Years after Acute Respiratory Distress Syndrome. *The New England Journal of Medicine*, *364*(14), 1293–1304. http://doi.org/doi:10.1056/NEJMoa1011802

Gruther, W., Benesch, T., Zorn, C., Paternostro-Sluga, T., Quittan, M., Fialka-Moser, V., … Crevenna, R. (2008). Muscle wasting in intensive care patients: Ultrasound observation of the M. quadriceps femoris muscle layer. *Journal of Rehabilitation Medicine*, *40*(3), 185–189. http://doi.org/10.2340/16501977-0139

Herridge, M. S., Cheung, A. M., Tansey, C. M., Matte-Martyn, A., Diaz-Granados, N., Al-Saidi, F., … Canadian Critical Care Trials, G. (2003). One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*, *348*(8), 683–693. http://doi.org/10.1056/NEJMoa022450

MacFarlane, I. A., & Rosenthal, F. D. (1977). Severe myopathy after status asthmaticus. *Lancet*, *2*. http://doi.org/10.1016/S0140-6736(77)91471-4

Mathur, S., Takai, K. P., Macintyre, D. L., & Reid, D. (2008). Estimation of thigh muscle mass with magnetic resonance imaging in older adults and people with chronic obstructive pulmonary disease. *Physical Therapy*, *88*(2), 219–230. http://doi.org/10.2522/ptj.20070052

Myhren, H., Ekeberg, O., & Stokland, O. (2010). Health-related quality of life and return to work after critical illness in general intensive care unit patients: a 1-year follow-up study. *Crit Care Med*, *38*(7), 1554–1561. http://doi.org/10.1097/CCM.0b013e3181e2c8b1

NICE. (2009). *Rehabilitation after critical illness in adults | Guidance and guidelines | NICE*. NICE. Retrieved from https://www.nice.org.uk/guidance/cg83

Oshima, T., Berger, M. M., De Waele, E., Guttormsen, A. B., Heidegger, C. P., Hiesmayr, M., … Pichard, C. (2016). Indirect calorimetry in nutritional therapy. A position paper by the ICALIC study group. *Clinical Nutrition*. http://doi.org/10.1016/j.clnu.2016.06.010

Paris, M., Mourtzakis, M., Day, A., Leung, R., Watharkar, S., Kozar, R., … Heyland, D. (2016). VALIDation of bedside Ultrasound of Muscle layer thickness of the quadriceps in the critically ill patient (VALIDUM study): A prospective

multicenter study. *Journal of Parenteral and Enteral Nutrition*, (1000460758). http://doi.org/10.1177/0148607116637852

Poulsen, J. B., Moller, K., Jensen, C. V, Weisdorf, S., Kehlet, H., & Perner, A. (2011). Effect of transcutaneous electrical muscle stimulation on muscle volume in patients with septic shock. *Critical Care Medicine*, *39*(3), 456–461. http://doi.org/10.1097/CCM.0b013e318205c7bc

Poulsen, J. B., Moller, K., Kehlet, H., & Perner, A. (2009). Long-term physical outcome in patients with septic shock. *Acta Anaesthesiol Scand*, *53*(6), 724–730. http://doi.org/AAS1921 [pii]\r10.1111/j.1399-6576.2009.01921.x [doi]

Reid, C. L., Campbell, I. T., & Little, R. A. (2004). Muscle wasting and energy balance in critical illness. *Clin Nutr*, *23*(2), 273–280. http://doi.org/10.1016/S0261-5614(03)00129-8

Roch, A., Wiramus, S., Pauly, V., Forel, J.-M., Guervilly, C., Gainnier, M., & Papazian, L. (2011). Long-term outcome in medical patients aged 80 or over following admission to an intensive care unit. *Critical Care (London, England)*, *15*(1), R36. http://doi.org/10.1186/cc9984

Seymour, J. M., Ward, K., Sidhu, P. S., Puthucheary, Z., Steier, J., Jolley, C. J., … Moxham, J. (2009). Ultrasound measurement of rectus femoris cross-sectional area and the relationship with quadriceps strength in COPD. *Thorax*, *64*(5), 418–423. http://doi.org/10.1136/thx.2008.103986

Sharshar, T., Bastuji-Garin, S., Stevens, R. D., Durand, M.-C., Malissin, I., Rodriguez, P., … De Jonghe, B. (2009). Presence and severity of intensive care unit-acquired paresis at time of awakening are associated with increased intensive care unit and hospital mortality. *Critical Care Medicine*, *37*(12), 3047–3053. http://doi.org/10.1097/CCM.0b013e3181b027e9

Singer, P., & Singer, J. (2016). Clinical Guide for the Use of Metabolic Carts: Indirect Calorimetry--No Longer the Orphan of Energy Estimation. *Nutrition in Clinical Practice*, *31*(1), 30–38. http://doi.org/10.1177/0884533615622536

Sipila, S., & Suominen, H. (1991). Ultrasound imaging of the quadriceps muscle in elderly. *Muscle & Nerve*, (June), 527–533. Retrieved from http://onlinelibrary.wiley.com/doi/10.1002/mus.880140607/abstract

van der Schaaf, M., Beelen, A., Dongelmans, D. A., Vroom, M. B., & Nollet, F. (2009). Functional status after intensive care: A challenge for rehabilitation professionals to improve outcome. *Journal of Rehabilitation Medicine*, *41*(5), 360–366. http://doi.org/10.2340/16501977-0333

Walton, J. M., Roberts, N., & Whitehouse, G. H. (1997). Measurement of the quadriceps femoris muscle using magnetic resonance and ultrasound imaging. *Br J Sports Med*, *31*(1), 59–64. http://doi.org/10.1136/bjsm.31.1.59