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Objectives:

This study identified the difference in energy expenditure and substrate utilization of patients during and upon liberation from mechanical ventilation.

Methods:

Patients under intensive care who were diagnosed with septic shock and mechanical ventilation-dependent were recruited. Indirect calorimetry measurements were performed during and upon liberation from mechanical ventilation.

Results:

Thirty-five patients were recruited (20 males and 15 females; mean age 69 ±10 years). Measured energy expenditures during ventilation and upon liberation were 2090 ±489 $kcal \cdot d^{-1}$ and 1910 ±579 $kcal \cdot d^{-1}$, respectively ($p<0.05$). Energy intake was provided at 1148 ±495 $kcal \cdot d^{-1}$ and differed significantly from all measured energy expenditures ($p<0.05$). Mean carbohydrate utilization was 0.17 ±0.09 $g \cdot min^{-1}$ when patients were on mechanical ventilation compared to 0.14 ±0.08 $g \cdot min^{-1}$ upon liberation ($p>0.05$). Mean lipid oxidation was 0.08 ±0.05 $g \cdot min^{-1}$ during and 0.09±0.07 $g \cdot min^{-1}$ upon liberation from mechanical ventilation ($p>0.05$).

Conclusions:

Measured energy expenditure was higher during than upon liberation from mechanical ventilation. This could be the increase in work of breathing from the continuous positive pressure support, repeated weaning cycles from mechanical ventilation and/or the asynchronization between patients' respiration and ventilator support. Future studies should examine whether more appropriately matching energy expenditure with energy intake would promote positive health outcomes.

Introduction

Critically ill populations are especially susceptible to malnutrition due to their hypermetabolic state combined with suboptimal nutrition support[1,43]. Sepsis is a complex and progressive physiological stress response to infection among patients, involving multiple organs and high mortality rate[2]. The related stress response changes energy expenditure and can differ during various stages of sepsis (i.e. highest in complicated sepsis but similar to healthy individuals in septic shock[5,6]).

Energy expenditure is positively related to the duration of sepsis[7] and substrate utilization can also be altered during such critical illness.[8,10]. In addition to the clinical condition *per se*, treatment with mechanical ventilation support has the capacity to increase a patient's energy expenditure[40]. This observation is particularly apparent amongst patients on partial pressure support, which requires increased work of breathing to reach the sensitivity threshold that triggers the ventilator to complete the respiration[36].

In this study, the focus was the change in energy expenditure during *liberation,* defined as cessation of any pressure support from the ventilator. A common technique in intensive care unit is to gradually liberate patients from mechanical ventilation using a repeated "work" and "rest" cycle. This cycle allows respiratory muscles to rest adequately with partial pressure support from the ventilator so that atrophied respiratory muscles may be strengthened and self-breathing can begin in a less fatigue state[30]. However, there is evidence that energy expenditure may gradually elevate through each "work" and "rest" cycle[30]. Based on the available evidence, we hypothesized that energy expenditure would vary over time in the process of weaning from mechanical ventilation to the fully liberated state when pressure support from the ventilator is entirely withdrawn.

I. Methodology

This study complied with the 2013 version of the Declaration of Helsinki and approval was obtained from the ethics committee of the Kowloon East Cluster hospitals, Hospital Authority, Hong Kong SAR (approval reference: KC/KE-09-0107/ER-2).

Participant Recruitment

Patients aged 18 and above who were admitted into the intensive care unit with initial diagnosis of septic shock and mechanical ventilation dependent were recruited. Patients must have been hemodynamically stable at the time of indirect calorimetry measurement. Patients with significant post-operative bleeding, major pulmonary complications, under isolation protocol and/or with comfort care directives were excluded.

The stature of patients was measured from the crown to the bottom of their feet in the supine position using a measuring tape. Body mass was obtained from either past records, next of kin or by calculating the ideal body weight. Length of stay, duration on ventilator and APACHEII[28] were collected (Table 1).

Indirect Calorimetry

CCM Express[29] was selected for indirect calorimetric measurement in this study. The connecting circuitry is composed of a DirectConnect$_{\text{TM}}$ volume-measuring flow sensor and umbilical, which connects to the terminal and all expiratory gas from patients directed through DirectConnect$_{\text{TM}}$. A face-mask and canopy were not options for measuring devices as patients had either tracheostomy or endotracheal tube insertion.

A system calibration on CCM Express is performed according to American Thoracic Society recommendation using a 3-liter syringe for volume calibration. A designated volume of air is introduced by the syringe into the flow sensor several times at different flow rates in three separate trials. CCM Express utilizes an external gas calibration device for calibration with two gases; reference gas (21% of gas volume oxygen and nitrogen typical of atmospheric composition) and calibration gas (12% oxygen, 5% carbon dioxide and nitrogen similar to atmospheric composition). An auto-calibration which includes correcting continuous bias flow was also performed. Bias flow minimizes the work of breathing by allowing the patient to tap into a continuous gas flow rather than initiate flow through a delivery circuit. The system is able to differentiate between gas delivery to the patient's lungs and gas continuously flowing through the circuit [33]. Measurements from indirect calorimetry were deemed valid once steady state can be achieved by the patients[20].

Nutrition support

Nutrition support was the provision of formulated enteral or parenteral nutrients to appropriate patients for maintaining or restoring nutrition balance[21]. It was provided to this cohort through either tube feedings or oral diets. The route of tube feedings was either nasal gastric, nasal jejunal tube or jejunosotmy. The rate of feeding was controlled by electric feeding pumps that dispensed feeding continuously at a fixed rate. All feeding regimens remained unchanged pre- and post-indirect calorimetry measurement. Tube feedings were withheld 4 hours prior to indirect calorimetry measurement in order to minimize the influence from thermogenesis of food.

Patients Care-Specific Measurement Protocols

Indirect calorimetry measurements only commenced after 90 minutes following procedures such as bathing, turning, physiotherapy, change of ventilator setting, change of dosage of sedatives or inotropes or hemodialysis with possibility of excess accumulation of bicarbonate in the blood. Physicians also gradually tapered the level of sedation with a decreased level of ventilator support. Energy expenditure was measured once during a stable ventilator setting (Pre-MEE). It was measured again after 90 minutes of liberation or cessation of pressure support from mechanical ventilation (Post-MEE). The results were deemed valid when the patient did not require reintubation for at least the following 12 hours.

Automatic Tube Compensation Protocol

Patients were often mechanically ventilated either by tracheostomy or endotracheal-tube to create an external airway to the lungs. The endotracheal-tube was used for short-term ventilator support and removed when the patients are able to wean themselves off mechanical ventilation. The direct connection of the endotracheal tube to the circuitry of the indirect calorimetry for measurement is then no longer available. Hence, a specific protocol was developed to accommodate the measurement for patients who utilized endotracheal tube for mechanical ventilation. Automatic Tube Compensation (ATC) mode in mechanical ventilators relieves the pressure imposed by the endotracheal-tube inside the airway and its subsequent impact on work of breathing. This ATC protocol allowed the cohort to retain the endotracheal tube for connecting to the indirect calorimeter circuitry. The setting of the ventilator was adjusted to supply only oxygen without pressure support to simulate self-breathing[16]. Indirect calorimetric measurements were performed after 90 minutes of cessation of pressure support for proper acclimatization and patients were then extubated after the measurement. Data were again deemed valid when patients did not require reintubation for the next 12 hours.

Modification In Resting Energy Expenditure and Substrate Utilization Calculation

The indirect calorimeter automatically determined the concentration of oxygen consumed and carbon dioxide produced by patients and data were converted into energy expenditure ($\text{kcal}\cdot\text{d}^{-1}$)[14] with carbohydrate utilization and lipid oxidation were then determined based on the respiratory exchange ratio[13]. Urinary nitrogen was not collected in this cohort because of practical limitations in laboratory capacity. Research indicated that there was only 1% of error for every 12.3% of total calories metabolized from protein and thus, the equation could be simplified by excluding urinary nitrogen[14].

$$(3.914 \cdot VO_2 \;\; L\min{}^{1}) + (1.106 \cdot VCO_2 \;\; L \;\; \min{}^{1})(2.17 \cdot \; n \;\; gm \;\; \min{}^{1}) \cdot 1400\min \; day^{\;1}$$

Statistical Analysis

All statistical analysis was performed by EXCEL 2010 version 12.0 (Microsoft Inc.). Mean values and standard deviation were used to express descriptive statistics. Paired-t tests were used to examine mean differences between during and following liberation from mechanical ventilation in energy expenditure (pre-MEE vs post-MEE), actual energy consumption (KCAL), oxygen consumption (V_{O2}), carbon dioxide production (V_{CO2}) and substrate oxidation. Spearman's correlation coefficient was used to assess the relationship among variables and significance accepted at $p \le 0.05$. Only correlations with 'good' agreement (i.e $r \ge 0.7$) were reported. Variability of data was expressed as standard deviation.

Results

There were originally 37 patients in the cohort and 2 patients terminated their indirect calorimetry measurements prematurely due to post-operative seizures, persistent restlessness and/or irritation during measurement. Thirty-three patients received actual calories from tube feeding, one patient did not receive any nutrition support and the remaining one was on oral diet during entire study period. Disease conditions of the cohort included:

- Central Nervous System (CNS) Infection
- Status epilepticus with sepsis
- Acute cholecystitis
- Type I respiratory failure and septic shock
- Herpes encephalitis

- Hospital-acquired pneumonia
- Pancreatitis and septic shock
- Urosepsis
- Perforated Peptic Ulcer
- Community-acquired pneumonia
- Parapharyngeal abscess and pneumonia
- Retropharyngeal abscess
- Liver abscess
- Methicillin-resistant Staphylococcus aureus (MRSA) pneumonia
- Neck abscess, right pneumothorax
- Pancreatitis with retroperitoneal collection
- Sepsis
- Septic shock and acute renal failure
- Appendicitis and gangrene
- Cholangitis, septic shock and multi-organ failure (MOF)
- Ischemic gangrenous large bowel
- Brochopneumonia
- Acute cholecystitis with liver abscess and septic shock
- Necrotizing fasciitis, septic shock with amputation
- Severe Community-acquired pneumonia
- Necrotizing fasciitis
- Hip implant infection
- Severe pneumonia with respiratory failure
- Klesbsiella septicemia with meningitis
- Retropharyngeal abscess
- Acute cholecystitis with pneumonia
- Necrotizing fasciitis with septic shock

Measured energy expenditure, actual calories received, oxygen consumption and carbon dioxide production during and upon liberation from mechanical ventilation were all statistically different (Table 2). Measured energy expenditure during mechanical ventilation was 9% higher than without (Figure 1) and the difference was statistically significant (Table 2). The range of PREMEE was 1299 to 3115 kilocalories and POSTMEE was 882 to 3290 kilocalories (Figure 2). The actual calories received met 55% of measured energy expenditure during ventilatory support and 59% upon liberation from ventilators (Figure 1). Furthermore, 94% (n=33) of patients during mechanical ventilation and 77% (n=27) of them upon liberation from ventilator support received actual calories that were less than their measured energy expenditures.

Mean respiratory exchange ratio (mean values of individual patient) shown in Figure 3 was higher during than upon liberation from mechanical ventilation but it was not statistically different (Table 2). The range of respiratory exchange ratios during mechanical ventilation was 0.74 to 1.32 and without ventilatory support was 0.66 to 1.22 (Figure 3)[20].

The cohort showed 11% higher oxygen consumption (Figure 4) during than upon liberation from mechanical ventilation (Table 2). The minimum oxygen consumption during mechanical ventilation was 0.180 l/min and maximum was 0.478 l/min, whereas without ventilatory support the range was 0.128 l/min to 0.514 l/min. Mean carbon dioxide production was 13% higher during mechanical ventilation than without ventilatory support (Table 2). Carbon dioxide production in patients on mechanical ventilation ranged from 0.184 l/min to 0.406 l/min and upon liberation from mechanical ventilation was 0.113 l/min to 0.365 l/min (Figure 5).

Figure 6 illustrates substrate utilization among the cohort. Carbohydrate utilization during mechanical ventilation was 238% of lipid oxidation whereas it was 167% upon liberation from ventilator support. Minimum carbohydrate utilization was 0.05 g/min and maximum was 0.49 g/min during mechanical ventilation and 0.00 g/min to 0.38 g/min upon liberation from ventilation (Figure 7). Minimum lipid oxidation was 0.00 g/min and maximum was 0.20 g/min during mechanical ventilation and 0.00 g/min to 0.25 g/min upon liberation from ventilation (Figure 8).

The Spearman correlation coefficients (Table 3) demonstrated strong positive relationship in which elevated oxygen production was observed with an increase in lipid utilization ($r = 0.74$) both during and upon liberation from mechanical ventilation ($r=0.82$). Similar correlation was found in carbon dioxide production that also increased with higher lipid utilization upon liberation from mechanical ventilation ($r=0.91$). Furthermore, the correlation was moderately strong in higher actual calories received with longer duration of mechanical ventilation support ($r=0.55$) and length of stay ($r=0.41$).

Discussion

Healthy people seldom realize the effort to breathe because it is a normal mechanical process and requires minimal metabolic effort in healthy individuals. Respiratory muscles including diaphragm and intercostal muscles between the ribcage are actively engaged in the ventilation mechanism and diaphragmatic fatigue contributes to respiratory failure. The positive relationship between use of various mode of mechanical ventilation including total and partial pressure support and rate of diaphragmatic atrophy has been identified among critically ill patients[15,44] and the current study documents changes in energy expenditure when liberated from mechanical ventilation. The current cohort exhibited significant negative energy balance both during and upon liberation from mechanical ventilation. Underfeeding is common[4] in intensive care because of conservative practice and frequent interruption by complications, procedures and examinations. A structured nutrition support protocol or algorithm could provide guidance for clinicians to prescribe nutrition support appropriately, heighten clinicians' awareness to minimize negative energy balance and reduce potential cumulative energy deficit with prolonged patients' length of stay.

In the present study, the absolute mass of carbohydrate utilized was higher than lipids oxidized with and without mechanical ventilation, so carbohydrate metabolism undoubtedly plays an important role among critically ill patients. However, when considering substrate selection data collected in this population, factors such as disruption in heart rate and adjustment of ventilator setting should be considered as these can alter minute ventilation and temporarily influence carbon dioxide production which can lead to errors. Similar to high-intensity exercise [18], potentially high rates of glycolytic flux and glycogenolysis during critical illness can confound standard estimates based on exclusive oxidation of glucose.

The limitation of using critically ill patients in clinical trials remains difficult and requires a lot of technical considerations because of the heterogeneous nature of the cohort. Recruitment criteria of critically ill patients in most studies are usually by location and seldom a specific disease and there are clinical conditions to the formation of syndromes rather than well-defined diagnosis. Moreover, patients whose disease progression warrants admission to the intensive care can be in their late and more severe stages. Nonetheless, increased understanding of the risk factors of selected conditions and limitations of the clinical syndrome will allow appropriate patients to be selected for specific trials[23].

Additional challenges and limitation in this study include variability in sedation management and body mass. Firstly, sedation prescription was protocol-driven and levels of sedation were similar among the cohort and throughout the study; the lower level of sedation upon weaning from mechanical ventilation in this study cannot therefore account for higher energy expenditure than during ventilatory support. In terms of metabolically active muscle mass, this can directly predict energy expenditure yet could not be directly ascertained or assumed stable in this study due to the addition/removal of resuscitation fluid and/or loss of muscle mass with prolong total bed rest. Finally, duration in intensive care represents a major confounding variable given that caloric intake was positively associated with how long a patient remained on the ward. The length of stay in intensive care was longer than duration on mechanical ventilation because patients would usually be weaned from mechanical ventilation prior to transfer to general care wards (Table 1).

Conclusion

This study provides novel insight regarding the metabolic profile of critically ill patients during mechanical ventilation and in the transition towards liberation. The observed responses in patients' respiration and ventilatory cycles hold potential implications for nutritional support with a view to improved clinical outcomes. The economic benefits of accurate metabolic profiling amongst critically ill populations can bring positive impact on healthcare savings[33,38] and should form the focus of future studies.

References

1. Plank, LD, Graham, LH. Energy balance in critically ill. *Proceedings of the Nutrition Society*. 2003:62:545-552.

2. Cunneen, J, Cartwright, M. The puzzle of sepsis fitting the pieces of the inflammatory response with treatment. *AACN Clinical Issues*. 2004;15:18-44.

3. Fontaine, E, Müller, MJ. Adaptive alterations in metabolism: practical consequences on energy requirements in the severely ill patient. *Current Opinion in Clinical Nutrition and Metabolic Care*. 2011;14:171–175.

4. Villet, S, Chiolero, RL, Bollmann, MD, Revelly, J, Cayeux, M, Delarue, J, Berger, MM. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. *Clinical Nutrition*. 2003;24:502-509.

5. Kreymann, G, Grosser, S, Buggisch, P, Gottschall, C, Matthaei, S, Greten, H. Oxygen consumption and resting metabolic rate in sepsis, sepsis syndrome, and septic shock. *Critical Care Medicine.* 1993;21:1012-1019.

6. Dickerson, RN, Vehe, KL, Mullen, JL, Feurer, ID. Resting energy expenditure in patients with pancreatitis. *Critical Care Medicine*. 1991;19:484-490.

7. Uehara, M, Plank, LD, Hill, GL. Components of energy expenditure in patients with severe sepsis and major trauma: A basis for clinical care. *Critical Care Medicine*. 1999; 27:1295-1302.

8. Wolfe, R. Substrate utilization/ insulin resistance in sepsis/ trauma. *Clinical Endocrinology and Metabolism.* 1997; 4:645-657.

9. Martinez, A, Chiolero, R, Bollman, M, Jean-Pierre, R, Berger, M, Cayeux, C, Tappy, L. Assessment of adipose tissue metabolism by means of subcutaneous microdialysis in patients with sepsis or circulatory failure. *Clinical Physiology and Functional Imaging*. 2003;23:286-292.

10. Jeevanandam, M, Young, DH, Schiller, WR. Nutritional impact on the energy cost of fat fuel mobilization in polytrauma victims. *The Journal of Trauma*. 1990;30:147-154.

11. Weissman, C, Kemper, M, Askanazi, J, Hyman, AI, Kinney, JM. Resting metabolic rate of the critically ill patient: measured versus predicted. *The Journal of Anesthesiology*. 1986; 64:673-679.

12. Askanazi J, Weissman C, Rosenbaum, SH, Milic-Emili J, Kinney JM. Nutrition and the respiratory system. *Critical Care Medicine*. 1982;10:163-172.

13. Frayn, KN. Calculation of substrate oxidation rates in vivo from gaseous exchange. *Journal of Applied Physiology*. 1983;55:628-634.

14. da Rocha E, Alves VGF, da Fonseca RBV. Indirect calorimetry: methodology, instruments and clinical application. *Clinical Nutrition and Metabolic Care.* 2006;9: 247-256.

15. Benotti PN, Bistrian B. Metabolic and nutritional aspects of weaning from mechanical ventilation. *Critical Care Medicine*. 1989;17:181-185.

16. Cohen JD, Shapiro M, Grozovski E, Lev S, Fisher H, Singer P. Extubation outcome following a spontaneous breathing trial with automatic tube compensation versus continuous positive airway pressure. *Critical Care Medicine.* 2006;34: 682–686.

17. Porter, C. Indirect calorimetry in critically ill patients: role of the clinical dietitian in interpreting results. *Journal of the American Dietetic Association.* 1996;96:49-54.

18. Jeukendrup, AR, Wallis, GA. Measurement of substrate oxidation during exercise by means of gas exchange measurements. *International Sports Medicine*. 2004;26:S28-37.

19. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods.* 2007;39:175-191.

20. McClave SA, Spain DA, Skolnick JL, Lowen CC, Kleber MJ, Wickerham PS, Vogt JR, Looney SW. Achievement of steady state optimizes results when performing indirect calorimetry. *Journal of Parenteral and Enteral Nutrition.* 2003;27:16-20.

21. Bloch, AS, Mueller, C. Enteral and Parenteral Nutrition Support. In Mahan, L.K. & Escott-Stump (Eds.), Krause's Food, Nutrition & Diet Therapy. Philadelphia: W.B. Saunders; 1991:464.

22. Savard J, Faisy C, Lerolle N, Guerot E, Diehl J, Fagon J. Validation of a predictive method for an accurate assessment of resting energy expenditure in medical mechanically ventilated patients. *Critical Care Medicine.* 2008;36:1175-1183.

23. Herbert, PC, Cook, DJ, Wells, G, Marshall, J. The design of randomized clinical trials in critically ill patients. *Chest.* 2002;121:1290-1300.

24. Terao, Y, Miura, K, Saito, M, Sekino, M, Fukusaki, M, and Sumikawa, K. *Critical Care Medicine.* 2003;31:830-833.

25. Benotti, PN, Bistrian, B. Metabolic and nutritional aspects of weaning from mechanical ventilation. *Critical Care Medicine.* 1989;17:181-185.

26. Akoumianaki, E, Lyazidi, A, Rey, N, Matamis, D, Perez-Martinez, N, Giraud, R, Mancebo, J, Brochard, L, Richard, J-CM. Mechanical ventilation-induced reverse-triaggered breaths. A frequently unrecognized form of neuromechanical coupling. *Chest.* 2013;143:927-938.

27. Taggert, J, Keating, KP, Evasovich, M, Donahue, S, Gleason, E. Indirect calorimetry as an adjunct to successful weaning from mechanical ventilation. *Chest.* 2000;118:3015.

28. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Critical Care Medicine.* 1985;13:818–29.

29. Medical Graphics Corporation. MedGraphics Systems User's Manual. Minneapolis: Medical Graphics Corporation; 2009.

30. Bellani, G, Foti, G, Spagnolli, E, Milan, M, Zanella, A, Greco, M, Patroniti, N, Pesenti, A. Increase of oxygen consumption during a progressive decrease of ventilatory support is lower in patients failing the trial in comparison with those who succeed. *Anesthesiology.* 2010;113:378–85.

31. Branson, R, Johannigman, J. The measurement of energy expenditure. *Nutrition in Clinical Practice*. 2004;19:622-636.

32. Holdy, KE. Monitoring energy metabolism with indirect calorimetry: instruments, interpretation and clinical application. *Nutrition in Clinical Practice*. 2004;19:447–454.

33. Braunschweig C, Gomez S, Sheean PM. Impact of declines in nutritional status on outcomes in adult patients hospitalized for more than 7 days. *Journal of American Dietetic Association.* 2000;100:1316-1322.

34. Neumayer, LA, Smout, RJ, Horn, HG, Horn, SD. Early and sufficient feeding reduces length of stay and charges in surgical patients. *Journal of Surgical Residence*. 2001;95:73-77.

35. Heyland, DK, Cahill, N, Day, AG. Optimal amount of calories for critically ill patients: depends on how you slice the cake! *Critical Care Medicine*. 2011;39:2619 –2626.

36. Hoher JA, Teixeira PJZ, Hertz F, Moreira JD. A comparison between ventilation modes: how does activity level affect energy expenditure estimates? *Journal of Parenteral and Enteral Nutrition.* 2008;32:176-183.

37. Kan, M, Chang, H, Sheu, W, Cheng, C, Lee, B, Huang Y. Estimation of energy requirements for mechanically ventilated critically ill patients using nutritional status. *Critical Care.* 2003;7:R108-R116.

38. Reid, C. Frequency of under- and overfeeding in mechanically ventilated ICU patients: causes and possible consequences. *Journal of Human Nutrition*. 2006;19:13-22.

39. Kiss, CM, Byham-Gray, L, Denmark, R, Loetscher, R, Brody, RA. The impact of implementation of a nutrition support algorithm on nutrition care outcomes in an intensive care unit. *Nutrition in Clinical Practice*. 2012;12:793-801.

40. Ireton-Jones C, Turner WW, Liepa GU, Baxter CR. Equations for the estimation of energy expenditures in patients with burns with special reference to ventilatory status. *Journal of Burn Care Rehabilitation.* 1992;13:330-333.

41. Frary, CD, Johnson, RK. Energy. In Krause’s Food, Nutrition and Diet Therapy. United States of America: Elsevier; 2000:23-36.

42. Brandi, LS, Santini, L, Bertolini, R, Malacarne, P, Casagli, S, Baraglia, AM. Energy expenditure and severity of injury and illness indices in multiple trauma patients. *Critical Care Medicine*. 1999;27:2684-2689.

43. Jeejeebhoy, KN. Malnutrition, fatigue, frailty, vulnerability, sarcopenia and cachexia: overlap of clinical features. *Current Opinion Clinical Nutrition Metabolism Care*. 2012;15:213 – 219.

44. Zambon, M, Beccaria, P, Matsuno, J, et al. Mechanical ventilation and diaphragmatic atrophy in critically ill patients: an ultrasound study. *Critical Care Medicine*. 2016;44:1347-1352.