CHEST™

Impact of Early Mobilization on Glycemic Control and ICU-Acquired Weakness in Critically Ill Patients Who Are Mechanically Ventilated

Bhakti K. Patel, MD; Anne S. Pohlman, MSN; Jesse B. Hall, MD, FCCP; and John P. Kress, MD, FCCP

BACKGROUND: ICU-acquired weakness (ICU-AW) has immediate and long-term consequences for critically ill patients. Strategies for the prevention of weakness include modification of known risk factors, such as hyperglycemia and immobility. Intensive insulin therapy (IIT) has been proposed to prevent critical illness polyneuropathy. However, the effect of insulin and early mobilization on clinically apparent weakness is not well known.

METHODS: This is a secondary analysis of all patients with mechanical ventilation (N = 104) previously enrolled in a randomized controlled trial of early occupational and physical therapy vs conventional therapy, which evaluated the end point of functional independence. Every patient had IIT and blinded muscle strength testing on hospital discharge to determine the incidence of clinically apparent weakness. The effects of insulin dose and early mobilization on the incidence of ICU-AW were assessed.

RESULTS: On logistic regression analyses, early mobilization and increasing insulin dose prevented the incidence of ICU-AW (OR, 0.18, $P = .001$; OR, 0.001, $P = .011$; respectively) independent of known risk factors for weakness. Early mobilization also significantly reduced insulin requirements to achieve similar glycemic goals as compared with control patients (0.07 units/kg/d vs 0.2 units/kg/d, $P < .001$).

CONCLUSIONS: The duel effect of early mobilization in reducing clinically relevant ICU-AW and promoting euglycemia suggests its potential usefulness as an alternative to IIT.

CHEST 2014; 146(3):583-589

Manuscript received August 28, 2013; revision accepted May 2, 2014; originally published Online First June 26, 2014.

ABBREVIATIONS: APACHE = Acute Physiology and Chronic Health Evaluation; AUC = area under the curve; ICU-AW = ICU-acquired weakness; IIT = intensive insulin therapy

AFFILIATIONS: From the Department of Medicine, Section of Pulmonary and Critical Care, University of Chicago, Chicago, IL.

FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

CORRESPONDENCE TO: John P. Kress, MD, FCCP, Department of Medicine, Section of Pulmonary and Critical Care, 5841 S Maryland Ave, MC6026, Chicago, IL 60637; e-mail: jkress@medicine.bsd.uchicago.edu

DOI: 10.1378/chest.13-2046

Neuromuscular weakness in the ICU can occur within hours of mechanical ventilation[1] and persist for years, resulting in long-term functional disability.[2,3] At least one-fourth of patients with prolonged mechanical ventilation[4,5] develop ICU-acquired weakness (ICU-AW), which can lengthen the duration of mechanical ventilation[6,7] and is associated with increased mortality.[8,9] ICU-AW is a clinically detected weakness in critically ill patients in whom there is no alternative plausible cause.[10] Several risk factors, including corticosteroids,[4] immobilization,[11] multiorgan failure, and hyperglycemia,[12] have been identified as potential targets to modify the incidence of ICU-AW.

Although the exact pathogenesis of ICU-AW remains unknown, sustained immobility and inflammation seem to play a role. Hyperglycemia in critical illness is often a consequence of this sustained inflammation coupled with enhanced hepatic gluconeogenesis and immobility causing decreased peripheral glucose uptake by skeletal muscle.[13] Hyperglycemia has been the subject of much study, with two randomized controlled single-center trials of intensive insulin therapy (IIT) in the medical and surgical ICU populations demonstrating a significant reduction in neuromuscular weakness identified by electromyographic studies.[14-16] Subsequent post hoc analysis suggested that euglycemia rather than insulin dose was related to the reduction of critical illness polyneuropathy.[17] However, multicenter studies of IIT failed to redemonstrate the mortality benefits of tight glycemic control and instead showed a significant increase in mortality,[18,19] cautioning the use of hyperinsulinemia to prevent neuromuscular complications of critical illness.

Exercise is known to improve hyperglycemia in other insulin-resistant states and has antiinflammatory effects suggesting its possible synergistic effect in preventing ICU-AW.[20,21] Therefore, we performed a secondary analysis of patients enrolled in an early mobility trial[11] during an era of widespread adoption of tight glycemic control. We sought to understand if increasing insulin dose decreases clinically relevant weakness as measured by bedside muscle strength testing. In addition, we sought to understand if early mobilization is associated with decreased incidence of ICU-AW when adjusting for other risk factors for weakness. Finally, given the effect of exercise on hyperglycemia and inflammation, we aimed to determine if early mobilization affects glycemic control and, in turn, exogenous insulin requirements in critical illness.

Materials and Methods

This study is a secondary analysis of a randomized controlled trial (N = 104) of patients in the medical ICU randomized to receive physical and occupational therapy within 72 h of mechanical ventilation (early mobilization) or standard care with therapy as ordered by the primary care team. Details of the entire patient population are published elsewhere.[11] All enrolled patients who were mechanically ventilated had daily interruption of sedatives,[22] protocol-based weaning from mechanical ventilation,[23] enteral feeding, and initiation of insulin infusion when three blood glucose concentration measurements exceeded 120 mg/dL. Insulin infusions were titrated to achieve a blood glucose level between 80 and 120 mg/dL throughout the ICU stay. All patients had an assessment by physical and occupational therapists blinded to randomization assignment on hospital discharge. Strength of three muscle groups in each upper and lower extremity was measured by Medical Research Council score on a scale from 0 to 5.[24,25] ICU-AW was diagnosed when an awake and attentive patient had a muscle strength sum score < 48 out of a maximal score of 60 when all muscle groups were able to be assessed.[4] Total daily insulin dose was collected during ICU stay and normalized to weight (kg). All blood glucose measurements were recording during the ICU stay. Cumulative daily corticosteroid doses were converted to prednisone equivalent dosing for comparison.[26]

Statistical Analysis

Data were analyzed using Stata 11.0 (StataCorp LP) software. Baseline and outcome variables were depicted as medians (interquartile ranges). We used Wilcoxon-Mann-Whitney two-sample rank-sum test to compare continuous variables and χ^2 test or Fisher exact test where appropriate to compare categorical variables. To avoid multiple comparisons of continuous variables with repeated measurements, we calculated area under the curve (AUC) for all measured glucose values as suggested by Matthews et al.[27]

A univariable analysis of the outcome of interest, ICU-AW, was performed, evaluating the effect of early mobilization, known risk factors for ICU-AW, and insulin dose (normalized by weight and ICU length of stay). To assess the effect of early mobilization and insulin dose on the occurrence of ICU-AW, logistic regression analysis was then performed, correcting for risk factors that showed at least a trend toward significance ($P \leq .1$) on univariable analysis and others that were linked to the outcome on a biologically plausible basis.

Results

A total of 41 of the 104 patients demonstrated ICU-AW on hospital discharge. Although the baseline characteristics of patients in the control and early mobilization treatment groups were comparable, the patients with ICU-AW were older, had higher APACHE (Acute Physiology and Chronic Health Evaluation) II scores, and had longer duration of mechanical ventilation (Table 1). There was no difference in total daily dosage of prednisone equivalents (mg/kg/d). Median AUC glucose level was comparable among patients with and without ICU-AW, indicating standardized application of IIT protocol.

TABLE 1] Univariable Analysis of Baseline and Outcome Characteristics of Patients by Incidence of ICU-AW

Characteristics	ICU-AW (n = 41)		No ICU-AW (n = 63)		*P* Value
Baseline characteristics					
Age	59.73	(52-70.13)	49.98	(25.45-63)	.002
Female sex	19	46	33	52	.55
Weight, kg	77.3	(66.7-99)	79.5	(70.5-103.4)	.49
BMI	28	(24.9-32.47)	27.5	(24.99-34.34)	.84
APACHE II	23	(19-25)	17	(13-21)	< .00001
Sepsis	36	88	51	81	.36
Diabetes	16	39	20	32	.45
Outcome characteristics					
Median AUC glucose,[a] mg/dL	131.4	(124.2-140.9)	131.1	(120.4-145.0)	.82
% Goal calories while intubated	38	(11-59)	33	(11-57)	.56
No. receiving corticosteroids in ICU	35	85	44	70	.07
Daily ICU prednisone,[b] mg/kg/d	1.34	(0.66-2.27)	1.57	(0.55-2.94)	.65
Daily ICU insulin, units/kg/d	0.11	(0.05-0.15)	0.11	(0.06-0.22)	.14
Ventilator days	9.28	(5.86-13.42)	6.47	(3.21-11.68)	.02

Data are No. patients (%) or median (IQR). APACHE = Acute Physiology and Chronic Health Evaluation; AUC = area under the curve; ICU-AW = ICU-acquired weakness; IQR = interquartile range.
[a]Median AUC of glucose measurements during ICU stay.
[b]Corticosteroid doses were converted to prednisone dose equivalents.

Based on this univariable analysis, age, APACHE II, early mobilization, and daily ICU insulin dose (units/kg/d) were entered as independent variables in the logistic regression for the incidence of ICU-AW. Increasing age and severity of illness (APACHE II) were associated with increased odds of developing ICU-AW (Table 2). Furthermore, early mobilization decreased the odds of weakness on hospital discharge by 82% ($P = .003$). Although patients with and without ICU-AW achieved similar glycemic control, increasing insulin dosage was also independently protective against the development of ICU-AW (OR, 0.001 per unit of insulin/kg/d; $P = .011$).

Although control and early mobilization patients achieved similar enteral feeding goals and glycemic targets, univariable analysis (Table 3) demonstrated that mobilized patients required less insulin (0.07 units/kg/d vs 0.2 units/kg/d, $P < .0001$). Interestingly, despite a slight but nonsignificant trend toward more daily prednisone dosage in early mobilization patients (Table 3), less insulin was required to achieve normoglycemia. Additional analysis of the risk of ICU-acquired weakness stratified by insulin dose suggested decreasing risk of weakness with increasing insulin dose and the prescription of early mobilization (Fig 1).

TABLE 2] Logistic Regression Analysis for the Development of ICU-AW

Variable	OR	95% CI	*P* Value
Age	1.04	1.00 to 1.07	.024
APACHE II	1.13	1.04 to 1.23	.004
Early mobilization	0.18	0.06 to 0.55	.003
Daily ICU insulin, units/kg/d	0.001	4.62×10^{-6} to 0.20	.011

See Table 1 legend for expansion of abbreviations.

Discussion

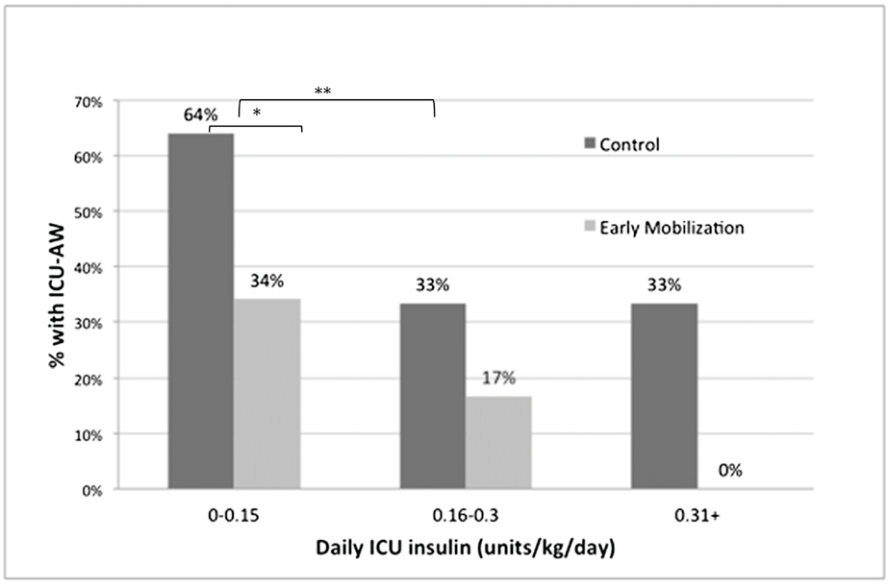
Hyperglycemia has been associated with poor outcomes, including increased infectious complications,[12,28,29] ICU-AW,[4,30] and mortality.[31-33] Targeting hyperglycemia pharmacologically to prevent these outcomes is complicated by hypoglycemic events and glucose variability, which in practice paradoxically increases mortality.[17] The benefits of euglycemia in preventing neuromuscular complications of critical illness identified by electromyographic testing are clear.[15] However, routine electromyographic examinations are costly, invasive, and limited by tissue edema and patient participation with the examination. In addition, the discriminatory value of these examinations in identifying weakness associated with true functional deficits is unknown. Our data suggest that the incidence of clinically significant weakness with IIT still approaches 50%. However, the addition of

TABLE 3] Univariable Analysis of Baseline and Outcome Characteristics of Patients by Randomization

Characteristics	Control (n = 55)		Early Mobilization (n = 49)		*P* Value
Baseline characteristics					
Age	54.4	(46.4-66.8)	57.7	(36.5-68.8)	…
Female sex	23	42	29	59	…
Weight, kg	79.6	(68.8-99)	79	(70.5-99.5)	…
BMI	28	(23.2-34.3)	27.4	(25.1-32.1)	…
APACHE II	19	(13-23)	20	(16-24)	…
Sepsis	45	82	42	86	…
Diabetes	18	33	18	37	…
Outcome characteristics					
Median AUC glucose,[a] mg/dL	130.6	(122.4-141.8)	131.9	(123.9-144.8)	.5
% Goal calories while intubated	34	(15-58)	37	(11-58)	.99
Daily ICU prednisone,[b] mg/kg/d	1.1	(0.6-2.4)	1.7	(0.9-3.0)	.15
Daily ICU insulin, units/kg/d	0.2	(0.1-0.2)	0.07	(0.03-0.1)	< .0001
ICU-AW on hospital discharge	26	47	15	31	.08
Ventilator days	6.1	(4.0-9.6)	3.4	(2.3-7.3)	.02

Data are No. patients (%) or median (IQR). See Table 1 legend for expansion of abbreviations.
[a]Median AUC of glucose measurements during ICU stay; of note, morning median glucose measurements were also not different (data not shown).
[b]Corticosteroid doses were converted to prednisone dose equivalents.

early occupational and physical therapy is associated with an 82% reduction in the odds of developing ICU-AW, when adjusting for other risk factors such as age and severity of illness. These data suggest that immobility may be a more potent risk factor for weakness, or perhaps the synergy of maintaining euglycemia with mobility and the antiinflammatory effects of exercise are highly protective.



* Difference in % with ICU-AW in control vs. Early Mobilization receiving 0-0.15 insulin units/kg/day (64% vs. 34% p=0.02)

** Difference in % with ICU-AW in Control patients receiving 0-0.15 vs. 0.15-0.3 insulin units/kg/day (64% vs. 33% p=0.04) ICU= Intensive Care Unit ICU-AW= ICU-Acquired Weakness

Figure 1 – *Percent at risk for ICU-AW at hospital discharge stratified by daily ICU insulin dose and randomization group.*

Interestingly, increasing insulin dose was protective for ICU-acquired weakness even with similar glycemic control among patients with and without weakness. Our findings are in contrast with a previous post hoc analysis of an earlier IIT trial[15] that used nerve conduction studies and demonstrated that euglycemia and not insulin dose was the primary effector of reduced critical illness polyneuropathy.[17] These findings are not surprising, given that insulin-independent tissues, such as nerves, likely require euglycemia to prevent the increased glucose flux and oxidative stress seen in hyperglycemic states.[34,35] In contrast, skeletal muscle uses insulin and exercise to mediate uptake of glucose, suggesting that insulin dose and mobilization may be the primary effectors of improved clinically apparent muscle strength. This theory is supported by increased insulin-mediated mRNA expression of glucose transporter-4 in postmortem skeletal muscle biopsies of patients receiving IIT in the surgical ICU tight glycemic control trial.[36] Although insulin dose may be associated with reduced ICU-AW, its safety profile in critically ill patients cautions against its use as a therapy to prevent weakness.

Our finding that mobilized patients achieved the same glycemic targets as control patients despite receiving approximately two-thirds less insulin suggests that the euglycemic effect of exercise is preserved in critical illness. Hyperglycemia in critical illness is in part a consequence of decreased peripheral glucose uptake by peripheral tissues. Glucose uptake in skeletal muscle is compromised by insulin resistance and loss of exercise-induced uptake during immobilization. It is conceivable that mobilization reduces the need to administer exogenous insulin as hyperglycemia is abated by increased glucose transport in contracting skeletal muscle. Clearly, early mobilization had a potent effect on hyperglycemia, since a daily mobility session (average duration, 25 min)[37] was sufficient to achieve greatly improved glucose homeostasis. Further, the metabolic effects of mobilization appear to persist well beyond the therapy session itself, given remarkably reduced daily insulin requirements in these patients. The mechanisms behind this interesting observation require further investigation. The pathway for contractile activation of skeletal muscle glucose transport has been shown to be normal in animal models of insulin resistance and in patients with type 2 diabetes.[20] Further, it appears that a single bout of 45 to 60 min of exercise in patients with type 2 diabetes can enhance glucose transport[38] and insulin sensitivity that persists up to 20 h after exercise.[39] Thus, the notion that early mobilization of patients may overcome the insulin resistance of critical illness, improving hyperglycemia and possibly insulin sensitivity, has biologic plausibility.

Our analysis has some important limitations. Secondary analysis of these data can merely suggest associations between insulin dose and mobilization on weakness. The original trial of early mobilization demonstrated a nonsignificant trend toward decreased ICU-AW with this intervention. Although the original study was not powered to detect a difference in the incidence of ICU-AW, this analysis presents the first data, to our knowledge, that suggest that mobilization is associated with reduced clinically apparent weakness and warrants further study. Also, the original study was done in an era of increased use of corticosteroids in septic shock, which contributed to a high proportion of patients receiving steroids (and likely requiring insulin). However, the dosage of corticosteroids did not seem to be associated with increased ICU-acquired weakness and seems consistent with other published data suggesting that the link between ICU-AW and corticosteroids remains unclear.[40,41] Despite an enriched population of critically ill patients receiving steroids, we were still able to demonstrate the possible protective association of insulin dose and early mobilization on weakness.

Our findings demonstrate contrasting relationships between insulin requirements, ICU-AW, and early mobilization. Increasing insulin administration was associated with decreased weakness, and yet mobilized patients required less insulin and were stronger. This paradox likely represents the tension between pharmacologic and physiologic approaches to the prevention of weakness. The therapeutic index of insulin therapy is narrow, and doses required to prevent weakness may be at the price of patient safety. Immobile patients may require excess exogenous insulin to overcome their insulin resistance, and perhaps the mechanism for reduced weakness is related to the anabolic effects of insulin counteracting the catabolic state in critical illness. Small human studies demonstrating increased muscle protein synthesis[42] and decreased protein breakdown[43] suggest biologic plausibility of this hypothesis. Thus, insulin may improve the imbalance of proteolysis over protein synthesis induced by inflammation, thereby preventing atrophy, a proposed mechanism of critical illness myopathy.[44] However, predicting insulin need and using hyperinsulinemia to prevent weakness in the immobile patient are problematic in the ICU. In contrast, mobilizing patients may physiologically

sensitize tissues to insulin and enhance endogenous insulin effects.

Conclusions

Early mobilization may be preferred to intensive insulin therapy and appears to have higher potency in the prevention of ICU-AW, possibly because of its dual effects in restoring glucose homeostasis and preventing disuse atrophy. Thus, early mobilization may provide a physiologic mechanism for overcoming insulin resistance of critical illness and ICU-AW and warrants further study.

Acknowledgments

Author contributions: B. K. P. is the guarantor of the contents of this manuscript and data collection/analysis. B. K. P. and J. P. K. contributed to conception and design of study, data analysis and interpretation, manuscript preparation, and final approval of version to be published; A. S. P. contributed to acquisition and interpretation of data, revising manuscript for important intellectual content, and final approval of version to be published; and J. B. H. contributed to conception and design of study, data analysis and interpretation, critical revision of manuscript for important intellectual content, and final approval of version to be published.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

References

1. Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med*. 2008;358(13):1327-1335.
2. Herridge MS, Tansey CM, Matté A, et al; Canadian Critical Care Trials Group. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364(14):1293-1304.
3. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304(16):1787-1794.
4. De Jonghe B, Sharshar T, Lefaucheur JP, et al; Groupe de Réflexion et d'Etude des Neuromyopathies en Réanimation. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA*. 2002;288(22):2859-2867.
5. de Letter MA, Schmitz PI, Visser LH, et al. Risk factors for the development of polyneuropathy and myopathy in critically ill patients. *Crit Care Med*. 2001;29(12):2281-2286.
6. Garnacho-Montero J, Amaya-Villar R, García-Garmendía JL, Madrazo-Osuna J, Ortiz-Leyba C. Effect of critical illness polyneuropathy on the withdrawal from mechanical ventilation and the length of stay in septic patients. *Crit Care Med*. 2005;33(2):349-354.
7. De Jonghe B, Bastuji-Garin S, Sharshar T, Outin H, Brochard L. Does ICU-acquired paresis lengthen weaning from mechanical ventilation? *Intensive Care Med*. 2004;30(6):1117-1121.
8. Leijten FS, Harinck-de Weerd JE, Poortvliet DC, de Weerd AW. The role of polyneuropathy in motor convalescence after prolonged mechanical ventilation. *JAMA*. 1995;274(15):1221-1225.
9. Garnacho-Montero J, Madrazo-Osuna J, García-Garmendia JL, et al. Critical illness polyneuropathy: risk factors and clinical consequences. A cohort study in septic patients. *Intensive Care Med*. 2001;27(8):1288-1296.
10. Stevens RD, Marshall SA, Cornblath DR, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. *Crit Care Med*. 2009; 37(suppl 10):S299-S308.
11. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009;373(9678):1874-1882.
12. de Jonghe B, Lacherade JC, Sharshar T, Outin H. Intensive care unit-acquired weakness: risk factors and prevention. *Crit Care Med*. 2009;37(suppl 10):S309-S315.
13. Langouche L, Van den Berghe G. Glucose metabolism and insulin therapy. *Crit Care Clin*. 2006;22(1):119-129.
14. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345(19):1359-1367.
15. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006;354(5):449-461.
16. Hermans G, Schrooten M, Van Damme P, et al. Benefits of intensive insulin therapy on neuromuscular complications in routine daily critical care practice: a retrospective study. *Crit Care*. 2009; 13(1):R5.
17. Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. *Crit Care Med*. 2003;31(2):359-366.
18. Finfer S, Chittock DR, Su SY, et al; NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283-1297.
19. Brunkhorst FM, Engel C, Bloos F, et al; German Competence Network Sepsis (SepNet). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008;358(2):125-139.
20. Henriksen EJ. Invited review: effects of acute exercise and exercise training on insulin resistance. *J Appl Physiol (1985)*. 2002;93(2):788-796.
21. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol (1985)*. 2005;98(4):1154-1162.
22. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342(20):1471-1477.
23. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371(9607):126-134.
24. Kleyweg RP, van der Meché FG, Meulstee J. Treatment of Guillain-Barré syndrome with high-dose gammaglobulin. *Neurology*. 1988;38(10):1639-1641.
25. Kleyweg RP, van der Meché FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barré syndrome. *Muscle Nerve*. 1991;14(11):1103-1109.
26. Meikle AW, Tyler FH. Potency and duration of action of glucocorticoids. Effects of hydrocortisone, prednisone and dexamethasone on human pituitary-adrenal function. *Am J Med*. 1977;63(2): 200-207.
27. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *BMJ*. 1990; 300(6719):230-235.
28. Gore DC, Chinkes D, Heggers J, Herndon DN, Wolf SE, Desai M. Association of hyperglycemia with increased mortality after severe burn injury. *J Trauma*. 2001;51(3):540-544.
29. Bochicchio GV, Sung J, Joshi M, et al. Persistent hyperglycemia is predictive of outcome in critically ill trauma patients. *J Trauma*. 2005;58(5):921-924.
30. Witt NJ, Zochodne DW, Bolton CF, et al. Peripheral nerve function in sepsis and multiple organ failure. *Chest*. 1991;99(1):176-184.
31. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc*. 2003;78(12):1471-1478.
32. Egi M, Bellomo R, Stachowski E, French CJ, Hart G. Variability of blood glucose concentration and short-term mortality

in critically ill patients. *Anesthesiology*. 2006;105(2):244-252.

33. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet*. 2000;355(9206):773-778.
34. Vincent AM, McLean LL, Backus C, Feldman EL. Short-term hyperglycemia produces oxidative damage and apoptosis in neurons. *FASEB J*. 2005;19(6):638-640.
35. Van Cromphaut SJ, Vanhorebeek I, Van den Berghe G. Glucose metabolism and insulin resistance in sepsis. *Curr Pharm Des*. 2008;14(19):1887-1899.
36. Mesotten D, Swinnen JV, Vanderhoydonc F, Wouters PJ, Van den Berghe G. Contribution of circulating lipids to the improved outcome of critical illness by glycemic control with intensive insulin therapy. *J Clin Endocrinol Metab*. 2004;89(1):219-226.
37. Pohlman MC, Schweickert WD, Pohlman AS, et al. Feasibility of physical and occupational therapy beginning from initiation of mechanical ventilation. *Crit Care Med*. 2010;38(11):2089-2094.
38. Kennedy JW, Hirshman MF, Gervino EV, et al. Acute exercise induces GLUT4 translocation in skeletal muscle of normal human subjects and subjects with type 2 diabetes. *Diabetes*. 1999;48(5):1192-1197.
39. Devlin JT, Hirshman M, Horton ED, Horton ES. Enhanced peripheral and splanchnic insulin sensitivity in NIDDM men after single bout of exercise. *Diabetes*. 1987;36(4):434-439.
40. Hermans G, Wilmer A, Meersseman W, et al. Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. *Am J Respir Crit Care Med*. 2007;175(5):480-489.
41. Hough CL, Steinberg KP, Taylor Thompson B, Rubenfeld GD, Hudson LD. Intensive care unit-acquired neuromyopathy and corticosteroids in survivors of persistent ARDS. *Intensive Care Med*. 2009;35(1):63-68.
42. Gore DC, Wolf SE, Sanford AP, Herndon DN, Wolfe RR. Extremity hyperinsulinemia stimulates muscle protein synthesis in severely injured patients. *Am J Physiol Endocrinol Metab*. 2004;286(4):E529-E534.
43. Agus MS, Javid PJ, Ryan DP, Jaksic T. Intravenous insulin decreases protein breakdown in infants on extracorporeal membrane oxygenation. *J Pediatr Surg*. 2004;39(6):839-844.
44. Batt J, dos Santos CC, Cameron JI, Herridge MS. Intensive care unit-acquired weakness: clinical phenotypes and molecular mechanisms. *Am J Respir Crit Care Med*. 2013;187(3):238-246.