Citation	<p>Van den Berghe G, (2016),</p> <p>The 2016 ESPEN Sir David Cuthbertson lecture: Interfering with neuroendocrine and metabolic responses to critical illness: From acute to long-term consequences</p> <p>Clin Nutr. 2016 Oct 18. pii: S0261-5614(16)31286-9</p>
Archived version	<p>Author manuscript: the content is identical to the content of the published paper, but without the final typesetting by the publisher</p>
Published version	<p>http://dx.doi.org/10.1016/j.clnu.2016.10.011</p>
Journal homepage	<p>http://www.journals.elsevier.com/clinical-nutrition/</p>
Author contact	<p>greet.vandenbergh@med.kuleuven.be</p> <p>+ 32 (0)16 344021</p>
IR	<p>https://lirias.kuleuven.be/handle/123456789/555448</p>

(article begins on next page)

Accepted Manuscript

The 2016 espen sir david cuthbertson lecture: interfering with neuroendocrine and metabolic responses to critical illness: from acute to long-term consequences

Greet Van den Berghe, MD, PhD

PII: S0261-5614(16)31286-9

DOI: [10.1016/j.clnu.2016.10.011](https://doi.org/10.1016/j.clnu.2016.10.011)

Reference: YCLNU 2955

To appear in: *Clinical Nutrition*

Received Date: 11 October 2016

Accepted Date: 12 October 2016

Please cite this article as: Van den Berghe G, The 2016 espen sir david cuthbertson lecture: interfering with neuroendocrine and metabolic responses to critical illness: from acute to long-term consequences, *Clinical Nutrition* (2016), doi: 10.1016/j.clnu.2016.10.011.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

THE 2016 ESPEN SIR DAVID CUTHBERTSON LECTURE:

**INTERFERING WITH NEUROENDOCRINE AND METABOLIC RESPONSES TO
CRITICAL ILLNESS: FROM ACUTE TO LONG-TERM CONSEQUENCES**

Greet Van den Berghe MD, PhD

Clinical Division and Laboratory of Intensive Care Medicine, Department Cellular and Molecular
Medicine, KU Leuven University and Hospitals, B-3000 Leuven Belgium

greet.vandenberghe@kuleuven.be

Work supported by the Research Foundation Flanders (G041712N), the Methusalem Program of the
Flemish Government (METH/14/06), and the European Research Council under the European Unions
Seventh Framework Program (FP7/2013-2018 ERC Advanced Grant Agreement n° 321670).

Running head: CUTHBERTSON LECTURE 2016

Keywords: critical illness, neuroendocrine, growth hormone, thyroid, adrenal, cortisol, nutrition, fasting,
glucose, hyperglycemia, insulin

Current word count main text: 281

SUMMARY (287 words)

The metabolic translational research - from bed to bench and back - performed by our team over the past 20 years resulted in a few paradigm-shifting insights with implications for intensive care medicine. It is an honor for the entire team that this work was awarded the 2016 Sir David Cuthbertson lecture. In the early years, we discovered that the acute neuroendocrine stress responses to severe illnesses are quite different from those during the chronic phase when patients remain depend on intensive medical care for a long period of time. Then, we have shown that severe hyperglycemia, when sustained beyond the acute phase of critical illness, is harmful for adults as well as children. In young children, hyperglycemia was also shown to have important deleterious long-term neurocognitive consequences. Our experimental studies uncovered the underlying mechanisms, in which damage to mitochondria plays a key role. Subsequently, we have discovered that autophagy, a cellular pathway crucial for removal of damaged mitochondria and proteins, becomes insufficient during critical illness, in part because patients are forcefully fed. These preclinical findings were translated back to the clinic by showing that tolerating the fasting response instead of feeding patients early reduced infections, prevented complications and accelerated recovery. Finally, we have shown that the hypercortisolemia of critical illness is driven by reduced breakdown rather than by increased production, a finding that challenged another long-standing dogma. It also provided an explanation for the risk of adrenal atrophy in the chronic phase of critical illness and called for caution regarding treatment with high doses of corticosteroids. When not metabolized as normal such an overtreatment can severely disrupt metabolic homeostasis. Future research focuses on the long-term legacy of critical illness and on how to potentially prevent it.

PROLONGED CRITICAL ILLNESS: A RECENT PHENOMENON IN THE EVOLUTION OF MANKIND

Intensive care medicine started in the 1950s with the polio epidemics in Scandinavia and the development of the iron lung. Over less than 7 decades, booming technological developments have enabled modern intensive care medicine to become a high-tech specialty which allows survival of previously lethal trauma or illnesses. The patients who are currently treated in ICUs worldwide have segregated out in two sub-populations. On the one hand there is the majority of patients who need intensive care only for a few days during which the high-tech interventions focus on the cause of the insult and on restoration and maintenance of homeostasis. These patients recover fast and the risk of death is 2%. On the other hand there is the smaller subgroup of patients who need prolonged intensive care for weeks or months. These patients, irrespective of the reason for which they were admitted to intensive care present uniformly with lingering multiple organ failure, a high risk of new infections and severe weakness. This 25% of all ICU patients, however, have a 20% risk of not leaving the ICU alive and consume 75% of the resources for intensive care medicine. The survivors also suffer from an important “legacy” of prolonged critical illness, that for adults comprises neurocognitive and psychiatric problems, persisting weakness and sarcopenia, loss of bone mass and a high fracture risk, and an increased risk of chronic renal failure, even after full recovery from acute kidney injury. Children who have been critically ill reveal growth retardation and a pronounced neurocognitive deficit 4 years later. Over the last 20 years, my research team has focused on “reverse” translational research, from the bed to the bench and back, in order to better understand why some patients do not swiftly recover and suffer from this important legacy, with a focus on endocrine and metabolic pathways. We have tried to learn from the responses that occur in the acute phase of illness, as evolution must have allowed adaptive responses to contribute to survival, and try to find implications for treatment of patients in that prolonged phase of illness, the latter being a “newly created” condition in the evolution of mankind. In

this narrative review, I briefly summarize the 4 major “discoveries” that have resulted from our team efforts.

THE NEURO-ENDOCRINE RESPONSE TO CRITICAL ILLNESS HAS A BI-PHASIC PATTERN

This insight followed after many years of research in patients and in animal models, but was sparked by a clinical observation early in my clinical career, when I, as a junior physician, was taking care of critically ill children after complex surgery for congenital heart anomalies. When these children did not recover swiftly and entered the chronic phase of critical illness, they physically started to resemble old people. The aging literature at that time was very much focusing on the hypothalamic-pituitary axes. We found that the phenotype of “accelerating aging” in prolonged critically ill patients was related to a suppression of these axes in the prolonged phase of critical illness that followed an initial hyperactive hypothalamic-pituitary system (Figure 1). Indeed, in the acute phase of illness (first hours to few days after onset), the growth hormone (GH), thyrotrophin (TSH) and corticotrophin (ACTH) secretory activity is amplified, whereas levels of active thyroid hormone (triiodothyronine, T3) and insulin-like growth factor-I (IGF-I) are low due to inactivation of anabolic pathways and the levels of the catabolic hormone cortisol are elevated. In prolonged critical illness, when patients depend on intensive care for weeks, we found that pulsatile secretion of GH, TSH and ACTH is uniformly suppressed which now drives the low circulating levels of IGF-I and thyroid hormones (1-14). In the prolonged phase of critical illness, plasma cortisol remains elevated in the presence of low ACTH largely due to, as I’ll explain later, a suppressed cortisol breakdown. In animal models we could identify that in prolonged but not acute critical illness indeed is hallmarked by a loss of expression of thyrotrophin releasing hormone in the hypothalamus and that there is a lack of activation of the ghrelin receptor. We could show, in animal studies and in patients, that by co-infusion the releasing factors that we identified to be missing in the prolonged phase of critical illness, GH and TSH secretion can be reactivated back to the patterns we observed

during the acute phase of illness. This reactivation of GH and TSH secretion also restored normal levels of IGF-I and thyroid hormones and resulted in a clear anabolic response in bone and skeletal muscle. These were quite exciting findings that we thought needed to be further explored as a potential treatment to accelerate recovery from critical illness. We were preparing for a large randomized controlled trial to test the impact of these releasing factors on survival and rehabilitation as clinically relevant endpoints, but then faced the problem that these compounds were no longer available for use in patients. And also, we got side tracked as we stumbled on something that lead us to our second “discovery”.

CONSEQUENCES OF PRONOUNCED HYPERGLYCEMIA DURING CRITICAL ILLNESS

Our previous animal and patient work on the neuroendocrine responses to critical illness had revealed that high circulating levels of IGF-binding protein-1 (IGFBP1), a protein that is normally suppressed by insulin, could quite accurately predict which patient would not survive the ICU phase of critical illness. Its predictive power was stronger than that of any other hormonal response to illness. As high levels of IGFBP1 reflect lack of insulin effect in the liver and as elevated blood glucose levels were clearly associated with risk of death, we hypothesized that normalizing blood glucose concentrations, and also lowering IGFBP1 levels, with insulin infusion could have the potential to improve survival.

In 3 large RCTs, 2 in adult patients and 1 in critically ill children we showed that titrating insulin infusion to achieve blood glucose levels within the healthy fasting ranges indeed reduced morbidity and mortality (15-18). The most robust benefits of such strict normalization of blood glucose during critical illness were less kidney and liver dysfunction, shorter time on the ventilator, and in 2 of the 3 studies also fewer severe infections, less polyneuropathy and most importantly, fewer deaths (Figure 2). In long-term follow up studies, we could show that these benefits were maintained 4 years later (19,20),

with in the children a better neurocognitive development. Via molecular studies and studies in animal models we could identify the most important mechanism of action (21-25). In the context of critical illness, accompanied by inflammation and hypoxia induced alterations in cells, high circulating blood glucose evoked high cellular glucose levels in those cells and tissues that do not require insulin for glucose uptake. These cells comprise hepatocytes and renal tubular cells, cells from the peripheral and the central nervous system, white blood cells and endothelial cells. Overload of glucose in those cells, at least in part via glycolysis-induced generation of toxic side products such as methylglyoxal, can damage the mitochondria and hereby hamper the function of several vital organ systems. Targeting and maintaining blood glucose within the healthy fasting ranges, with use of insulin infusion, has the potential to prevent this additional “hit” to these vital organs, whereby it can improve the chances for survival. This potential is conditional on preventing life-threatening hypoglycemia, which may occur but may not be picked up when the required logistics and experience are lacking. This was something we realized quite early in this research program: tight glucose control with insulin in ICU patients is difficult outside the setting of centers of excellence and holds risk of hypoglycemia. Later pragmatic multicenter trials investigating the impact of blood glucose control in real life intensive care showed this painful truth: more hypoglycemia was the reason why this intervention increased rather than reduced mortality in that pragmatic real-life setting (26).

Since we anticipated this potential risk soon after our original and positive studies, together with the engineers in our university we quickly set out to develop a computer algorithm, based on the expertise of the nurses who took part in the pioneer studies. After years of optimization, this algorithm - labeled the LOGIC-insulin algorithm - was proven to be very effective and safe and allowed to export the quality of blood glucose control that could be obtained in the earlier pioneers studies to less expert centers while virtually eliminating hypoglycemia. We are currently in the preparation phase of a new multicenter randomized controlled trial to investigate the effectiveness and safety of strict blood glucose control with use of the LOGIC-insulin algorithm.

While we were doing studies on tissue biopsies in the context of the mechanistic studies to understand how blood glucose control could be beneficial, we again stumbled on something unexpected that lead us to a third important “discovery”.

ON THE ROLE OF AUTOPHAGY FOR RECOVERY FROM ILLNESS AND THE NEGATIVE IMPACT HEREON OF EARLY PARENTERAL FEEDING

As damaged organelles, such as mitochondria, and protein aggregates in cells can cause cellular dysfunction, these need to be removed in order for recovery to ensue. The only cellular housekeeping system that can remove damaged mitochondria and large protein aggregates is autophagy. Our study of human biopsies in relation to the mitochondrial damage induced by hyperglycemia, by chance, also revealed that during critical illness autophagy is insufficiently activated to cope with this damage (28). We found that suppressed autophagy was related to the use of intravenous feeding, most so to the dose of amino-acids in this feeding. We further investigated the impact of nutrition on autophagic damage removal in our animal models and performed clinical studies to investigate the benefit of withholding parenteral nutrition early during critical illness (29,30). Our groups performed 2 large multicenter randomized controlled trials, one in adults and one in children, comparing the use of early parenteral nutrition - at that time state of the art - with not using parenteral nutrition before day 8 in the ICU and thus tolerating a very important macronutrient deficit in the early phase of critical illness (31,32). The results were striking (Figure 3). Both in adults and in children, accepting virtual fasting in the early course of illness accelerated recovery from organ failure and prevented new infections. The effect size was the largest in those patients who were at highest risk, such as those adult patients who could not be fed via the enteral route because of a non-functional gastrointestinal tract, and the youngest infants at highest nutritional risk. The more at risk, the more the patients were harmed by

early parenteral nutrition. Again these findings were explained by the dose of amino-acids, and not by the amount of glucose, as shown by studies of human biopsies and in the animal models (29, 33, 34). Not feeding early also strikingly prevented muscle weakness and allowed a better recovery from weakness, explained by more autophagic cell damage removal when the fasting response was allowed to do its job in the absence of early parenteral feeding (35). Together with the earlier work on glucose control, these studies revealed that hyperglycemia is a metabolic stressor that increases cellular damage during critical illness, and early forceful feeding a metabolic stressor that prevents the damage from being removed. The worst combination thus is hyperglycemia with early parenteral nutrition. With these insights, it remains to be investigated whether strict glucose control with an effective algorithm that can avoid hypoglycemia is necessary in the absence of early parenteral nutrition. The new multicenter randomized controlled trial that is in the planning phase, with the LOGIC-insulin algorithm, will be performed in the context of no longer using early parenteral nutrition and thus will allow to answer this important question. In addition these studies raised the question whether activation of autophagy during critical illness can be achieved with a pharmacological intervention. Pilot studies with rapamycin have shown that this should be possible (36).

Parenteral nutrition is one intervention that increases the risk of hyperglycemia. But also glucocorticoids have that effect. Many ICU physicians treat patients with high doses of glucocorticoids for the presence of what is called “relative adrenal insufficiency” during critical illness. Again, based on a coincidental finding, we came to a striking new insight on the role and regulation of hypothalamus-pituitary adrenocortical axis which again shifted a paradigm.

ON THE KEY ROLE OF THE LIVER AND BILE ACIDS IN CONTROLLING HYPERCORTISOLISM DURING CRITICAL ILLNESS

All textbooks state that in order to cope with the stress of critical illness, an activation of the hypothalamus-pituitary-adrenocortical axis is essential. Indeed, patients with Addison's disease cannot survive the stress of illness or surgery without an additional dose of hydrocortisone. If an activation of the hypothalamus-pituitary-adrenocortical axis is present during the course of critical illness one expects to find elevated circulating levels of ACTH and cortisol in the blood of critically ill patients. However, such a high ACTH level is only present very acutely (37), and after this brief rise, we showed that plasma ACTH levels are lower than in healthy matched subjects while plasma total and free cortisol concentrations are high (38). We documented that the cortisol production rate during the daytime is either unaltered or only slightly elevated and that during the night, the secretion of both ACTH and of cortisol is actually lower than in healthy subjects (39). Our group has shown that the major driver of hypercortisolism in the prolonged phase of critical illness is a reduced breakdown, via suppressed expression and activity of the A-ring reductases in the liver and via suppressed activity of 11-beta-hydroxysteroid-dehydrogenase-2 in kidney (Figure 4). The low plasma ACTH was explained at least in part via negative feedback inhibition exerted by elevated plasma cortisol. A potential cause of such a suppressed expression and activity of the cortisol metabolizing enzymes are high levels of bile acids. Bile acids have shown to be powerful suppressors of these enzymes. We showed that elevated circulating levels of bile acids are indeed part of the stress response to critical illness and that these correlated tightly and inversely with the expression of the A-ring reductases in liver biopsies (38). This suggests that the liver, and more specifically nutritionally regulated compounds such as bile acids, may play a key role in bringing about and maintaining increased cortisol availability during the stress of illness, which is crucial for survival. We also showed that the suppressed ACTH levels with time in ICU may contribute to the risk of adrenal atrophy (40,41), a finding that requires further investigation. In the context of the suppressed cortisol breakdown, this form of adrenal atrophy should perhaps be treated,

not with high but with normal doses of hydrocortisone in order to avoid overdosing and side effects on metabolic homeostasis.

QUO VADIS?

Our research group will further focus our efforts on the understanding of why certain patients do not swiftly recover from critical illness as compared with others, and which mechanisms play a role in the long-term legacy of critical illness, with a focus on endocrine and metabolic pathways. We have shown that the long-term legacy can at least partially be improved via metabolic interventions. Indeed, the improvement of the neurocognitive development 4 years after critical illness, when strict blood glucose control was performed during critical illness in young children, is a proof of concept observation. But the deficit these children face is huge and is still largely unexplained. Recently we have shown that plastic softeners, more specifically phthalates, leach from catheters and tubing when used for intensive medical care in young children and this causes very high levels of phthalates in the blood of these patients (42). Exposure to phthalates during pediatric critical illness showed to be a factor that very specifically explained the very large attention deficit in children who suffered from critical illness 4 years earlier. Our ongoing long-term follow-up studies will hopefully further clarify which preventive actions can be taken to reduce the devastating legacy of critical illness in children as well as in adults. Our group is strongly committed to pursuing this goal.

On a personal note, and looking back on 20 years of researching the endocrinology and metabolism of critical illness, there are a few other insights that I would like to convey to the younger generation of metabolic researchers. One, never believe the textbooks if what is written is not properly referenced with hard evidence and do not be afraid to challenge these expert opinions via excellent new research. Two, don't fight over who is right or wrong when results of good studies are conflicting at first sight. One should always learn from the data, as the data are always right. They just need to be understood

correctly and should form the basis for the next step in research. Three, “primum non nocere” remains the basis for clinical practice and for research. And four, only translational research, from the bed to the bench and back, has the power to move clinical practice towards more effective and safer treatments in the future.

A SELECTION OF KEY REFERENCES

1. Van den Berghe G, de Zegher F, Bouillon R. Acute and prolonged critical illness as different neuroendocrine paradigms. *J Clin Endocrinol Metab* 1998;83:827–1834.
2. Vanhorebeek I, Langouche L, Van den Berghe G. Endocrine aspects of acute and prolonged critical illness. *Nat Clin Pract Endocrinol Metab* 2006;2:20-31.
3. Van den Berghe G, de Zegher F, Veldhuis JD, Wouters P, Awouters M, Verbruggen W, Schetz M, Verwaest C, Lauwers P, Bouillon R, Bowers CY. The somatotrophic axis in critical illness: effect of continuous growth hormone (GH)-releasing hormone and GH-releasing peptide-2 infusion. *J Clin Endocrinol Metab* 1997;82:590–599.
4. Van den Berghe G, de Zegher F, Baxter RC, Veldhuis JD, Wouters P, Schetz M, Verwaest C, Van der Vorst E, Lauwers P, Bouillon R, Bowers CY. Neuroendocrinology of prolonged critical illness: effects of exogenous thyrotropin-releasing hormone and its combination with growth hormone secretagogues. *J Clin Endocrinol Metab* 1998;83:309–319.
5. Van den Berghe G, Wouters P, Weekers F, Mohan S, Baxter RC, Veldhuis JD, Bowers CY, Bouillon R. Reactivation of pituitary hormone release and metabolic improvement by infusion of growth hormone-releasing peptide and thyrotropin-releasing hormone in patients with protracted critical illness. *J Clin Endocrinol Metab* 1999;84:1311–1323.
6. Peeters RP, Wouters PJ, Kaptein E, van Toor H, Visser TJ, Van den Berghe G. Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients. *J Clin Endocrinol Metab* 2003;88:3202-11.
7. Peeters RP, Wouters PJ, van Toor H, Kaptein E, Visser TJ, Van den Berghe G. Serum 3,3',5'-triiodothyronine (rT3) and 3,5,3'-triiodothyronine/rT3 are prognostic markers in critically ill patients and are associated with postmortem tissue deiodinase activities. *J Clin Endocrinol Metab* 2005;90:4559-65.
8. Van den Berghe G, de Zegher F., Veldhuis JD, Wouters P, Gouwy S, Stockman W, Weekers F, Schetz M, Lauwers P, Bouillon R, Bowers CY. Thyrotrophin and prolactin release in prolonged critical illness: dynamics of spontaneous secretion and effects of growth hormone-secretagogues. *Clin Endocrinol (Oxf)* 1997;47:599-612.

9. Mebis L, Debaveye Y, Ellger B, Derde S, Ververs EJ, Langouche L, Darras VM, Fliers E, Visser TJ, Van den Berghe G. Changes in the central component of the hypothalamus-pituitary-thyroid axis in a rabbit model of prolonged critical illness. *Crit Care* 2009;13:R147.
10. Langouche L, Princen L, Gunst J, Guiza F, Derde S, Van den Berghe G. Anterior pituitary morphology and hormone production during sustained critical illness in a rabbit model. *Horm Metab Res* 2013;45:277-282.
11. Mebis L, Paletta D, Debaveye Y, Ellger B, Langouche L, D'Hoore A, Darras VM, Visser TJ, Van den Berghe G. Expression of thyroid hormone transporters during critical illness. *Eur J Endocrinol* 2009;161:243-250.
12. Mebis L, Langouche L, Visser TJ, Van den Berghe G. The type II iodothyronine deiodinase is up-regulated in skeletal muscle during prolonged critical illness. *J Clin Endocrinol Metab* 2007;92:3330-3333.
13. Van den Berghe G, Baxter RC, Weekers F, Wouters P, Bowers CY, Iranmanesh A, Veldhuis JD, Bouillon R. The combined administration of GH-releasing peptide-2 (GHRP-2), TRH and GnRH to men with prolonged critical illness evokes superior endocrine and metabolic effects compared to treatment with GHRP-2 alone. *Clin Endocrinol (Oxf)* 2002;56:655-669.
14. Weekers F, Michalaki M, Coopmans W, Van HE, Veldhuis JD, Darras VM, Van den Berghe G. Endocrine and metabolic effects of growth hormone (GH) compared with GH-releasing peptide, thyrotropin-releasing hormone, and insulin infusion in a rabbit model of prolonged critical illness. *Endocrinology* 2004;145:205-213.
15. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive Insulin Therapy in Critically Ill Patients. *N Engl J Med* 2001;345:1359-1367
16. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive Insulin Therapy in the Medical ICU. *N Engl J Med* 2006;354:449-461
17. Vlasselaers D, Milants I, Desmet L, Wouters PJ, Vanhorebeek I, van den Heuvel I, Mesotten D, Casaer MP, Meyfroidt G, Ingels C, Muller J, Van Cromphaut S, Schetz M, Van den Berghe G. Intensive Insulin Therapy for Patients in Paediatric Intensive Care: a Prospective Randomized Controlled Study. *Lancet* 2009;373:547-556
18. Van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ. Insulin protects the entral and peripheran nervous system of intensive care patients. *Neurology* 2005;64:1348-1353.
19. Ingels C, Debaveye Y, Milants I, Buelens E, Peeraer A, Devriendt Y, Vanhoutte T, Van Damme A, Schetz M, Wouters PJ, Van den Berghe G. Strict blood glucose control with insulin during intensive care after

- cardiac surgery: impact on 4-years survival, dependency on medical care, and quality-of-life. *Eur Heart J*. 2006 ;27:2716-24.
20. Mesotten D, Gielen M, Sterken C, Claessens K, Hermans G, Vlasselaers D, Lemiére J, Lagae L, Gewillig M, Eyskens B, Vanhorebeek I, Wouters PJ, Van den Berghe G. Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control: a randomized controlled trial. *JAMA*. 2012;308:1641-1650.
 21. Van den Berghe G. How does blood glucose control with insulin save lives in intensive care ? *J Clin Invest*. 2004;114:1187-1195.
 22. Langouche L, Vanhorebeek I, Vlasselaers D, Vander Perre S, Wouters PJ, Skogstrand K, Hansen TK, Van den Berghe G. Intensive insulin therapy protects the endothelium of critically ill patients. *J Clin Invest*. 2005;115:2277-2286.
 23. Vanhorebeek I, De Vos R, Mesotten D, Wouters PJ, De Wolf-Peeters C, Van den Berghe G. Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. *Lancet*. 2005;365:53-59.
 24. Vanhorebeek I, Ellger B, De Vos R, Boussemaere M, Debaveye Y, Perre SV, Rabbani N, Thornalley PJ, Van den Berghe G. Tissue-specific glucose toxicity induces mitochondrial damage in a burn injury model of critical illness. *Crit Care Med*. 2009 Apr;37(4):1355-64
 25. Langouche L, Vanhorebeek I, Van den Berghe G. Therapy insight : the effect of tight glycemic control in acute illness. *Nat Clin Pract Endocrinol Metab*. 2007;3:270-278.
 26. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009 ;360 :1283-1397
 27. Van Herpe T, T, Mesotten D, Wouters PJ, Herbots J, Voets E, Buyens J, De Moor B, Van den Berghe G. LOGIC-insulin algorithm-guided versus nurse-directed blood glucose control during critical illness: the LOGIC-1 single-center, randomized controlled clinical trial. *Diabetes Care*. 2013;36:188-194
 28. Vanhorebeek I, Gunst J, Derde S, Derese I, Boussemaere M, Güiza F, Martinet W, Timmermans JP, D'Hoore A, Wouters PJ, Van den Berghe G. Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients. *J Clin Endocrinol Metab*. 2011;96:E633-645

29. Derde S, Vanhorebeek I, Güiza F, Derese I, Gunst J, Fahrenkrog B, Martinet W, Vervenne H, Ververs EJ, Larsson L, Van den Berghe G. Early parenteral nutrition evokes a phenotype of autophagy deficiency in liver and skeletal muscle of critically ill rabbits. *Endocrinology*. 2012;153:2267-2276.
30. Vanhorebeek I, I, Gunst J, Derde S, Derese I, Boussemaere M, D'Hoore A, Wouters PJ, Van den **Berghe G**. Mitochondrial fusion, fission and biogenesis in prolonged critically ill patients. *J Clin Endocrinol Metab*. 2012;97:E59-64
31. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, Van Cromphaut S, Ingels C, Meersseman P, Muller J, Vlasselaers D, Debaveye Y, Desmet L, Dubois J, Van Assche A, Vanderheyden S, Wilmer A, Van den Berghe G. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med* 2011;365:506-517.
32. Fizez T, Kerklaan D, Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I, Debaveye Y, Vlasselaers D, Desmet L, Casaer MP, Garcia Guerra G, Hanot J, Joffe A, Tibboel D, Joosten K, Van den Berghe G. Early versus Late Parenteral Nutrition in Critically Ill Children. *N Engl J Med* 2016;374:1111-22.
33. Casaer MP, Wilmer A, Hermans G, Wouters PJ, Mesotten D, Van den Berghe G. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. *Am J Respir Crit Care Med* 2013;187:247-55.
34. Gunst J, Vanhorebeek I, Casaer MP, Hermans G, Wouters PJ, Dubois J, Claes K, Schetz M, Van den Berghe. G Impact of early parenteral nutrition on metabolism and kidney injury. *J Am Soc Nephrol* 2013;24:995-1005.
35. Hermans G, Casaer MP, Clerckx B, Güiza F, Vanhullebusch T, Derde S, Meersseman P, Derese I, Mesotten D, Wouters PJ, Van Cromphaut S, Debaveye S, Gosselink R, Gunst J, Wilmer A, Van den Berghe G, Vanhorebeek I. Impact of tolerating macronutrient deficit on the development of intensive care unit-acquired weakness. *Lancet Resp Med* 2013;1:621-629.
36. Gunst J, Derese I, Aertgeerts A, Ververs EJ, Wauters A, Van den Berghe G, Vanhorebeek I. Insufficient autophagy contributes to mitochondrial dysfunction, organ failure and adverse outcome in an animal model of critical illness. *Crit Care Med*. 2013 Jan;41(1):182-94
37. Vermes I, Beishuizen A. The hypothalamic-pituitary-adrenal response to critical illness. *Best Pract Res Clin Endocrinol Metab* 2001;15:495-511.

38. Boonen E, Vervenne H, Meersseman P, Andrew R, Mortier L, Declercq PE, Vanwijngaerden YM, Spriet I, Wouters PJ, Vander Perre S, Langouche L, Vanhorebeek I, Walker BR, Van den Berghe G. Reduced cortisol metabolism during critical illness. *N Engl J Med* 2013;368:1477-1488.
39. Boonen E, Meersseman P, Vervenne H, Meyfroidt G, Guiza F, Wouters PJ, Veldhuis JD, Van den Berghe G. Reduced nocturnal ACTH-driven cortisol secretion during critical illness. *Am J Physiol Endocrinol Metab* 2014;306:E883-92.
40. Boonen E, Langouche L, Janssens J, Meersseman P, Vervenne H, De Samblanx E, Pironet Z, Van Dyck L, Vander Perre S, Derese I, Van den Berghe G. Impact of duration of critical illness on the adrenal glands of human intensive care patients. *J Clin Endocrinol Metab* 2014;99:4214-22.
41. Barquist E, Kirton O. Adrenal insufficiency in the surgical intensive care unit patient. *J Trauma* 1997;42:27-31.
42. Verstraete S, Vanhorebeek I, Covaci A, Güiza F, Malarvannan G, Jorens PG, Van den Berghe G. Circulating phthalates during critical illness in children are associated with long-term attention deficit : a study of a development and a validation cohort. *Intensive Care Med* 2016; 42:379-392

Figure legends**Figure 1**

Hypothalamic suppression drives suppression of target organs and may hereby contribute to the “accelerated aging” phenotype of prolonged critical illness.

Figure 2

Strictly normalizing blood glucose levels within the healthy fasting ranges has shown to reduce mortality in surgical adult ICU patients and in critically ill children.

Figure 3

Not providing parenteral nutrition, and hereby accepting a large macronutrient deficit, up to one week in the ICU increases the likelihood of an earlier live discharge of critically ill adults and children.

Figure 4

In critically ill patients, cortisol production is not or only slightly increased whereas suppressed expression and activity of the cortisol metabolizing enzymes in liver and kidney to large extent brings about the maintenance of hypercortisolism

Figures for review Cuthbertson lecture

Greet Van den Berghe

Clinical Nutrition 2016

Figure 1

Survival of surgical adult ICU patients

Figure 2

Mortality of pediatric ICU patients

Figure 3

Figure 4