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Author contact	<p>greet.vandenbergh@med.kuleuven.be + 32 (0)16 344021</p>
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Blood glucose control in the ICU: don't throw out the baby with the bathwater!

Jan Gunst, MD, PhD and Greet Van den Berghe, MD, PhD

Clinical Division and Laboratory of Intensive Care Medicine,
Department of Cellular and Molecular Medicine, KU Leuven,
Herestraat 49, B-3000 Leuven, Belgium

Correspondence to:

Prof Greet Van den Berghe, MD, PhD
Clinical Division and Laboratory of Intensive Care Medicine,
Department of Cellular and Molecular Medicine,
KU Leuven,
Herestraat 49, B-3000 Leuven, Belgium
Phone +32-16-344021
Fax +32-16-344015
e-mail greet.vandenberghe@med.kuleuven.be

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Running title: glycemic control in the ICU

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In this issue of Intensive Care Medicine, Dr. Paul Marik presents his personal critical viewpoint on the use of tight glycemic control (TGC) in the intensive care unit (ICU) [1]. He recommends to abandon glycemic control all together for critically ill patients, based upon a risk of harm that, in his interpretation, would outweigh any possible benefit. At first sight, dr. Marik's arguments appear reasonable. However, in our opinion, his argumentation was built on a biased/incomplete analysis of the evidence. We here present another (in our view more balanced) analysis. We argue that dr. Marik is inadvertently recommending clinicians to throw out the baby with the bathwater.

Dr. Marik starts his case with an evolutionary perspective, stating that humans and animals alike reveal hyperglycemia when exposed to stress, and thus that this must be beneficial. We do not agree. Fasted young and lean human patients, as well as laboratory mice, in the absence of forced artificial nutrition and hyperglycemic drugs such as steroids, indeed mount a metabolic response to stress meant to maintain glucose availability for organ systems such as the brain, but this does not - or only very briefly - result in pronounced hyperglycemia. Since such a metabolic response to stress is selected by evolution to deal with the inevitable fasting that goes along with severe illness or trauma in prehistorical times, an adaptive/beneficial nature is likely. However, the patients that we treat in our ICUs worldwide anno 2016 are all but young, lean and without drugs. Our patients are supported with interventions and drugs to postpone death that would follow in the pre-ICU era. Dr. Marik recommends blood glucose targets up to 220-260 mg/dl as "optimal" for ICU patients, with even higher ranges for patients suffering from diabetes. However, there are no RCTs to support this recommendation. In fact, all association studies reported a J-shaped curve, with the lowest risk of death present for a blood glucose level within or close to the normal fasting range for the age group (80-110 mg/dl for adults, 60-100 mg/dl for children, 50-80 mg/dl for infants), with increasing risk on the hyperglycemic side and a sharper increasing risk on the hypoglycemic end of the spectrum [2]. Of course, associations are no proof of causality, as this requires RCTs.

The 3 pioneer RCTs on TGC performed in Leuven, showed that targeting age-adjusted normoglycemia (in the association studies the lowest risk of death) with insulin improved outcome as compared with tolerating hyperglycemia up to the renal threshold (215 mg/dl, above which osmotic diuresis occurs) [3-5]. These benefits comprised less morbidity in all three studies and less mortality in the adult surgical ICU population and in critically ill infants/children. Thereafter, several large implementation studies and a few small RCTs confirmed better outcomes with prevention of severe hyperglycemia [2]. As dr. Marik rightly recalls, after these studies, the concept of TGC was (too) rapidly and broadly implemented worldwide which changed the standard of care. Most ICUs implemented some sort of glycemic control to prevent excessive hyperglycemia. This response of the clinical community, unfortunately, complicated the design of the later "repeat" multicenter trials that are needed for generalisability. As a result of the changed standard of care, the "control group" was no longer allowed to mount that severe hyperglycemic stress response up to the renal threshold (215 mg/dl) as was done in the Leuven RCTs. Instead, the control group was treated with insulin to keep blood glucose somewhere between 140-180 mg/dl. TGC (mostly targeting 80-110 mg/dl), as compared with that intermediate target range in these studies, either did not alter clinical outcomes or, in the largest NICE-SUGAR trial, caused harm [6]. This harm was subsequently attributed to the 13-fold increase in hypoglycemia. This contrasted sharply with the outcomes of the Leuven RCTs. A careful and critical comparative analysis is needed to provide a scientifically sound explanation.

Dr Marik claims that the beneficial effects of TGC observed in the Leuven RCTs are simply explained by the administration of a 'toxic' dose of IV glucose as part of the early parenteral nutrition standard of care at that time. His claim was based on the results of the multicenter EPaNIC RCT that compared the impact of withholding any parenteral nutrition until day 8 in ICU with early initiation of parenteral feeding [7]. The early parenteral nutrition comprised intravenous glucose only until the morning of day 3 in ICU, followed by an up-to-target all-in-one parenteral nutrition thereafter to supplement any insufficient enteral feeding. The EPaNIC trial showed that early parenteral nutrition caused more infections and organ failure and slowed down recovery. Although this harmful effect of early parenteral nutrition could theoretically be due to the glucose load, a post-hoc analysis of the EPaNIC trial clearly showed that the higher load of amino-acids, rather than glucose, statistically explained the harm [8]. This finding was confirmed by a randomized animal study comparing doses of the various parenteral substrates [9]. There is ample evidence from experimental studies that (a) IV glucose does not cause harm as long as glycemia is kept normal with insulin [10-12] and (b) that the benefits of TGC are brought about by avoiding toxicity from hyperglycemia to cells that do not need insulin for glucose uptake [10, 13-15]. Such cells comprise neurons, endothelial cells, hepatocytes, immune cell, renal tubular cells (figure 1). We agree with dr. Marik that early parenteral nutrition increases the severity of hyperglycemia. It is thus possible that without early parenteral nutrition, benefit from TGC could be less.

But there are other differences to consider, besides the glycemic targets and feeding regimens, that may have contributed to the different outcomes of the Leuven RCTs and subsequent trials as NICE-SUGAR [2].

First, the accuracy of glucose measurement tools should be considered [2]. In order to target a narrow glycemic range, an accurate measurement of glycemia is essential. Without a tool that has an error range several fold smaller than the target range, reaching that target is virtually impossible and the risk of dangerous (undetected and prolonged) hypoglycemia and glycemic variability inflates dramatically. In the 3 Leuven RCTs, glycemia was measured with an accurate blood gas analyzer on arterial blood [3-5]. In many other studies, including NICE-SUGAR, a variety of inaccurate hand-held glucometers were used, often on capillary blood samples, the latter also yielding unreliable measurements in particular during shock.

A second factor that increases glycemic variability and hypoglycemia is the use of insulin boluses or inaccurate infusion pumps. In the Leuven RCTs, in contrast to other studies, insulin was only administered continuously (no boluses) with use of accurate syringe pumps connected closely to the patient, through a dedicated lumen of a central venous line [3-5].

A third issue is the level of experience of the nursing team. In the Leuven RCTs, the insulin dose was adjusted according to a guideline that allowed intuitive decision-making rather than a simple and unvalidated if-then approach in NICE-SUGAR. High level of expertise in the Leuven RCTs explained that 70% of patients were strictly within target range (based on average morning glycemia), compared to <50% in NICE-SUGAR (based on all measurements) [2]. The Leuven team has subsequently developed a reliable and validated computer algorithm [16] that allowed to safely export the concept of TGC to other centers (unpublished).

Fourth, in the Leuven RCTs, TGC in ICU was stopped when the patient was able to resume oral feeding. In some other RCTs, TGC was continued with oral feeds, with intuitively more hypoglycemia and glucose variability.

Fifth, the way hypoglycemia was corrected may have determined eventual harm. In the Leuven RCTs, any rebound hyperglycemia was avoided by an immediate but gentle correction of hypoglycemia. Hyperglycemia

rebound after hypoglycemia, rather than hypoglycemia per se, brings about neuronal damage [17]. A four-year follow-up study of the Leuven pediatric RCT showed that TGC improved neurocognitive development, despite hypoglycemia [18].

It is clear that insights in blood glucose management have expanded over the past 15 years. The pioneer RCTs showed benefit from preventing severe hyperglycemia but safe and effective implementation requires experience and accurate tools. Hypoglycemia and glycemic fluctuations should be avoided, achievable with a validated glucose control computer algorithm. However, the optimal blood glucose targets and the interaction with feeding strategies remain unclear. Open questions should be the objective of well-designed, adequately powered RCTs. They cannot be answered by opinion papers. While awaiting these new RCTs, common sense supports avoiding excessive hyperglycemia with targets adjusted to the logistic context per center. It is our opinion that there is currently no need to throw out the baby with the bathwater!

Figure legend

Fig. 1 Pathological effects of severe hyperglycemia during critical illness.

Severe hyperglycemia has been shown to induce mitochondrial damage¹⁻³, endothelial dysfunction^{4,5}, increased tissular inducible NO synthase (iNOS) expression^{4,6}, altered lipid metabolism⁷ and systemic inflammation^{5,8-10} in critically ill patients and/or animal models, which in turn lead to an increased risk of muscle weakness¹¹⁻¹², acute kidney injury (AKI)^{3,5,13}, liver dysfunction^{2,5,14}, infections^{15,16} and impaired neurocognitive development¹⁷. This results in an increased short-term mortality risk^{15,16} as well as an increased risk of long-term neurocognitive impairment¹⁷.

¹ Vanhorebeek et al. *Lancet* 2005; ² Vanhorebeek et al. *Crit Care Med* 2009; ³ Vanhorebeek et al. *Kidney Int* 2009; ⁴ Langouche et al. *J Clin Invest* 2005; ⁵ Ellger et al. *Diabetes* 2006; ⁶ Ellger et al. *Intensive Care Med* 2008; ⁷ Mesotten et al. *J Clin Endocrinol Metab* 2004; ⁸ Vlasselaers et al. *Ann Thorac Surg* 2010; ⁹ Weekers et al. *Endocrinology* 2003; ¹⁰ Ingels et al. *J Clin Immunol* 2013; ¹¹ Van den Berghe et al. *Neurology* 2005; ¹² Hermans et al. *Am J Resp Crit Care Med* 2007; ¹³ Schetz et al. *J Am Soc Nephrol* 2008; ¹⁴ Mesotten et al. *J Clin Endocrinol Metab* 2009, ¹⁵ Van den Berghe et al. *N Engl J Med* 2001; ¹⁶ Vlasselaers et al. *Lancet* 2009; ¹⁷ Mesotten et al. *JAMA* 2012

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Severe hyperglycemia

Mitochondrial damage

Endothelial dysfunction

Increased tissular iNOS expression

Altered lipid metabolism

Systemic inflammation

Peripheral nervous system

Renal tubular cell

Hepatocyte

Immune cells

Central nervous system

Weakness

AKI

Hepatic dysfunction
Cholestasis
Biliary sludge

Infections

Impaired neurocognitive development

Short-term mortality

Long-term neurocognitive deficiencies