Tight Blood Glucose Control With Insulin in "Real-Life" Intensive Care

Throughout the past decades, development of high-tech monitoring systems as well as mechanical and pharmacological support of vital organs has enabled physicians to "rescue" patients who would otherwise die of insults that induce profound hypoxia or shock. Despite this technological revolution, which also allowed intensive care medicine to be recognized as a medical subspecialty, outcome of many diseases for which patients are being treated in intensive care units (ICUs) has not improved dramatically. Recently, however, a few randomized controlled clinical studies have shown that survival of critically ill patients can be improved simply by rethinking and fine-tuning some of the routine strategies that have formed the basis of intensive care medicine. These include mechanical ventilation, fluid administration, inotropic support, and metabolic control. Indeed, using lower tidal volumes for mechanical ventilation of patients with acute lung injury,[1] early goal-directed hemodynamic support of patients with the sepsis syndrome,[2] and strict blood glucose control with insulin during intensive care[3] has reduced morbidity and mortality substantially. Follow-up studies on the impact of these altered therapeutic paradigms, when they are being implemented in "real-life" intensive care, are of utmost importance.

In the current issue of the *Mayo Clinic Proceedings*, Krinsley[4] reports the results of a prospective interventional study performed in a medical-surgical ICU of 14 beds. Krinsley assessed the clinical outcome of 800 consecutive patients before and after implementing, as the new standard of care, tighter insulin-titrated glycemic control. This study showed that the clinical benefits of tight blood glucose control, as revealed by the original randomized controlled study that was performed in a predominantly surgical ICU at the Leuven University,[3] were reproducible in a medical-surgical setting.

The aim of the Leuven study was to maintain blood glucose levels lower than 110 mg/dL by using a continuous insulin infusion in the intervention group vs the standard of care, which advocated insulin infusion only when blood glucose levels exceeded 200 mg/dL. This simple intervention reduced intensive care mortality by 43%, overall in-hospital mortality by 34%, newly developed kidney failure requiring dialysis by 41%, bacteremia by 46%, the number of red blood cell transfusions by 50%, and critical illness polyneuropathy by 44%, and it decreased the requirement of prolonged mechanical ventilation and intensive care. The study by Krinsley aimed for an intermediate blood glucose level lower than 140 mg/dL, a somewhat less strict regimen chosen primarily for safety and designed to avoid inadvertent hypoglycemia. Krinsley achieved, on average, a blood glucose level of 131 mg/dL in his patients, and this coincided with a 29% reduced in-hospital mortality, decreased new organ failure, fewer blood transfusions, and shorter ICU stay compared with the historical control group. Nursing staff conditions had not changed, and hypoglycemia did not increase.

Krinsley and his team are to be congratulated for thoroughly studying the impact of implementation of a novel "routine" strategy in the ICU on patients' outcome and on the workload of the unit. The fact that they were able to reproduce the results from the one available randomized controlled trial is important information for the scientific and clinical community. In addition, they further extended the knowledge by showing that this benefit is present in a medical-surgical intensive care population. Krinsley recognized the weakness of his nonrandomized study and pointed out that further studies are needed to confirm his findings and to extrapolate them to other patient groups. Indeed, no final proof exists that the data apply to an exclusively medical ICU setting. Likewise, it is unclear whether controlling blood glucose levels is equally effective in critically ill children or in nondiabetic but hyperglycemic patients on a regular medical or surgical ward.

See also page 992

One could wonder, however, how far one should go in repeating the study in similar patient populations when indirect data, such as those by Krinsley, are accumulating and confirm the results of the large randomized controlled trial. The intervention is inexpensive and simple, and the potential benefits clearly outweigh the risks, at least within the highly monitored setting of an ICU. When comparing this novel therapeutic paradigm with other more expensive novel treatments, such as activated protein C for sepsis,[5] one notices the scrutiny with which it is being evaluated before being widely implemented. Activated protein C proved to reduce mortality associated with sepsis in a predominantly medical ICU population; however, despite the paucity of data in surgical ICU patients and the associated risk of bleeding, the drug was approved for treatment of sepsis in surgical patients. This decision was probably wise because there is little reason to believe that outcome of

Dr Van den Berghe has received research grants from the Fund for Scientific Research, Flanders, Belgium (G.0278.03; G.3C05.95N), and the Catholic University of Leuven (OT03/56) and an unrestricted research grant from Novo Nordisk Denmark.

Address reprint requests and correspondence to Greet Van den Berghe, MD, PhD, Department of Intensive Care Medicine, University of Leuven, B-3000 Leuven, Belgium (e-mail: greta.vandenberghe@med.kuleuven.ac.be).

sepsis would differ in medical and surgical patients. Likewise, blood glucose control prevents dangerous complications in ICU patients that are not specific for the initial disease that warranted ICU admission. Furthermore, the benefits of tight blood glucose control are scientifically based on a vast amount of data from patients with diabetes,[6,7] and these benefits have been proved for patients in the ICU.

However, at this stage, several important questions remain unanswered. First, what level of blood glucose is considered ideal to achieve the most benefit combined with the lowest risk of adverse events? Second, how do the benefits occur—is glycemic control the most important factor or are other metabolic or even nonmetabolic effects of insulin playing a more important role? This is related to the question of how blood glucose should be controlled. Is insulin infusion the best method based on its many other effects besides blood glucose control, or should we seek alternatives that may have a lower risk of hypoglycemia?

The level of blood glucose needs to be considered. The Leuven study used a lower threshold compared with that used by Krinsley. The mortality benefit in Krinsley's study was somewhat smaller than that in the Leuven study. Furthermore, a post hoc analysis of the Leuven study showed that an intermediate blood glucose level was effective in reducing mortality but much more could be gained by targeting true normoglycemia.[8] In fact, for most of the effects on morbidity, including the prevention of severe infections, an effect that was absent in the Krinsley study, a lower blood glucose level appeared necessary. Furthermore, the maintenance of moderate hyperglycemia in the presence of hyperinsulinemia may theoretically accentuate potential adverse effects of insulin in a setting of partial insulin resistance,[9,10] which would then offset some of the benefits of glycemic control unless glycemic control is strict. This is one of the reasons why strict normoglycemia, to prevent endothelial dysfunction, is also the new target for patients with type 2 diabetes. Hence, I believe that adequately designed and powered studies that investigate this important aspect of the optimal level of blood glucose control are more important than repeated studies on clinical outcome.

This leads to the issue of which mechanisms explain the observed benefits. In view of the emerging evidence from studies of diabetes, it is clear that the clinical benefits seen in critically ill patients are not due to just one single phenomenon. Many pathways are likely being affected and presumably play a role, some of them being more dependent on achieving only normal blood glucose levels whereas others are likely to be affected by nonglycemic and even nonmetabolic effects of insulin. Regarding reduced mortality, statistical analysis indicates that glycemic control is more important than the amount of insulin.[8] However, glycemic control achieved with intensive insulin titration obviously mimics other concomitant effects of insulin. Results from recent studies indicate that these alternative effects of tight glycemic control with insulin involve improvement of the dyslipidemia of critical illness[11] and attenuation of the pronounced inflammatory response[12] irrespective of the reduced incidence of serious infections evoked by intensive insulin therapy. Particularly, the effect on lipids seems to surpass the effect of blood glucose control in explaining the survival benefit associated with intensive insulin therapy.[11] Furthermore, the immune paralysis that has been described in critically ill patients appears to be ameliorated,[13] as evidenced by improved phagocytosis of monocytes obtained from experimental animals with critical illness in which blood glucose was controlled with insulin infusion. Many more pathways are presumably involved and should be studied in detail, both in clinical studies and in experimental animal models. Only then will the full impact of this intervention be clear and will it be possible to further optimize and fine-tune the simple but lifesaving intervention of metabolic control in critically ill patients.

Greet Van den Berghe, MD, PhD
Department of Intensive Care Medicine
University of Leuven
Leuven, Belgium

1. Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med*. 1998;338:347-354.

2. Rivers E, Nguyen B, Havstad S, et al, Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345:1368-1377.

3. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359-1367.

4. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc*. 2004;79:992-1000.

5. Bernard GR, Vincent JL, Laterre PF, et al, Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*. 2001;344:699-709.

6. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977-986.

7. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) [published correction appears in *Lancet*. 1999;354:602]. *Lancet*. 1998;352:837-853.

8. 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;31:359-366.

9. Golovchenko I, Goalstone ML, Watson P, Brownlee M, Draznin B. Hyperinsulinemia enhances transcriptional activity of nuclear factor-κB induced by angiotensin II, hyperglycemia, and advanced glycosylation end products in vascular smooth muscle cells. *Circ Res*. 2000;87:746-752.

10. Montagnani M, Golovchenko I, Kim I, et al. Inhibition of phosphatidylinositol 3-kinase enhances mitogenic actions of insulin in endothelial cells. *J Biol Chem*. 2002;277:1794-1799.

11. Mesotten D, Swinnen J, 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;89:219-226.

12. Hansen TK, Thiel S, Wouters PJ, Christiansen JS, Van den Berghe G. Intensive insulin therapy exerts antiinflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. *J Clin Endocrinol Metab*. 2003;88:1082-1088.

13. Weekers F, Giulietti AP, Michalaki M, et al. Metabolic, endocrine, and immune effects of stress hyperglycemia in a rabbit model of prolonged critical illness. *Endocrinology*. 2003;144:5329-5338.