

Continuous Glucose Monitoring during Critical Care

IN this edition of *ANESTHESIOLOGY*, Skjaervold *et al.* report preliminary data on a novel indwelling vascular continuous glucose sensor.¹ The investigators have conducted a rigorous assessment of the device, and its performance was strikingly good in their porcine model. Technology, such as this, should be of significant interest to clinical investigators and practitioners interested in the science, as well as the logistics, of acute glucose management in critically ill patients.

The control of blood glucose in the critical care setting has received much attention throughout the past decade. Interest was initially piqued after the 2001 publication of a single-center study from Belgium.² In this investigation, mortality was significantly reduced in 1,548 surgical intensive care unit (ICU) patients whose blood glucose concentrations were maintained in the normal range (80–110 mg/dl) with intravenous insulin infusion. These data built upon extensive epidemiologic evidence correlating hyperglycemia during acute illness with mortality, as well as preliminary indications from smaller or nonrandomized studies that aggressive glycemic management in the critically ill was associated with a wide array of clinical benefits. However, during the 8 yr that followed, several additional randomized trials in various ICU patient populations were not able to reproduce these positive results. Indeed, one very large multicenter trial suggested a higher risk of mortality with attaining euglycemia in the ICU setting.³ A significantly greater risk of severe hypoglycemia with intensive insulin therapy has been a consistent theme in each of these investigations. In synthesizing such conflicting data, professional groups recently have updated their guidelines, recommending more conservative treatment thresholds and glucose targets in the hospital.⁴ There remains, however, substantial discussion in the literature regarding the clinical effectiveness and safety of glucose lowering and the optimal inpatient glycemic goals.

There are less data, but no less controversy, on glycemic management during surgery. Here, too, epidemiologic evidence has suggested that intraoperative hyperglycemia was linked to adverse postoperative outcomes, especially in cardiac surgical patients. More recently, however, a large retrospective study, involving more than 4,000 patients undergoing major cardiothoracic procedures, appeared to indicate that outcomes were best when blood glucose concentrations were maintained in a mildly hyperglycemic range (140–170 mg/dl) intraoperatively.⁵ There is a paucity of randomized clinical trials in this area. One investigation of nearly 400 patients found no benefit when blood glucose was rigidly maintained between 80 and 100 mg/dl during coronary bypass.⁶

It is possible that the conflicting results from previous studies may be in part related to the mechanics of blood glucose monitoring and treatment in the inpatient setting. Indeed, glycemic variability⁷ and the incidence of hypoglycemia⁸ themselves have been independently associated with adverse clinical outcomes in the critically ill; both may be heightened when intravenous insulin is used. The precise explanations for these associations remain unclear. Rapid fluctuations in blood glucose concentrations have been linked to increased oxidative stress and endothelial dysfunction.⁹ Hypoglycemia, when severe or protracted, is not only associated with obvious detrimental effects on central nervous system function but also has recently been associated with a proinflammatory state.¹⁰

Germane to this discussion, both glycemic variability and hypoglycemia may directly stem from the current glycemic monitoring paradigms in our modern ICUs and operating rooms, which actually have remained stagnant for decades. Most published intravenous insulin protocols have been focused on the intermittent acquisition of blood glucose data on, at most, an hourly basis. Given the inherent risks of intravenous insulin, such a strategy might be viewed as analogous to driving the interstate in a vehicle with an opaque windshield—one that becomes transparent to reveal the road ahead only for a brief moment every hour. The potential hazards here are obvious. Furthermore, when one superimposes the recognized differences between the various sources of blood in which glucose is typically measured (*i.e.*, capillary *vs.* venous *vs.* arterial), along with the imprecision of current analytical instruments, truly excellent glycemic management in the critically ill remains somewhat illusory.

In this light, the report by Skjaervold *et al.* is a timely one. The sensor tested by the investigators employed a unique hydrogel matrix that changes size continuously in relationship to ambient glucose concentrations, providing ongoing real-time reporting of results. The sensor was assessed over a wide blood glucose range, from less than 1 mM (less than 18 mg/dl) to more than 15 mM (more than 270 mg/dl)—well within the limits typically seen in most critical care patients. The mean bias between the sensor and a gold standard method of assaying glucose in arterial blood was only 0.01 mM (less than 1 mg/dl) with a ± 0.4 mM (± 7 mg/dl) SD and a ± 0.9 mM (± 16 mg/dl) 95% CI. These outstanding correlations appeared to be even tighter in the severely hypoglycemic range—an important feature of any glucose-measuring device, especially in the context of intensive insulin therapy. Outlier measures, which might lead to erroneous changes in therapy, were few, and their affect would likely

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be substantially mitigated by the continuous nature of the data collected. Clearly, these results appear to be at least as good as current technology available, with the additional and potentially important benefit of continuously available information. Conceivably, the anesthesiologist or other critical care physician could then use these voluminous data to more precisely and more smoothly address hyperglycemia in hospitalized patients.

The field of continuous glucose monitoring is rapidly advancing.¹¹ Such devices are now approved for use in outpatients with diabetes on intensive insulin regimens, especially those with type 1 diabetes on insulin pumps. Their availability has led to a reconsideration of how we monitor and manage blood glucose in the hospital because continuous glucose monitoring offers two distinct advantages over frequent point-of-care testing. First, it may help avoid excessive glucose variability by providing continuous information on glucose trends, potentially reducing personnel response time to glycemic excursions. Second, the discomfort and nuisance of very frequent fingersticks, an inherent part of most intensive glucose control protocols, is a frequent concern among both patients and nurses. Continuous glucose monitoring systems carry a promise to nearly eliminate this issue.

However, preliminary data in the ICU setting of currently available subcutaneous sensors have been mixed.^{12–14} Concerns over their ability to reliably detect hypoglycemia as well as the well-known lag phenomenon between blood and interstitial glucose concentrations remain, particularly during episodes of metabolic flux. An indwelling vascular sensor, particularly one as accurate as the model tested by Skjaervold *et al.*, should be viewed as a significant advancement.

Before these more invasive sensors are considered for human use and embraced by the clinical community, their potential benefits need to be balanced against possible hazards. Specifically, systemic anticoagulation with heparin was required to prevent clotting in the pigs studied by the Norwegian investigators. This introduces obvious additional risks, and future devices in man will need to minimize the risk of thrombosis without requirement for anticoagulation. Placement of the sensor also required central venous catheterization, and, although such lines are already indwelling in many critically ill patients, the possibility of procedure-related and downstream infectious complications will need careful scrutiny. Finally, current insulin infusion algorithms are based on less frequent glucose measurements. More continuous data will obviously mandate new and more nimble approaches to adjusting insulin infusion rates based on continuously updated glucose concentrations and their rates of change. Until a functional closed-loop system (*i.e.*, artificial pancreas with sensor communicating to the infusion pump) is designed and validated, such adjustments will necessarily require more intensive nursing support.

Obviously, these concerns are all above and beyond the overriding question of how important stringent glycemic control really is during intensive care. The correct answer is increasingly uncertain the closer we approach euglycemia—a range that may indeed be facilitated by the more meticulous monitoring made possible by continuous sensors. Until the clinical benefit and safety of such state-of-the-art glucose management systems is clearly demonstrated in human studies, continuous glucose monitoring will not be ready for prime time in hospitalized patients. Nevertheless, the article by Skjaervold *et al.*, as a proof-of-concept study, is important and may open newer and safer avenues to glucose control in our operating theaters and critical care units.

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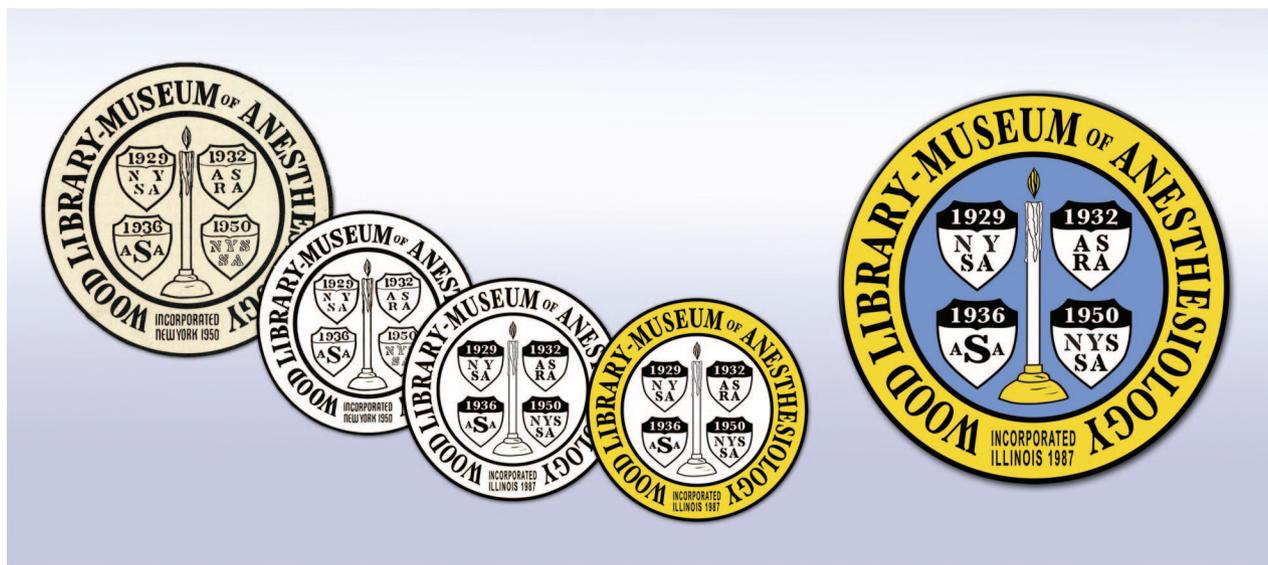
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ANESTHESIOLOGY REFLECTIONS

From Print to Web: The Wood Library-Museum Seal



Designed originally by Founder Paul M. Wood, M.D. (1894–1963), the seal of the Wood Library-Museum of Anesthesiology has evolved as the WLM’s incorporation has switched from New York to Illinois and its media, from black-and-white print (*far left*) to colorful web platforms. Colorizing the seal (*far right*) was inspired originally by color families in flags from Indiana and New York, the states, respectively, of Paul Wood’s birth and long-term residence. To maximize the seal’s legibility for small-scale and online use, lettering and spacing were redrawn professionally, and contrast was reversed on the tops of the shields of the “sponsoring organizations” which were originally named: the New York Society of Anesthetists (NYS A), the American Society of Regional Anesthesia (ASRA), the American Society of Anesthetists (ASA), and the New York State Society of Anesthesiologists (NYS SA). Paul Wood himself may have etched the central candlestick with its lit “candle of learning.” (Copyright © the American Society of Anesthesiologists, Inc. This image also appears in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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