

## Con: Tight Perioperative Glycemic Control: Poorly Supported and Risky

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**M**AINTEINING A PERIOPERATIVE SERUM GLUCOSE CONCENTRATION of less than 120 mg/dL (6.6 mmol/L) has uncertain benefit and considerable risk. In a large randomized controlled trial (RCT) of 1548 critically ill patients in Belgium, Van den Berghe et al<sup>1</sup> demonstrated a 42% relative reduction in mortality with the use of an insulin infusion to maintain tight glycemic control in a mixed medical and surgical population. Many cite these and other data to support the application of insulin infusions to varied intensive care unit (ICU) populations and, by extension, intraoperative care. Such assertions are overzealous. They outpace available clinical science, are based on poorly substantiated assertions, and fail to recognize an ongoing fundamental lack of understanding about the role of insulin in stress metabolism. Given these differences, attempting to “normalize” glucose values during surgery is at least risky, and perhaps harmful.

Enthusiasm for tight glycemic control deserves a more deliberate, perhaps even skeptical, approach. Details from available clinical data and basic clinical science suggest that inappropriate insulin use may be associated with harm. Any time clinical data are extrapolated to new populations there is this risk. The medical community, is committed to providing the maximal help to patients, but must remember to “first, do no harm.” Areas of concern include population selection, mechanism of benefit (and potential harm), appropriate end points, risk for hypoglycemia, and the burden of liability.

Incomplete understanding of risks and benefits confounds the further selection of patient populations for whom this therapy might be beneficial. Specific conditions uniquely benefit from the effects of insulin, tightly regulated glucose, or both. There are studies that support tight glycemic control or insulin therapy in certain populations. Hyperglycemia is detrimental in the setting of cerebral ischemia.<sup>2</sup> Insulin may exert benefits to myocardial metabolism independent of the level of glycemic control,<sup>3,4</sup> and there may exist specific indications for directed metabolic therapy. However, use for these purposes should not be confused with therapies that target specific serum glucose concentrations in all surgical patients. In fact, few data exist to support the appropriateness of tight control in intraoperative patients. It is interesting to note that the original Belgian study population consisted of medical and postoperative surgical patients, more than 60% of whom were cardiac surgery patients, who may derive unique benefit from insulin. Not only might this therapy be appropriate only in specific conditions, but favorable response might depend on the state of recovery. Response to, and perhaps benefit from, insulin changes over the course of illness. Looking at the Van den Berghe data, it might be concluded that the benefits of glycemic control come relatively late during the ICU stay. Most of the benefits seen in the study were in patients who spent more than 5 days in the ICU. This is consistent with the current understanding of the stress response.<sup>5</sup> As the response to tissue injury abates, an anabolic hormone such as insulin has a more important role in the metabolic process. During acute injury such as surgery, treatment with an anabolic hormone might be harmful. Finally, other factors, such as the provision of nutrition, may have a role in the response to glycemic control strategies. The ICU popu-

lation in the Belgian study benefited from aggressive nutritional supplementation. Most operative patients do not. There are more differences than similarities between most surgical patients in the operating room and patient populations benefiting from tight glycemic control in the literature.

The mechanisms by which tight glycemic control provides benefit are not clear. Insulin is not merely a hypoglycemic agent. It is a complex hormone that affects multiple signaling pathways. Some of these are helpful; others may be harmful. Indeed, improved glycemic control may not be the mechanism of benefit. In a subgroup study from the original RCT, effects on cholesterol levels correlated more closely with survival than did effects on glucose.<sup>6</sup> Insulin also has profound effects on protein metabolism.<sup>7</sup> Recent research suggests that the benefit of tight glycemic control may arise from modulation of asymmetric dimethylarginine, a modulator of nitric oxide activity.<sup>8</sup> Without deeper insight into the mechanisms of action and benefit, it is difficult to prescribe or extrapolate a controversial therapy. While insulin is praised as an “anti-inflammatory” hormone, evidence suggests it may “prime” the immune cell inflammatory response to certain triggers, including hyperglycemia!<sup>9</sup> Further, although resistance to the hypoglycemic effects of insulin is a normal response to stress, other responses to the hormone do not show the same tendency, meaning that increasing insulin dose to counteract resistant hyperglycemia may lead to exaggeration of other effects, such as mitogenesis and nuclear factor- $\kappa$ b (NF- $\kappa$ b) upregulation.<sup>10</sup> That insulin dose correlates positively with mortality at every level of glycemic control in both the Van den Berghe study and a subsequent large observational study by Finney et al<sup>11</sup> further suggests that harm may result from inappropriate insulin administration. Seeking improved glycemic control by restricting dextrose infusions is likely far safer than using insulin in pursuit of this goal in unselected patients.

Even if it is postulated that insulin therapy is not harmful, and may even be beneficial, it is unclear what targets of glycemic control are appropriate. The only large RCT compared 2 ranges: 90 to 110 mg/dL (5-6.05 mmol/L) versus a liberal goal of 180 to 200 mg/dL (10-11.1 mmol/L). The large observational study of Finney et al<sup>11</sup> argued for maximal benefit in the range of 144 to 180 mg/dL (8-10 mmol/L). Because tighter control necessitates more insulin (and its potential harmful effects) and increases the risk for hypoglycemia, it is not self-evident that lower levels are desirable. Considering the dynamics of the stress response, it seems reasonable to hypoth-

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esize that the role for ultratight control is in the anabolic phase of recovery and in the basal unstressed state. In other words, tight control in unstressed ambulatory patients makes more sense than intensive control in operative or early postoperative patients.

Hypoglycemia is a risk to intensive insulin therapy. Approximately 5% of the patients in the Belgian study had hypoglycemic episodes despite the increased scrutiny of an intensive care study. Patients under general anesthesia in a high workload environment might have silent episodes of hypoglycemia at a much higher rate. One study, which sought to normalize serum glucose in cardiac surgery patients, demonstrated large variability in insulin requirement, and found postoperative hypoglycemia to be a real risk of the therapy.<sup>12</sup> Because hypoglycemia under anesthesia may be longer in duration and more severe than in patients who might manifest symptoms, the actual detriment from tight intraoperative glycemic control is unknown and cannot be inferred from the literature.

These insights challenge the putative benefit of tight intraoperative glycemic control. Equally important and closely related is the liability of such therapies. Hospital administrative and regulatory bodies, with little knowledge of the nature of

work in the operating room, can easily advocate this therapy with little insight into or liability from its consequences. Similarly, surgeons may have an interest in this unproved practice, but incur little of the liability for adverse outcomes related to hypoglycemic episodes. It is thus the anesthesiologist who is left holding the proverbial bag. In the face of unknown risk and benefit, this is a risky position. Indeed, the benefit is potentially nil, and the liability is substantial.

Although at first glance it seems promising, a therapy as "simple" as maintaining tight glycemic control in the operating room is perilous. The appropriate population or target for such a therapy are not known, and the contention that unselected intraoperative patients are the wrong population cannot be refuted. Mechanism of action and appropriate end points are still poorly understood. The common view of insulin as "anti-glucose" is an oversimplification. Hypoglycemia is a real and potentially substantial risk in anesthetized patients and represents a source of complications for which the anesthesiologist will likely be fully responsible. The current state of knowledge with regard to this therapy mandates further study, rather than ambitious application.

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