Scientific Principles and Clinical Implications of Perioperative Glucose Regulation and Control

Shamsuddin Akhtar, MBBS*
Paul G. Barash, MD*
Silvio E. Inzucchi, MD†

Development of hyperglycemia after major operations is very common and is modulated by many factors. These factors include perioperative metabolic state, intraoperative management of the patient, and neuroendocrine stress response to surgery. Acute insulin resistance also develops perioperatively and contributes significantly to hyperglycemia. Hyperglycemia is associated with poor outcomes in critically ill and postsurgical patients. A majority of the investigations use the term “hyperglycemia” very loosely and use varying thresholds for initiating treatment. Initial studies demonstrated improved outcomes in critically ill, postsurgical patients who received intensive glycemic control (IGC) (target serum glucose <110 mg/dL). These results were quickly extrapolated to other clinical areas, and IGC was enthusiastically recommended in the perioperative period. However, there are few studies investigating the value of intraoperative glycemic control. Moreover, recent prospective trials have not been able to show the benefit of IGC; neither an appropriate therapeutic glycemic target nor the true efficacy of perioperative glycemic control has been fully determined. Practitioners should also appreciate technical nuances of various glucose measurement techniques. IGC increases the risk of hypoglycemia significantly, which is not inconsequential in critically ill patients. Until further specific data are accumulated, it is prudent to maintain glucose levels <180 mg/dL in the perioperative period, and glycemic control should always be accompanied by close glucose monitoring.

Accepted for publication September 28, 2009.

Silvio E. Inzucchi received research funding from Eli Lilly Co. and honoraria for speaking engagements from Novo Nordisk, manufacturers of insulin products, including those used in the hospital setting. He has also served as a consultant to Medtronic, a manufacturer of glucose sensors with potential use in the hospital setting.

Reprints will not be available from the author.

From the Departments of *Anesthesiology, and †Internal Medicine/Endocrinology, Yale University School of Medicine, New Haven, Connecticut.

Fasting plasma glucose (FPG) levels are tightly regulated typically between 60 and 90 mg/dL, and postprandial glycemic excursions to >140 mg/dL are unusual in normal healthy individuals. Chronic hyperglycemia has significant long-term deleterious health effects. According to the current guidelines by the American College of Endocrinology and the American Diabetes Association (ADA), individuals with an FPG of 100 to 125 mg/dL are considered prediabetic, whereas those with FPG levels ≥126 mg/dL have diabetes mellitus. Based on the current National Health and Nutritional Examination Survey, the crude prevalence of diabetes (diagnosed and undiagnosed) in the United States is 12.9% of the population older than 20 years, and approximately 40% of these individuals are unaware of the diagnosis. A further 26% of the population has impaired fasting glucose (which increases the risk of diabetes), making the burden of disease to be 73 million people. Between 60% and 70% of patients with prediabetes will progress to develop frank diabetes. Eighty percent of the cases in North America and Western Europe are Type 2 diabetes, which is characterized by variable degrees of insulin deficiency and resistance. Type 1 diabetes accounts for another 5% to 10% of cases and is characterized by pancreatic β-cell destruction and absolute requirement of insulin. Other diseases such as genetic defects, malfunction of the exocrine pancreas, other endocrinopathies, certain medications and gestation may cause the other 5% to 10% of the cases of diabetes.

Although patients with diabetes have a higher incidence of operative complications, development of acute hyperglycemia perioperatively per se (i.e., even in those with previously normal glucose tolerance) is also recognized as a predictor of adverse
outcomes. This association implies, but certainly does not prove, that controlling hyperglycemia during and after surgery may lead to improved outcomes, and has been the focus of recent reviews. A number of articles advocating "intensive glycemic control" (IGC) in the perioperative and hospital setting have been published, but the potential clinical benefit of IGC during and after surgery has not been tested rigorously. Thus, there is significant allocation of resources and adoption of perioperative practices that have not been substantiated by large, randomized clinical trials. Moreover, according to a recent, large multicenter trial involving mixed medical/surgical intensive care unit (ICU) patients, there may be some harm associated with IGC. This review discusses our current understanding of glucose homeostasis, the scientific basis for hyperglycemia in the perioperative period, and critically analyzes the contemporary literature addressing perioperative glycemic control.

**PHYSIOLOGY OF GLYCEMIC CONTROL**

**Glucose Transport**

The principal organs involved in glucose homeostasis include the brain, pancreas, muscle, adipose tissue, liver and sensors in the hepatopancreatic area, and the kidneys (Fig. 1). The interactions of these organs to maintain stable glycemia are complex. Glucose enters the cell by 1 of 2 methods: facilitated diffusion or active transport. Facilitated diffusion requires specific glucose transporters (GLUTs) (GLUT-1 to -12, H+/myo-inositol transporter, and sodium-dependent glucose cotransporters 1–6). Insulin is one of several hormones involved in glucose homeostasis, albeit the most important. However, all cells are dependent on insulin for glucose transport. Insulin-independent glucose transport is most notable in the pancreas, brain, and immune and endothelial cells. In contrast, cells that are dependent on insulin for glucose transport include skeletal and cardiac muscle, adipose tissue (where GLUT-4 predominates), and the liver, whose glucose uptake is primarily regulated by GLUT-2. Glucose transport into muscle and adipose tissue via a pool of GLUT-4 membrane proteins that move rapidly to the cell surface upon activation of the insulin receptor (IR) is the rate-limiting step in insulin-mediated glucose disposal (Fig. 2). Hence, any condition that reduces the amount of insulin secretion or decreases the cellular sensitivity to insulin's action, or both, will result in hyperglycemia.

**Insulin Secretion and its Regulation**

Increased levels of glucose in the plasma trigger the release of insulin from β-cells in the pancreatic islets of Langerhans. The basal rate of insulin secretion is on the order of 0.4 to 0.7 U/l, increasing rapidly by 4- to 5-fold after ingestion of food. The half-life of insulin in the blood is approximately 5 to 6 minutes, although its cellular activity upon binding to the IR is substantially longer.

The secretion of insulin is not exclusively governed by the plasma glucose level. It is also modulated by other pancreatic hormones (glucagon, somatostatin, and pancreatic polypeptide) and by intestinal hormones collectively known as incretins (glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1). Other intestinal hormones such as cholecystokinin and gastrin promote islet cell neogenesis and may indirectly influence glucose homeostasis. Insulin-like growth factors (IGF-1 and IGF-2) also seem to affect glucose metabolism, but their importance in humans remains unclear. Glucose homeostasis results from the complex interaction between each of these factors, the nature of which continues to be revealed. For example, the more recently discovered modulatory role of the incretins explains the higher levels of insulin that are observed after oral administration of carbohydrates than after an equivalent amount of IV administered dextrose.
Additional factors affect insulin secretion: nitric oxide, arginine, leucine, and β-keto acids, which can each stimulate pancreatic insulin output. Any agent that increases cytosolic cyclic adenosine monophosphate and hence intracellular calcium can also potentially enhance insulin secretion. These agents include β-adrenergic agonists and phosphodiesterase inhibitors such as theophylline. Intracellular calcium can also be increased by acetylcholine; hence, vagal stimulation may also increase insulin secretion.

Conversely, sympathetic stimulation inhibits insulin secretion. This action is mediated by norepinephrine and galanin (a protein that activates KATP channels). Catecholamines also inhibit insulin secretion via α-2 adrenergic receptor stimulation. Hence, the net effect of epinephrine and norepinephrine is inhibition of insulin secretion. However, in the setting of α-blockade, these catecholamines may actually enhance insulin secretion via unopposed β-adrenergic stimulation. Intracellular potassium depletion also attenuates pancreatic insulin output.

Inhaled anesthetics depress glucose-stimulated insulin release, an effect that seems to be relatively consistent among the various agents. Isoflurane and sevoflurane impair glucose tolerance in this manner, but it remains unclear whether the effect is dose dependent. One study suggested that the effect is independent of the dose up to 1.5 minimum alveolar concentration. Desflurane/remifentanil anesthesia maintained insulin levels; however, glucose levels still increased modestly, likely because of a superimposed decrease in insulin sensitivity. Propofol and opioids blunt the neuroendocrine response, and various combinations of other IV anesthetics have also demonstrated this effect. However, this response is restricted to the intraoperative period because the anesthetics are discontinued or administered at a much lower dose in the postoperative period. Clonidine can blunt the neuroendocrine response through its α2-agonist action, but it may promote perioperative hyperglycemia by decreasing insulin secretion from the pancreatic β-cells. For reasons that are unclear, an increase in plasma glucose has not been observed with the use of dexmedetomidine, even though it may also decrease insulin secretion.

Signal Transduction
Insulin exerts its action through the cell surface IR. Notably, IRs are not only limited to the cells that are intricately involved in glucose transport but are also present in many other cells. These include endothelial cells, lymphocytes, macrophages, and monocytes. Binding of insulin to its receptor activates multiple

**Figure 2.** Signal transduction pathway of insulin. Insulin exerts its action through the cell-surface insulin receptor (IR). Binding of insulin to its receptor activates multiple downstream substrates through a series of complex phosphorylation reactions. Activation of these substrates triggers other downstream pathways, which can be loosely grouped into metabolic pathway and proliferative pathways, although they are not mutually exclusive. Metabolic pathway involves phosphatidylinositol-3 (PI3) kinase and casitas b-lineage protooncogene (CBL), whereas the proliferative ones involve mitogen-activated protein kinase (MAP kinase). IRS = insulin receptor substrate; CBL/CAP = an oncogene; aPKC/AKT = atypical protein kinase C; GLUT-4 = glucose transporter 4; FOXO-1 = forkhead transcription factor 1; TC10 = small GTPase Tc10; NO = nitric oxide; mTOR = mammalian target of rapamycin; CSK-3 = glycogen synthase kinase 3; SREBP-1c = sterol response element-binding protein-1c.
downstream substrates through a series of complex intracellular phosphorylation reactions. Activation of these substrates triggers other downstream pathways, which can be loosely grouped into metabolic and proliferative (mitogenic) pathways, although they are not always mutually exclusive. Metabolic pathways involve signaling via phosphatidylinositol-3 (P13) kinase and casitas b-lineage proteins, whereas the proliferative ones involve signaling through mitogen-activated protein kinase (MAPK). The Metabolic Effects of Insulin

Activation of the P13 kinase pathway has 3 principal actions on glucose metabolism: (1) promotion of glucose uptake in insulin-sensitive cells by translocation of a specific glucose transporter (GLUT-4) to the cell membrane; (2) promotion of glycogen synthesis, the chief storage form of intracellular glucose; and (3) phosphorylation of transcription factor (forkhead transcription factor-1), which regulates expression of genes involved in the adaptation to fasting and feeding (gluconeogenesis, glycolysis, lipogenic and sterol synthetic pathways, and hepatic insulin sensitivity). The P13 kinase pathway also stimulates transcription factors that affect nitric oxide production, lipogenesis, and protein synthesis (Fig. 2). Physiologically, insulin reduces circulating glucose concentrations by increasing the uptake of glucose into peripheral tissues, especially skeletal muscle. In the liver, insulin activates glycogen synthase and decreases endogenous (primarily hepatic) glucose production by reducing gluconeogenesis and glycogenolysis.

Nonmetabolic Effects of Insulin

Some of the beneficial effects of insulin are attributed to its nonmetabolic actions, exerted primarily, although not exclusively, through the MAPK pathway (Fig. 2). It suppresses several proinflammatory transcription factors (nuclear factor-κB, early growth response-1, and activating protein-1) and decreases the expression of endotoxin-mediated inflammatory mediators (interleukin [IL]-1β, IL-6, macrophage migration inhibitor factor, and tumor necrosis factor [TNF]-α). Furthermore, inhibitory factor-κB expression is increased (which counters the actions of proinflammatory intracellular signal, nuclear factor-κB). Insulin augments nitric oxide production (via the P13 kinase pathway) in both platelets and the endothelium, thereby acting as an inhibitor of platelet aggregation and a selective vasodilator (Fig. 2). Insulin decreases expression of tissue factor, plasminogen activator inhibitor-1, reactive oxygen species, intracellular adhesion molecule-1, and monocyte chemotactic protein-1 generation, highlighting its antioxidant, antithrombotic, and antiinflammatory properties. Antiapoptotic properties of insulin have also been well described. In contrast, insulin also increases endothelin-1 expression via the activation of the

MAPK pathway. However, in the setting of "selective insulin resistance" as seen in obesity and diabetes, this pathway likely remains intact and, in the setting of hyperglycemia and hyperinsulinemia, may manifest insulin's vasoconstrictive and potentially proatherosclerotic actions.

Detrimental Effects of Acute Hyperglycemia

Diabetic patients have significant cardiovascular disease and compromised immune function, which makes them prone to perioperative cardiac complications and surgical wound infection. However, acute hyperglycemia may also have its own deleterious effects that can lead to poor perioperative outcomes (Fig. 3). It can suppress various aspects of immune function (chemotaxis, phagocytosis, generation of reactive oxygen species, and intracellular killing of bacteria) and increase the
circulating inflammatory cytokine concentrations. Some of the effects of hyperglycemia are reported at glucose concentrations >200 mg/dL. Decreased nitric oxide production, increased angiotensin II levels, and increased systemic vascular resistance can lead to altered vascular reactivity in hyperglycemia. Once the renal threshold is crossed, osmotic diuresis leads to dehydration and electrolyte and acid-base imbalance. Hyperosmolality leads to central nervous system dysfunction, and its rapid correction can worsen cerebral edema.

### MODULATORS OF HYPERGLYCEMIA IN THE PERIOPERATIVE PERIOD

Hyperglycemia is a ubiquitous phenomenon in the perioperative period, linked to the preoperative metabolic state of the patient, neuroendocrine stress response, and acute perioperative insulin resistance, as well as his or her intraoperative management. These factors are not necessarily independent of each other (Fig. 4). Patients with diabetes, metabolic syndrome, preexisting insulin resistance (due to obesity, etc.) or those with underlying β-cell dysfunction (previously unrecognized under basal conditions) are more likely to develop perioperative hyperglycemia. However, development of stress-induced hyperglycemia in patients without diabetes portends poorer outcomes than those in patients with diabetes.

Activation of the neuroendocrine system contributes significantly to perioperative hyperglycemia. Glucagon, epinephrine, and cortisol (counterregulatory hormones) are the primary hormones that are secreted in the setting of perioperative stress. These counterregulatory hormones work in concert to maintain hyperglycemia by targeting substrate supply, capacity of the liver to take up gluconeogenic precursors, mobilization of glycogen stores in the perioperative fasting state, and facilitation of glucose release by the liver, while minimizing hepatic glucose entry. Gluconeogenesis contributes >90% to the total glucose production under perioperative conditions. Glucose production increases by approximately 30% after surgery, whereas glucose clearance decreases. The reduction in glucose clearance is related to decreased glucose use by the skeletal muscle, which is secondary to increased insulin resistance. Endotoxin also contributes to hyperglycemia by stimulating the adrenergic system and increasing the levels of cytokines that cause insulin resistance.

Insulin resistance is a state of decreased biological effect to any given concentration of insulin. When it occurs acutely, in some individuals, the pancreas may not be able to respond with appropriate hyperinsulinemia, and the result is hyperglycemia. Insulin resistance is affected by age, genetic predisposition, ethnicity, physical activity level, and body weight. Poor perioperative caloric intake and negative nitrogen balance also increase insulin resistance. Insulin resistance is also mediated by proinflammatory molecules, free fatty acids, and counterregulatory hormones. During surgical or traumatic injury, peripheral resistance to the action of insulin may be profound at the level of the prime controllers of glucose (adipose tissue, liver, heart, and skeletal system).

The exact mechanism of insulin resistance in the inflammatory and perioperative state is far from settled. It is most likely attributable to many factors acting at various levels of the signal transduction pathways. Of note is a decrease in tyrosine phosphorylation of IRS substrate (IRS) and activation of proteins that suppress cytokine signaling, called suppressor of cytokine signal. TNF-α has been shown to induce phosphorylation of IRS-1, which in turn phosphorylates the IR, making it resistant to normal phosphorylation by insulin. In addition, TNF-α and IL-6 have been shown to induce suppressor of cytokine signal-3.
The degree of hyperglycemia is also dependent on the medications used during surgery (e.g., steroids, epinephrine, or IV fluids containing dextrose) and the dextrose in pump prime fluid during cardiopulmonary bypass. Patients who undergo cardiac surgery with cardiopulmonary bypass, especially under deep hypothermic circulatory arrest, frequently develop hyperglycemia. This is likely due to the profound inflammatory and stress response of cardiopulmonary bypass and/or hypothermia, which decrease insulin secretion and further augment insulin resistance. Hyperglycemia during cardiopulmonary bypass may also be related to increased reabsorption of glucose in the renal tubules.

It is predictable that any anesthetic technique that modifies the neuroendocrine stress response intraoperatively could also modulate the subsequent metabolic sequelae and mitigate perioperative hyperglycemia. In operations involving the lower part of the body, spinal and epidural anesthesia can blunt such a stress response. In contrast, for upper abdominal surgeries, neuraxial anesthetic techniques seem to be less efficient in doing so. Propofol and opioids blunt the neuroendocrine response, and various combinations of IV anesthetics have also demonstrated this effect; however, the modulation of the stress response in this manner is restricted to the intraoperative period, likely because such drugs are either discontinued or administered at a much lower dose in the postoperative period. Generally, the metabolic effects of noncardiac surgery are most evident postoperatively. Furthermore, postoperative alterations in physical activity (which has a major impact on glucose utilization) and medications (which directly interfere with insulin secretion or enhance insulin resistance) affect postoperative glycemic levels.

To summarize, the perioperative stress response leads to insulin resistance. This may be modulated further by many factors, including anesthetic technique, perioperative medications, surgical location and extent, and operative duration and technique. Insulin secretion is also directly affected by anesthetics and various vasoactive medications. It is therefore not surprising that hyperglycemia is extremely common in the postoperative setting.

### Hyperglycemia and Perioperative Outcomes

Recognizing the potential deleterious effects of hyperglycemia, its association with poor perioperative outcomes and salutary effects of insulin, it would be logical to advocate glycemic control in the perioperative period. Currently, there is no unified or well-accepted value to define perioperative “hyperglycemia.” Investigators have used serum glucose values of >100 mg/dL to >270 mg/dL to define clinically relevant hyperglycemia in adult surgical populations. Similarly, the therapeutic threshold to treat glucose levels in adults periopeatively has ranged from >110 mg/dL to >200 mg/dL in...
the context of this review, the term “intensive glycemic control (IGC)” means the attempt to maintain all glucose levels >70 to 80 mg/dL and <110 mg/dL, and the discussion focuses predominantly on the adult surgical population, unless specifically mentioned. Most of the evidence for the improved outcomes of glycemic control is derived from retrospective or prospective observational studies. There have been few prospectively randomized controlled trials, and even fewer studies have focused specifically on the intraoperative period. For the purpose of this review, first we discuss retrospective studies, followed by prospective trials. To highlight the level of evidence for each phase in the perioperative period, we further divide the discussion into the preoperative, intraoperative, and postoperative periods.

**Retrospective Studies**

**Preoperative Hyperglycemia**

Patients with diabetes have an established association with adverse perioperative outcomes. However, 10% to 15% of patients without diagnosed diabetes may present with hyperglycemia preoperatively. A number of studies have shown a strong association between perioperative hyperglycemia (>200 mg/dL) and poor perioperative outcomes, regardless of diabetic status (Table 1). A retrospective analysis of 1201 patients who underwent carotid endarterectomy revealed that perioperative glucose >200 mg/dL on the day of surgery and increasing levels of operative-day glucose were associated with increased risk of perioperative (30-day) stroke, myocardial infarction, and death. A case-control retrospective study of 108,593 patients who underwent noncardiac, nonvascular surgery showed that perioperative hyperglycemia (>200 mg/dL) was associated with increased mortality (odds ratio [OR], 1.7). Similarly, abnormal hemoglobin (HbA1c >7%) is associated with increased risk of infection and morbidity after cardiac and noncardiac surgeries.

**Intraoperative Hyperglycemia**

A number of retrospective studies in cardiac surgery patients have demonstrated a link between intraoperative glycemic levels and adverse outcomes. This association was not clearly established in earlier studies, but more recent investigations have been able to show a strong association between glycemic levels and outcomes. With the exception of one study, all retrospective studies in cardiac surgery patients have used a glucose level of >110 mg/dL as their association or therapeutic cutoff threshold (Table 1). An initial retrospective analysis of 409 patients revealed that for each 20 mg/dL increase in serum glucose levels >100 mg/dL, the risk for adverse events increased by 30%. These results, however, were not supported by a subsequent prospective study from the same group. Ouittara et al. analyzed 200 diabetic patients who underwent cardiac surgery and demonstrated an association between intraoperative hyperglycemia (defined as >4 consecutive values >200 mg/dL despite treatment) and poor cardiac and noncardiac outcomes. Doenst et al. assessed the influence of hyperglycemia (highest glucose level) during cardiopulmonary bypass on perioperative morbidity and mortality in patients with or without diabetes. A peak glucose level >360 mg/dL during cardiopulmonary bypass was an independent predictor of mortality both in patients with diabetes (OR, 1.2) and in those without diabetes (OR, 1.12). These investigators determined that a peak intraoperative glucose level <270 mg/dL during cardiopulmonary bypass was not associated with poor outcomes. In an interventional trial by Fumary et al. of glycemic control in 3550 diabetic patients undergoing cardiac surgery, outcomes were compared with historical controls. Insulin was initiated intraoperatively and continued for 3 days postoperatively. A significant reduction in mortality and a decrease in cardiovascular morbidity and infection were demonstrated compared with historical controls who received insulin subcutaneously. However, IGC was not the aim of this study, and glucose levels were initially targeted to <200 mg/dL, but during subsequent years of the study, to 100 to 150 g/dL.

There are few retrospective studies in the noncardiac surgery literature that only correlate intraoperative glycemic levels with outcomes. A recent post hoc analysis of the Intraoperative Hypoglycemia for Anesthesia Surgery Trial suggested an association of increased neurologic deficits with hyperglycemia (>129 mg/dL) at the time of cerebral aneurysm clipping. In patients with severe traumatic brain injury, IGC was associated with increased markers of cellular stress; however, no difference in mortality or functional outcomes was noted. Thus, the evidence in support of IGC intraoperatively, even in retrospective and observational studies, remains scant.

**Postoperative Hyperglycemia**

A metabolic impact of neuroendocrine perturbations secondary to surgical stress is most noticeable postoperatively. Postoperative hyperglycemia is associated with poor outcomes. Most patients studied are status post–cardiac surgery, although there are some data on vascular, neurosurgical, and trauma patients as well. Two studies, one in a trauma ICU and another in a mixed medical-surgical ICU, were able to show a correlation between better clinical outcomes and lower glucose level (<140 mg/dL). One investigation in a neurosurgical ICU did not show a difference in outcomes in the first week of admission, although there was a decreased infection rate and a statistical decrease in the intracranial pressure in the second week in glycemic controlled patients. Another recent study investigated the effect of glycemic control (<120 mg/dL) in 834 patients with aneurysmal subarachnoid hemorrhage and did not
<table>
<thead>
<tr>
<th>Study type</th>
<th>Study type</th>
<th>Number and type of patients</th>
<th>Design</th>
<th>Glycemic goal or range</th>
<th>Salient findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative</td>
<td>Retrospective</td>
<td>267 patients, head trauma</td>
<td>Nonstandardized protocol</td>
<td>None</td>
<td>Severity of head injury correlated with admission and postoperative glucose levels. Only postoperative glucose levels &gt;300 mg/dL were predictors of poor outcomes. Hyperglycemia (glucose &gt;200 mg/dL) was associated with higher rate of mortality.</td>
</tr>
<tr>
<td>Anездевsky et al.83</td>
<td>Retrospective</td>
<td>738 patients, trauma</td>
<td>Nonstandardized protocol</td>
<td>None</td>
<td>Admission glucose &gt;200 mg/dL was associated with increased mortality, increased hospital and ICU LOS, and increased rate of infection. Hypoglycemia (glucose &lt;100 mg/dL) had higher incidence of infection and hospital LOS.</td>
</tr>
<tr>
<td>Iud et al.83</td>
<td>Retrospective</td>
<td>516 patients, trauma</td>
<td>Nonstandardized protocol</td>
<td>None</td>
<td>Preoperative glucose &gt;250 mg/dL was associated with increased incidence of stroke, TIA, MI, and death. Mild hyperglycemia (150-199 mg/dL) was not associated with difference in the incidence of stroke, TIA, MI, and death.</td>
</tr>
<tr>
<td>Sung et al.88</td>
<td>Prospective</td>
<td>1035 patients, trauma</td>
<td>Nonstandardized protocol</td>
<td>None</td>
<td>A HbA1C &lt; 7% associated with decreased incidence of infectious complications. In patients with pre-diabetes 3-fold increase while in patients with diabetes 4-fold increase in cardiovascular mortality.</td>
</tr>
<tr>
<td>McGirt et al.86</td>
<td>Retrospective</td>
<td>1201 patients, cardiac surgery</td>
<td>Nonstandardized protocol</td>
<td>&lt;200 mg/dL</td>
<td>No association between maximum blood glucose concentration and mortality (univariate analysis). Patients with diabetes were more prone to infectious complications. Preoperative hyperglycemia was an independent predictor of short-term infectious complications and the total hospital LOS.</td>
</tr>
<tr>
<td>Oceaner et al.90</td>
<td>Retrospective</td>
<td>1090 patients, CABG</td>
<td>Nonstandardized protocol</td>
<td>HbA1c</td>
<td>Hyperglycemia did not predict increased mortality. Continuous IV insulin therapy (preoperative to 3 days postoperative) improved survival (2.5% vs 3.3%). Peak glucose &gt;300 mg/dL was associated with adverse events and mortality.</td>
</tr>
<tr>
<td>Estrada et al.99</td>
<td>Retrospective</td>
<td>1374 patients, CABG</td>
<td>Nonstandardized glucose</td>
<td>150-200 mg/dL</td>
<td>Maximal and mean intraoperative glucose predicted increased morbidity and mortality (multivariate analysis). Increase in mean intraoperative glucose level (20 mg/dL) associated with a 30% occurrence (30%) of an adverse event.</td>
</tr>
<tr>
<td>Fontary et al.90</td>
<td>Prospective</td>
<td>3554 patients, CABG</td>
<td>Nonstandardized glucose</td>
<td>Insulin by bolus during CPB</td>
<td>No difference in cardiac, pulmonary, neurological, renal, and infectious complications. Decreased mortality in treatment group (1.5% vs 4.0%).</td>
</tr>
<tr>
<td>Doire et al.90</td>
<td>Retrospective</td>
<td>6283 patients, CABG</td>
<td>Nonstandardized glucose</td>
<td>N/A</td>
<td>At 6 wk, non-diabetic patients. glucose &gt;200 mg/dL was associated with decreased cognitive dysfunction. In patients with diabetes, hyperglycemia had no effect on cognitive dysfunction. (Continued)</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Number and type of patients</th>
<th>Design</th>
<th>Glycemic goal or range</th>
<th>Salient findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative Findley et al.</td>
<td>Prospective observational</td>
<td>533 patients, medical (12%), surgical (88%) ICU</td>
<td>Insulin by nonstandardized protocol</td>
<td>90-145 mg/dL</td>
<td>Patients divided into 6 groups. Best outcomes noted in patients with glucose levels between 145 and 180 mg/dL. In all glucose groups, insulin administration was associated with increased risk of death. Hyperglycemia on POD 3 was an independent predictor of adverse outcomes. Perioperative infection rate correlated with hyperglycemia.</td>
</tr>
<tr>
<td>McNab et al.</td>
<td>Retrospective</td>
<td>291 patients, CABG</td>
<td>92% received IV insulin by protocol</td>
<td>164-209 mg/dL</td>
<td>Lower incidence of mortality (20.9% vs 14.3%), renal dysfunction (5% vs 17%), and PRBC transfusion (33.5% vs 25.5%). No difference in infection and LOS. No benefit of hyperglycemic control if APACHE score &gt;35.</td>
</tr>
<tr>
<td>Vriesendorf et al.</td>
<td>Retrospective</td>
<td>275 patients, vascular surgery</td>
<td>Nonstandardized protocol</td>
<td>None</td>
<td>High glucose (&gt;220 mg/dL), worsening, or highly variable glucose levels associated with increased risk of infection, ICU LOS, H-LOS, and mortality. Blood glucose level &gt;140 mg/dL was associated with increased morbidity and mortality.</td>
</tr>
<tr>
<td>Krinsley</td>
<td>Retrospective</td>
<td>1669 patients, medical (65%)/surgical (35%) ICU</td>
<td>Insulin by standardized protocol</td>
<td>&lt;140 mg/dL</td>
<td>Blood glucose level &gt;200 mg/dL on admission to the ICU was associated with increased morbidity and mortality. Decreased incidence of intraabdominal abscesses. Decreased number of days on the ventilator.</td>
</tr>
<tr>
<td>Bochicchio et al.</td>
<td>Prospective observational</td>
<td>42 patients, trauma</td>
<td>Nonstandardized protocol</td>
<td>None</td>
<td>Decreased incidence of intraabdominal abscesses. Decreased number of days on the ventilator.</td>
</tr>
<tr>
<td>Gele et al.</td>
<td>Retrospective</td>
<td>103 patients, trauma ICU</td>
<td>SQ insulin by standardized protocol</td>
<td>&lt;140 mg/dL</td>
<td>Mean blood glucose levels &gt;140 mg/dL were strongly associated with mortality but not with infection rate.</td>
</tr>
<tr>
<td>Sachar et al.</td>
<td>Retrospective</td>
<td>614 patients, cardiothoracic surgery</td>
<td>Insulin by standardized protocol</td>
<td>80-110 mg/dL</td>
<td>Glucose level &gt;200 mg/dL on admission during the first 5 days was associated with increased in-hospital morbidity and mortality.</td>
</tr>
<tr>
<td>Reed et al.</td>
<td>Retrospective</td>
<td>7261 patients, trauma</td>
<td>Progressively stringent insulin protocol</td>
<td>Mean glucose decreased from 141 to 129</td>
<td></td>
</tr>
<tr>
<td>Wahl et al.</td>
<td>Prospective observational</td>
<td>513 patients, trauma</td>
<td>Insulin by standardized protocol</td>
<td>&lt;140 mg/dL</td>
<td>No difference in hospital mortality with glycemic control. 4X higher incidence of hypoglycemia with glycemic control.</td>
</tr>
<tr>
<td>Ascione et al.</td>
<td>Retrospective</td>
<td>877 patients, cardiac surgery</td>
<td>Insulin by standardized protocol</td>
<td>90-144 mg/dL</td>
<td>No difference in outcome during the first week. Decreased ICP and infection rate in the second week. Postoperative infection rate was associated postoperative hypoglycemia.</td>
</tr>
<tr>
<td>Treggiari et al.</td>
<td>Retrospective</td>
<td>10,456 patients, medical/surgical</td>
<td>Progressively stringent insulin protocol</td>
<td>None 80-130 mg/dL 80-110 mg/dL</td>
<td>No difference in hospital mortality with glycemic control. 4X higher incidence of hypoglycemia with glycemic control.</td>
</tr>
<tr>
<td>Meier et al.</td>
<td>Retrospective</td>
<td>228 patients, neurotrauma</td>
<td>Insulin by standardized protocol</td>
<td>70-140 mg/dL</td>
<td>No difference in outcome during the first week. Decreased ICP and infection rate in the second week. Postoperative infection rate was associated postoperative hypoglycemia.</td>
</tr>
<tr>
<td>Ramos et al.</td>
<td>Retrospective</td>
<td>905 patients, general/vascular surgery</td>
<td>Nonstandardized protocol</td>
<td>None</td>
<td>No difference in hospital mortality with glycemic control. 4X higher incidence of hypoglycemia with glycemic control.</td>
</tr>
<tr>
<td>Thiele et al.</td>
<td>Retrospective</td>
<td>834 neurosurgical points with SAH</td>
<td>Insulin by standardized protocol</td>
<td>&lt;120 mg/dL</td>
<td>No difference in hospital mortality with glycemic control. 4X higher incidence of hypoglycemia with glycemic control.</td>
</tr>
</tbody>
</table>

ICU = intensive care unit; LOS = length of stay; TIA = transient ischemic attack; MI = myocardial infarction; HbA1c = hemoglobin A1c; PRBC = packed red blood cells; CABG = coronary artery bypass surgery; ICU-LOS = intensive care length of stay; H-LOS = hospital length of stay; ICP = intracranial pressure; SAH = subarachnoid hemorrhage; POD = postoperative day.

show an effect on in-hospital mortality. In cardiac surgery patients, blood glucose levels >200 mg/dL on admission to the ICU or anytime between 1 to 5 days after the procedure were correlated with morbidity and mortality. Another investigation involving 521 patients, of whom 88% were postischemic cardiac patients, divided the cohort into 6 groups (≤79, 80-110, 111-144, 145-180, 181-200, and ≥200 mg/dL); the investigators were able to demonstrate better outcomes in those patients with glucose levels between 145 and 180 mg/dL than in those patients with higher levels. Although increased postoperative blood glucose levels were associated with poor outcomes, the glucose thresholds associated with good outcomes seemed to be much higher than 110 mg/dL.
Collective analysis of retrospective studies suggests a strong association between perioperative hyperglycemia and patient outcome. However, a majority of the investigations use the term "hyperglycemia" very loosely and establish the association with poor perioperative outcomes to glucose levels that are much higher than 110 mg/dL. In addition, it remains unclear from such investigations whether correcting the hyperglycemia will improve clinical outcomes. That is, it remains poorly understood whether hyperglycemia mediates poor operative outcomes or whether it is simply an "innocent bystander," i.e., a marker of the sickest patients or those with, or predisposed to, the most underlying metabolic derangements.

Prospective Studies
Preoperative
There has been no prospective, randomized control trial that has demonstrated that controlling glucose or decreasing HbA1c to a given level, for a certain duration, before elective surgery improves the overall perioperative outcomes. Practically, anesthesiologists are unlikely to have a significant role in managing chronic perioperative hyperglycemia. However, perioperative evaluation provides a unique opportunity to screen patients for hyperglycemia. Clearly, patients presenting with very poor glycemic control, especially if exhibiting features of ketoacidosis or hyperosmolar state, should not undergo elective procedures and would benefit from aggressive stabilization before surgery. However, it is less clear whether there is any value in acutely controlling hyperglycemia in those who are chronically hyperglycemic, especially for short, minimally stressful outpatient procedures. Most of the recent randomized clinical trials have been conducted on cardiac surgery patients with the aim of controlling glucose levels or administering insulin intraoperatively and/or postoperatively (Table 2).115

Intraoperative
In the contemporary noncardiac surgical literature, prospective, randomized, controlled data investigating the efficacy of intraoperative IGC are lacking. A recent trial of 236 patients undergoing vascular surgery showed a decrease in major cardiovascular events when glucose was maintained between 100 and 150 mg/dL with continuous insulin infusion.120 However, the trial had to be terminated early for logistical reasons and was underpowered.121 A trial of 78 patients involving aneurysm clipping after acute subarachnoid hemorrhage did not show a mortality benefit of IGC.117 Notably, the brain is particularly sensitive to hypoglycemia, with evidence that glucose levels both <80 mg/dL and >170 mg/dL can be harmful.122 Larger, well-designed trials are required to confirm the therapeutic benefit of IGC intraoperatively in neurosurgical and other noncardiac surgery patients.

Insulin in combination with glucose (and potassium) has been used for myocardial protection in patients presenting with myocardial ischemia or infarction123 and has also been tested with variable success for decades during cardiac surgery. Most of the earlier trials did not control for glucose levels; however, some recent studies have adopted an IGC approach. A decrease in inflammatory markers (IL-6, IL-8, and TNF-α) has been shown with high-dose insulin treatment (approximately 21 U/h for a 70-kg person or 5 mU/kg·min−1) while maintaining glucose between 80 and 110 mg/dL with exogenous dextrose.124 Other reports have shown increased phagocytic capacity118 or improved myocardial function with intraoperative insulin use.119 However, no difference was noted in clinical outcomes. Larger studies by Rao et al.111 (1127 patients receiving insulin during cardioplegia) and Butterworth et al.112 (381 patients) were unable to show any difference in myocardial injury and/or low cardiac output states or neurologic complications, respectively.

There is only one study that has assessed the value of intraoperative IGC prospectively.107 Four hundred cardiac surgery patients were randomly assigned to receive either continuous insulin infusion to maintain glucose levels between 80 and 100 mg/dL or conventional treatment to treat glucose levels >200 mg/dL. Postoperatively, both the treatment group and the control group received insulin to maintain normoglycemia after surgery. No significant difference was noted in the composite outcomes (death, sternal wound infection, prolonged infection, cardiac arrhythmias, stroke, and renal failure) between the treatment (44%) and conventional (46%) groups. ICU and hospital length of stay were also not significantly different. Importantly, more deaths (4 vs 0) and strokes (8 vs 1) were actually noted in the IGC group. Although it is a single-center study with low frequency of mortality and inability to differentiate between diabetics and nondiabetics, the study questions the utility of intensive intraoperative glycemic control in patients undergoing surgery.

Postoperative
The strongest support for IGC therapy comes from a single-center study of 1548 mechanically ventilated patients (predominantly cardiac surgical ICU patients) by van den Berghe.114 It was a prospective, randomized, controlled trial. The treatment group received IGC by IV infusion for the duration of the ICU stay, whereas in the control group, plasma glucose was treated only if >215 mg/dL and was maintained in a conservative range of 180 to 210 mg/dL. During the trial, the mean morning blood glucose in the 2 IGC and control groups was 103 and 153 mg/dL, respectively. The authors demonstrated a significant decrease in ICU mortality, renal dysfunction, need for dialysis, and neuropathic changes in the IGC group. However, caregivers were not blinded to therapy, all...
Table 2. Prospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Study design</th>
<th>Glycemic goal or range</th>
<th>Salient findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative</td>
<td>RCT</td>
<td>30 patients, CABG</td>
<td>Insulin by standardized protocol</td>
<td>75-125 mg/dL</td>
<td>Increased total neurophilic pathologic capacity in insulin treatment group</td>
</tr>
<tr>
<td>Rasas et al.10</td>
<td>RCT</td>
<td>1127 patients, CABG</td>
<td>Insulin by standardized protocol</td>
<td>100 mg/dL</td>
<td>No difference in myocardial infarction and/or low cardiac output syndromes between treatment and control groups</td>
</tr>
<tr>
<td>Butterworth et al.112</td>
<td>Prospective</td>
<td>361 patients, CABG</td>
<td>Insulin by standardized protocol</td>
<td>108-180 mg/dL</td>
<td>No difference in short- and long-term neurological complications between the groups</td>
</tr>
<tr>
<td>Koskenkari et al.113</td>
<td>RCT</td>
<td>40 patients, CABG  + AVR</td>
<td>Insulin by standardized protocol</td>
<td></td>
<td>Improved myocardial contractile function and decreased inotropic support. No difference in clinical outcomes</td>
</tr>
<tr>
<td>Gandhi et al.107</td>
<td>RCT</td>
<td>400 patients, CABG</td>
<td>Intraoperative insulin by standardized protocol</td>
<td>80-100 mg/dL</td>
<td>No difference in composite outcomes. Increased number of deaths (4 vs 9) and stroke (8 vs 1) in the intensive insulin group</td>
</tr>
<tr>
<td>Postoperative</td>
<td>RCT</td>
<td>1548 patients, surgical ICU</td>
<td>Intensive insulin by standardized protocol</td>
<td>&lt;110 mg/dL</td>
<td>Significant difference in morbidity and mortality, in patients who bled &gt;5 d. No difference in mortality in patients who stayed &lt;5 d (13% vs 18%)</td>
</tr>
<tr>
<td>van den Berghe et al.114</td>
<td>RCT</td>
<td>61 patients, general surgery</td>
<td>Intensive insulin by standardized protocol</td>
<td>80-120 mg/dL</td>
<td>Decrease in nosocomial infection rate</td>
</tr>
<tr>
<td>Grey and Perrier115</td>
<td>RCT</td>
<td>20 patients, postcardiac surgery</td>
<td>Insulin by standardized protocol</td>
<td>80-110 mg/dL</td>
<td>No difference in outcomes between treatment groups (P&lt;0.01; transfusion, time on ventilator; ICU LOS; or renal dysfunction). No difference in IL-10, IL-6 levels between treatment groups. Infection rate was lower in treatment group. No difference in postoperative vasospasm, neurologic outcome, and mortality rates</td>
</tr>
<tr>
<td>Hoedemaekers et al.116</td>
<td>RCT</td>
<td>78 patients, aneurysm clipping/ neurosurgery</td>
<td>Insulin by standardized protocol</td>
<td>80-120 mg/dL</td>
<td>Decreased length of ICU stay. No difference in infection rate and mortality</td>
</tr>
<tr>
<td>Bilotta et al.117</td>
<td>RCT</td>
<td>97 patients, traumatic brain injury requiring surgery</td>
<td>Insulin by standardized protocol</td>
<td>80-120 mg/dL</td>
<td>Decreased length of ICU stay. No difference in infection rate and mortality</td>
</tr>
<tr>
<td>Bilotta et al.118</td>
<td>RCT</td>
<td>463 patients, neurosurgery</td>
<td>Insulin by standardized protocol</td>
<td>80-110 mg/dL</td>
<td>Decreased length of ICU stay. No difference in infection rate and mortality</td>
</tr>
<tr>
<td>Bilotta et al.119</td>
<td>RCT</td>
<td>614 patients, medical/surgical ICU</td>
<td>Insulin by standardized protocol</td>
<td>81-108 mg/dL</td>
<td>Increased mortality in ICG group. No difference in number of days in the ICU, hospital, on mechanical ventilation, or renal replacement therapy</td>
</tr>
<tr>
<td>Finner et al.11</td>
<td>RCT</td>
<td>236 patients, vascular surgery</td>
<td>Continuous insulin infusion versus SQ, started intraoperatively and continued 48 h</td>
<td>100-150 mg/dL</td>
<td>Decreased major cardiovascular events in patients who received continuous insulin infusion</td>
</tr>
</tbody>
</table>

ICU = intensive care unit; LOS = length of stay; RBC = red blood cells; CABG = coronary artery bypass surgery; AVR = aortic valve replacement; ICU-LOS = intensive care length of stay; H-LOS = hospital length of stay; IL-6 = interleukin 6; IL-10 = interleukin 10; ICG = intensive glucose control; RCT = randomized controlled trial.

patients had received a significant amount of exogenous glucose (>160 g/d) and enteral/parenteral nutrition, and there was also an unusually high mortality in the control group, based on disease severity. These results were initially supported by other observational studies. A meta-analysis of 35 randomized, controlled trials in critically ill hospitalized patients showed significant benefit of insulin therapy. Of the 35 trials included in this meta-analysis, 14 trials involved postoperative patients, and 11 of these 14 trials used glucose-insulin-potassium infusions. Another meta-analysis involving 14 trials in surgical patients showed some benefit of perioperative insulin infusion on mortality (risk ratio [RR], 0.69; confidence interval [CI], 0.51–0.94). No data from medical ICUs were included in either of these meta-analyses.

Collectively, the results from the study by van den Berghe in predominantly surgical patients, in conjunction with other retrospective cardiac surgery studies, were quickly extrapolated to imply that ICG is...
Hypoglycemia

Low glucose levels initiate a compensatory stress response and a typical set of symptoms. However, in the perioperative period and during critical illness, the signs of hypoglycemia may be masked, the compensatory response may be blunted, and the affected patients may be incapable of communicating the symptoms. The ischemic brain reverts to anaerobic metabolism and lactate production and is dependent on lactate for its source of energy. Decreasing glucose levels rapidly and acutely may decrease the lactate supply to the ischemic brain and potentially exacerbate brain injury. Moreover, unrecognized hypoglycemia can have deleterious consequences and has been associated with increased mortality.

Hypoglycemia may be a complication of aggressively and rapidly treating hyperglycemia, especially if tight glucose control is desired. The incidence of severe hypoglycemia (defined as <40 mg/dL), in various ICU studies, ranges from 5.1% to 25.3% of patients in IGC groups and is between 3 and 13 times more common in patients in the intensive control arms of these trials. A higher incidence of mortality in ICU patients who develop hypoglycemia has also been reported. It is not known whether the higher mortality noted is related to increased levels of insulin (which can lead to sympathetic discharge, sodium retention, and various mitogenic actions) or to hypoglycemia.

One recent report from the cardiac literature suggests that hypoglycemia after insulin therapy carries with it no subsequent effect on post-myocardial infarction mortality, whereas the same was not true for spontaneous hypoglycemia, likely reflecting underlying comorbidities. In addition, there is some inherent variability in the point-of-care monitoring techniques that are currently in use. Significantly low blood glucose levels may develop without the practitioners realizing the severity of the hypoglycemia.

Continuous glucose monitors may improve hypoglycemia detection and facilitate more intense glucose lowering. However, more rigorous data are required before their use can be advocated.
Certain patients may be more prone to hypoglycemia, and special attention and modifications to the insulin protocol may be warranted. Independent risk factors include female gender, sepsis, history of diabetes, interrupted or reduced nutritional support without adjustment of insulin dose, continuous venovenous hemofiltration, especially with bicarbonate-based substitution fluid, and need for inotropic support. Patients with significant hepatic, renal, or adrenal insufficiency are prone to hypoglycemia, irrespective of intensive insulin therapy. Insulin, when improperly used, is dangerous, has the highest rate of errors, and is considered 1 of the 5 most common drugs associated with medication errors of clinical significance.

**AREAS OF UNCERTAINTY**

It is becoming increasingly clear that the ideal glucose levels <110 mg/dL that were advocated for critically ill patients and were quickly extrapolated to the perioperative period may have been too rigorous and are not strongly substantiated in multicenter clinical trials. However, this does not imply that glucose control should be totally abandoned and that any hyperglycemic levels are acceptable. Moreover, many questions remain unanswered.

First, the ideal intraoperative and postoperative glycemic target is unknown. Whether clinicians should use mean glucose levels or absolute peak glucose levels as markers of glycemic control is also poorly understood. Some investigators have shown a good correlation of outcomes with decreased glycemic variability, which may be more important than maintaining the blood glucose within a certain range. Glucose fluctuations may trigger adverse physiologic events (increased apoptosis, cytokine expression, and oxidative stress) beyond those sustained from chronic hyperglycemia.

Second, if used, the ideal duration of more intensive insulin therapy and glycemic control is also unknown. In cardiac surgery, investigators have used a multitude of different protocols for variable durations. The Portland protocol adopted in the study by Fumary et al advocates at least 3 days of IV insulin therapy during and after surgery. The ICU protocols typically treat patients only for the duration of ICU stay. Once the patients are transferred to the floor, protocols for glucose monitoring are less stringent, and episodes of hypoglycemia may be missed.

Third, there has been less vigorous discussion of the risk/benefit ratio of IGC interventions. Egi et al studied patients from their large prospective database who were closely matched to the control patients in the van der Berghe surgical ICU population and calculated the number of patients who would need to be treated with IGC to save one life (number needed to treat [NNT]) and to cause harm (number needed to harm [NNH]). NNT varied between 38 and 125, whereas NNH varied from 7 to 13 between institutions. In the NICE-SUGAR study, which predominantly enrolled patients in Australia and New Zealand, a 3.6% increase in mortality rate was noted in the ICG group. Even in the patients studied by Van der Berghe, the NNT was very similar to NNH. Although the potential benefits and potential harm may not be equivalent, such analyses suggest that the beneficial effects of IGC may not be universal, may come at some cost, and can vary significantly among populations and institutions. That is, the NNH might be lower than the NNT in certain cohorts; hence, harm could occur more frequently than benefit. One should also realize that there is significant variation in perioperative outcomes in different regions of the world. Although significant hyperglycemia should be addressed, the aggressiveness of IGC and the need for intensive insulin therapy may ultimately be determined by local practices and the overall morbidity and mortality of the selected patient population.

Fourth, lack of evidence for tight glycemic control may not be a function of glycemic control per se, but may be related to limitation in the glucose monitoring and management technologies. Current commercially available technology does not enable us to consistently achieve IGC without overshooting glycemic goal (with potential detrimental consequences such as significant hypoglycemia). Improvement in glucose monitoring technology and insulin delivery devices is the future may allow smoother achievement of IGC and improved outcomes, without the current incidence of 3 to 6 times higher hypoglycemic episodes.

Finally, the investigations and discussions have centered predominantly on "hyperglycemia" and not necessarily on "patients with diabetes." The value of short-term tight glycemic control in patients with diabetes has not been proven, and IGC seems to be less effective in critically ill patients with diabetes than in patients without diabetes. In patients with diabetes, intraoperative hyperglycemia does not influence postoperative cognitive dysfunction, or higher glucose levels may not be as deleterious as patients without diabetes. This may be related to the chronic adaptive changes to hyperglycemia in patients with diabetes. Thus, it is difficult to advocate the same glucose threshold for patients with diabetes for patients without diabetes. There is a clear difference in the management of patients with Type 1 versus Type 2 diabetes and especially patients with insulin diabetes (because of Type 1 or advanced Type 2 diabetes). Patients with Type 1 diabetes are prone to ketosis and will require a basal level of insulin throughout the perioperative period either via I.V. acting insulin or insulin infusion. The use of IGC in patients with Type 1 diabetes in the perioperative period has not been specifically addressed in any of the trials.
PRACTICAL MANAGEMENT OF PERIOPERATIVE HYPERGLYCEMIA

Glucose Measurement and Monitoring

Ideally, blood glucose should be determined by the central laboratory or onsite blood-gas analyzers; as a rule, point-of-care capillary meters are less reliable, especially in hypoperfused, hypothermic, or anemic patients. The practitioners should keep in mind that the accuracy varies with each modality and some error is allowed when accuracy of these devices is tested. The National Committee for Clinical Laboratory Standards recommends the difference between a glucose meter and a conventional laboratory meter not exceed ±15% for glucose concentrations 100 mg/dL and ±20% for glucose concentrations 100 mg/dL. Although not typically considered, such errors may be significant when trying to establish tight glycemic control. The actual concentration of glucose (amount of glucose per volume of specimen) differs significantly between plasma and whole blood because glucose dissolves in the aqueous but not the solid components of the specimen. The plasma glucose concentration is approximately 11% higher than that in whole blood. The majority of bedside/home glucose meters actually convert their whole blood glucose results to the higher plasma equivalents by a multiplying factor of approximately 1.12 depending on the meter.

Glucose levels in arterial blood are higher than in the venous or capillary blood (because glucose has not been extracted by the tissues). Furthermore, the hemodynamic state of a patient may also affect the accuracy of the blood glucose measurement by the point-of-care devices. In hemodynamically stable patients, point-of-care measurements correlate well with laboratory reference values. However, in patients with poor peripheral perfusion and shock, there is significant variation between laboratory reference values and point-of-care measurements. A recent study showed that 15% of the capillary blood glucose values differed by >20% from the laboratory reference value in hemodynamically compromised patients. Therefore, there is a real possibility of overdosing or underdosing a critically ill patient with insulin. Other factors, such as variation in sample volume, may also affect point-of-care measurements. Excess sample volume can result in spuriously high levels, whereas too small a sample volume may result in low glucose levels. Worsening anemia may result in spuriously high levels of glucose (because of increased volume of plasma). Some medications and conditions also may interfere with glucose measurements. These include t-dopa, dopamine, mannitol, acetaminophen, severe unconjugated bilirubin, severe hyperlipidemia, increased uric acid, maltose (present in immunoglobulin solution), and icodextrin (present in peritoneal dialysis fluid).

In view of the variations between point-of-care devices, it is important that care providers know whether the device in their hospital reports true whole blood glucose or converts to plasma glucose. In addition, individual institutions should specify blood glucose targets based on the institutional methodology of glucose testing and use devices approved by the Food and Drug Administration. It is imperative that in any circumstance in which there is a discrepancy between the measured glucose level and a patient’s clinical condition, that the glucose concentration be confirmed by central laboratory measurement.

Insulin Protocols for Perioperative Glycemic Control

In view of the complex nature of glycemic control in the perioperative period, maintaining glucose levels within a specific range is resource intensive. By some estimates, each point-of-care glucose measurement adds 3.5 to 9 minutes to patient care. Aggregate time spent by the caregivers to monitor glucose and achieve target glucose levels safely may be substantial. The narrower the desired glycemic range, the more resource intensive the protocol will be. Many protocols have been tried and advocated, and many institutions have established their own regimens. Discussion of each protocol is beyond the scope of this review. Subcutaneous insulin administration is not recommended in the intraoperative and immediate postoperative periods and in critically ill postoperative patients because there is a significant variation in skin perfusion and, therefore, absorption. In addition, the onset of action for subcutaneously administered insulin, even the rapid-acting analogs, may be too sluggish for this setting. Most study protocols that have achieved desirable glycemic control (regardless of therapeutic benefit) in acute care settings have used continuous IV insulin infusion combined with IV bolus injections. Targeted glucose levels can be achieved successfully and in a timely manner using these dynamic scale protocols, considering the rate of change in blood glucose levels, combined with frequent blood glucose determinations.

Perioperative Glycemic Goals

The National Health and Nutritional Examination Survey data suggest that 30% to 40% of the population has impaired glycemic control and can be classified as having either diabetes or prediabetes. Thus, a significant proportion of patients presenting for perioperative evaluation are likely to have unrecognized impaired glycemic control and are also more likely to develop intraoperative and postoperative hyperglycemia. Perioperative physicians recognize the multisystem impact of diabetes (chronic hyperglycemia) and its relationship to poor perioperative outcomes. Modification of oral hypoglycemic and insulin regimens is an integral component of the perioperative preparation of patients diagnosed with diabetes. However, the preoperative visit also provides a unique opportunity
<table>
<thead>
<tr>
<th>Location</th>
<th>American College of Endocrinology&lt;sup&gt;171&lt;/sup&gt;</th>
<th>Canadian Diabetes Association&lt;sup&gt;172&lt;/sup&gt;</th>
<th>American Diabetes Association&lt;sup&gt;171&lt;/sup&gt;</th>
<th>American Heart Association/American College of Cardiology&lt;sup&gt;173&lt;/sup&gt;</th>
<th>Society of Thoracic Surgeons (for cardiac surgery)&lt;sup&gt;174&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive care unit</td>
<td>Between 140 and 180 mg/dL; generally &lt;180 mg/dL</td>
<td>&lt;110 mg/dL</td>
<td>Between 140 and 180 mg/dL; generally &lt;180 mg/dL</td>
<td>110-180 mg/dL</td>
<td>Generally; &lt;180 mg/dL ventilator dependent in ICU &gt;3 d; &lt;150 mg/dL.</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>&lt;150 mg/dL</td>
<td>90-180 mg/dL</td>
<td>&lt;150 mg/dL</td>
<td>NA</td>
<td>&lt;180 mg/dL</td>
</tr>
<tr>
<td>Perioperative</td>
<td>&lt;140 mg/dL</td>
<td>90-180 mg/dL</td>
<td>&lt;140 mg/dL</td>
<td>NA</td>
<td>&lt;180 mg/dL</td>
</tr>
<tr>
<td></td>
<td>premeal or random</td>
<td></td>
<td>premeal or random</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NA = not addressed specifically; ICU = intensive care unit.

Guidelines were based on earlier studies and older recommendations from the American College of Endocrinology and the American Diabetes Association.

to screen for diabetes and prediabetes in specific risk groups. The ADA recommends that the following individuals be screened for diabetes: patients who are older than 45 years; patients who have a body mass index >25 kg/m² and have the following additional risk factors: first-degree relatives with diabetes, women with gestational diabetes or history of delivering a baby >4.1 kg, hypertension, history of cardiovascular disease, high-density lipoprotein cholesterol <35 mg/dL or triglycerides >250 mg/dL, women with polycystic ovarian syndrome, or physical inactivity.<sup>3</sup>

Preoperative measurement of HbA1c is used as a marker for long-term glycemic control and may identify patients with chronic hyperglycemia. However, practitioners should recognize that it is not currently endorsed by the ADA, American College of Endocrinology, or the World Health Organization to diagnose diabetes. Some have suggested that high HbA1c (>6%) should lead to more formal evaluation for diabetes. No prospective study has shown that decreasing HbA1c preoperatively to a certain level will improve outcomes. The effect of acute glycemic control preoperatively (<100 mg/dL) is unknown and unlikely to be advocated based on current evidence. However, it is hoped that identifying patients with impaired glycemic control can lead to their early medical management and improved long-term outcomes.<sup>170</sup>

Elective surgery should be avoided in the presence of ketoacidosis or a hyperglycemic hyperosmolar state. Although a fasting glucose level >100 mg/dL is considered abnormal in the nonoperative setting, as discussed earlier, it has been difficult to assign a specific glucose level that should trigger treatment in the perioperative period. There is a significant heterogeneity in recommendations that have been proposed by various organizations, which include the American College of Endocrinology, Canadian Diabetes Association, ADA, American Heart Association, and the Society of Thoracic Surgeons (Table 3).<sup>172-176</sup>

In light of the recent data, older recommendations by the American College of Endocrinology and the ADA have been revised.<sup>173</sup> A general theme that emerges in these guidelines is to at least maintain glucose levels <180 mg/dL perioperatively. Although it is recommended to maintain a glucose level of <150 mg/dL in cardiac surgery patients with a complicated ICU course, it should be recognized that the recommendation is not based on a high level of evidence.<sup>174</sup> Similarly, the authors believe that in the intraoperative period, there is no evidence to compel IGC. Maintaining glucose levels to <180 mg/dL intraoperatively is a reasonable goal in most situations. This would potentially decrease the probability of hypoglycemia. Furthermore, in view of recent negative studies and 3-fold increased probability of severe hypoglycemia, IGC (<110 mg/dL) in critically ill postoperative patients cannot be advocated.

The Surgical Care Improvement Project has adopted a new measure that requires glucose levels <200 mg/dL by 6:00 AM of the second postoperative day in cardiac surgical patients.<sup>177</sup> Although it is possible to institute protocols for glucose control that can be followed by nurses without much physician input, the practice can be significantly resource intensive. Necessary resources should be allocated to achieve the goals safely.

**CONCLUSION**

Perturbations in glycemic control after intermediate- to high-risk surgery are dependent on many factors and can lead to increased glucose levels perioperatively. A patient's perioperative metabolic state, intraoperative anesthetic management, exogenous glucose administration, endogenous glucose production and utilization, neuroendocrine response, development of acute insulin resistance, and variations in endogenous insulin secretion all determine the absolute perioperative glucose level. Irrespective of the cause, hyperglycemia is associated with poor perioperative outcomes, but...
whether correction of hyperglycemia reduces surgical morbidity and mortality is not entirely clear. Moreover, neither a universally appropriate therapeutic glycemic target nor the true efficacy of perioperative glycemic control has been fully determined. Although a number of studies to assess this question have been conducted (especially in the postoperative period), significant heterogeneity in patient populations, glycemic targets, and measurement protocols for glucose will leave many questions unanswered. To answer some of the lingering questions pertaining to IGC, several trials are currently underway. The efficacy of perioperative IGC (\( < 110 \) mg/dL) is unproven, underscored by several recent negative trials, and it increases the risk for hypoglycemia by 3- to 6-fold, which is not inconsequential in critically ill patients. IGC is also resource intensive. Although the potential benefits and harm of IGC may not be equivalent, such analyses suggest that the beneficial effects of IGC may not be universal and can vary significantly among populations and institutions. Currently, it is not advisable to abandon glucose control altogether and until further specific data are accumulated, it is prudent to maintain glucose levels \( < 180 \) mg/dL in the perioperative period. Insulin therapy should preferably be administered IV in the perioperative period and should always be accompanied by close glucose monitoring. Improvement in glucose monitoring technology and insulin delivery devices in the future may allow better-controlled achievement of IGC with improved outcomes in specific patient populations.

REFERENCES

20. de Weille J, Schmidt-Antomarchi H, Fussel M, Lazzoruski M. ATP-sensitive K+ channels that are blocked by hypoglycaemia-inducing sulfonylureas in insulin-secreting cells are activated by galanin, a hyperglycaemia-inducing hormone. Proc Natl Acad Sci USA 1988;85:1512–16

© 2010 International Anesthesia Research Society


