Chapter 29
Glycemic Control Does Matter in the Cardiac Surgery Patient

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Introduction

Hyperglycemia is common in patients undergoing cardiac surgery, and likely represents a maladaptive response influenced by factors associated with the perioperative period, including co-existing diabetes and the stress response to surgery. Myocardial ischemia and infarction, fluid and vasopressor administration, and exposure to the cardiopulmonary bypass circuit also contribute. When one considers the increase in the incidence of diabetes and obesity in the population at risk, perioperative hyperglycemia may become an increasingly common condition [1].

Hyperglycemia in the perioperative or postoperative ICU period is associated with a host of detrimental effects, particularly with respect to the cardiovascular system. At a cellular level, these include an imbalance of myocardial oxygen supply and demand, maladaptive diversion of glucose from dependent organs, endothelial dysfunction, platelet aggregation, and impaired immune function [1, 2]. Hyperglycemia is associated with poorer clinical outcomes including increased short and long-term mortality, impaired wound healing, and most notably deep sternal wound infections, increased hospital and ICU length of stay, cognitive dysfunction, renal dysfunction, increased transfusions, and increased costs to the healthcare system [2, 3]. Perioperative glycemic control with insulin therapy has therefore been studied in an effort to determine if its control would improve clinical outcomes by tempering its detrimental effects.

The exact metric which best reflects glycemic control, target blood sugar concentrations and the method and protocol for insulin delivery continues to be controversial, as existing studies have widely varied methodologies. This chapter, therefore, attempts to address the following question- Is there a uniform postoperative

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glycemic control target and a preferred protocol known to improve outcomes in patients undergoing cardiac surgery?

Search Strategy

We performed a literature search of English language publications to identify published data on perioperative glycemic control in adult cardiothoracic surgical patients in accordance with the PICO outline (Table 29.1). PubMed, EMBASE, and Cochrane Library databases were searched. Terms searched include "cardiothoracic," "thoracic surgery," "cardiac surgery," "aortic valve replacement," "coronary artery bypass," "heart valve prosthesis implantation," "postoperative period," "postoperative care," "postoperative," "post-operative," and "glycemic control." Duplicates and articles with pediatric subjects were excluded. Regarding optimal glycemic target in postoperative cardiac surgical patients, nine studies resulted. Of these, there were five randomized controlled trials, two prospective cohort studies, and two retrospective case-control studies. Data was assessed using the GRADE system.

Results

Pathophysiology of Hyperglycemia in Cardiac Surgery Patients

Hyperglycemia has a variety of deleterious effects on the heart, all of which appear to mediate increases in morbidity and mortality during the care of the critically ill, and specifically, the postoperative cardiac surgery patient. Experimental evidence in animal models implicates hyperglycemia as a factor associated with increased infarct size after an ischemic insult [4]. In human cardiomyocytes, hyperglycemia abolishes the protective effect of ischemic [4, 5] and anesthetic preconditioning [6, 7] and furthermore, exacerbates the injury associated with reperfusion [8]. At a cellular level, hyperglycemia has been linked with greater degrees of hypophosphatemia [9] and lactemia [10]. Clinically, hyperglycemia may induce further myocardial damage in diabetics undergoing coronary artery bypass, evidenced by decreased troponin I release with tight glycemic control [11]. Diabetics may suffer more

Table 29.1 PICO table for glycemic control in the cardiac surgery patient

Patient	Intervention	Comparator	Outcome
Adult cardiothoracic surgical patients	Tight glycemic control	Moderate glycemic control, liberal glycemic control	Mortality, ICU length of stay, hospital length of stay, ventilator time, acute kidney injury, postoperative cognitive dysfunction, postoperative atrial fibrillation, recurrent ischemia, cost

myocardial hypertrophy due to longstanding effects of hyperglycemia, and similarly, diabetics undergoing surgical or trans-catheter aortic valve replacement for severe aortic stenosis exhibit poorer left ventricular mass regression following correction [12]. Hyperglycemia also potentiates vasospasm as it interferes with endothelin mediated relaxation [13, 14]. Additionally, fluctuations in blood sugar concentrations may increase oxidative stress, mediating an additional mechanism for endothelial cell dysfunction [15].

Adverse Effects of Preoperative Hyperglycemia

HbA1c

HbA1c is an important marker for long term glucose control in the diabetic population. In hyperglycemia, a vulnerable NH2 moiety of the hemoglobin molecule becomes irreversibly glycosylated, an event that lasts the duration of that red cell, 90–120 days. This glycosylation event occurs commonly in all of us, not just diabetic patients, but normally accounts for <6% of our Hemoglobin. Any value over 6.5% can be used for the diagnosis of diabetes; in the poorly controlled diabetic, the percent glycosylation can affect upwards of 10–12% of hemoglobin. Importantly, the HbA1c concentration represents, in effect, a window into the average glucose control of a patient over the previous 3–4 months, i.e. the lifespan of a red cell. The American Diabetes Association recommends that diabetics target a HbA1c level of <6.5% to mitigate the complications associated with their disease [16].

The relationship between an elevated HbA1c level and postoperative complications in cardiac surgery have addressed the issue almost solely in coronary artery bypass surgery (CABG) patients. Interestingly, the specific results are mixed, but in a recent systematic review, Tennyson et al. evaluated 11 publications which they felt represented the best evidence on the subject [17]. In that paper, only five studies were prospective, none were randomized, and there were no attempts to look at the data in a propensity matched way. Nonetheless, in all prospective studies there was a strong signal for increased complications for elevated HbA1c levels. The lack of significance seen in some of the studies was, in general, the result of small numbers of subjects. The fourfold increase in mortality seen by Halkos et al. [18] for HbA1c >8.5% was striking, as was the correlation those authors found between increased risk of morbidity and mortality for every percent increase in HbA1c above 6%. In the most recent paper addressing this topic, Narayan et al. [19] performed a retrospective look at close to 4700 patients, three quarters of whom had an off-pump approach. He found a 25% increase in respiratory complications and a more than twofold increase in deep sternal wound complications in that population with a preoperative HbA1c >6.5%. The observed 36% increase in mortality was at the $p = 0.08$ level.

There are no intervention trials addressing elevated HbA1c levels, nor have there been any attempts in the literature at propensity matching to isolate the HbA1c con-

centration as an independent risk factor for adverse outcomes after CABG. The most we can say at this moment is that there is a strong signal for an association. Justification for the postponement of surgery to lower the HbA1c concentration similarly has no evidentiary basis. Even were that to exist, 1 month of superb glucose control, yielding a concentration of 6% during that period would only have a partial effect on the overall HbA1c concentration, never lowering it more than 10–15% of the difference between the observed value and 6%. Thus, at least at present, there is only theoretical justification for postponing surgery for patients exhibiting recent, poorly controlled diabetes.

Admission Hyperglycemia and Coronary Artery Bypass Surgery

Given the experimental evidence alluded to in the introduction to this chapter, it is not surprising that the outcomes of any presentation of an acute coronary syndrome are much worse in the presence of hyperglycemia. Furthermore, the commonly prescribed oral hypoglycemic sulfonylureas, so frequently taken by diabetic patients, inhibit myocardial K_{ATP} channels, a structure intrinsically involved with the protective mechanisms of preconditioning, thereby worsening any ischemic insult. As a result, the ACC/AHA guidelines advise strict glucose control for all patients admitted with an acute coronary syndrome [20]. Similar reasoning provided the foundation for the Surgical Care Improvement Project emphasis on perioperative glucose control in postop coronary artery bypass patients [21].

To date, the focus of perioperative glucose control in the cardiac surgery patient has been on the intra- and postoperative phases of care. Few data exist regarding the effect of admission hyperglycemia on this group of patients. In 2001, Zindrou et al. [22] found in female patients who did not carry a diagnosis of diabetes, but had an admission glucose concentration >110 mg/dl, a fourfold increase in coronary artery surgery mortality. Surprisingly, this increase in mortality was not seen in men, at any given admission glucose level. In a more recent study, Thiele et al. [23] looked at 240 emergency coronary bypass patients, and found on multivariable analysis an independent effect of admission hyperglycemia on mortality, with a mortality increase of 16% for every 10 mg/dl increment in admission blood sugar for patients admitted with a blood sugar concentration >120 mg/dl.

Ascribing a causal effect to an elevated admission glucose may not be appropriate as the elevated blood glucose concentration may simply reflect the severity of illness of the patient. Nevertheless, we have referenced many important deleterious effects of acute hyperglycemia [7, 20, 22–28], and so it might be reasonable to implicate hyperglycemia as causal. However, this attribution of causation to admission hyperglycemia should be tentative, as, for example, the stress associated with an acute coronary syndrome may in and of itself cause a sympathetic mediated rise in serum glucose, and thereby account for an associative but not causal role of hyperglycemia and increased mortality and morbidity in this setting.

In summary, although admission hyperglycemia could be a marker for critical illness and thereby simply be associated with poor outcomes, the significant evi-

dence for toxic effects of hyperglycemia at the cellular and biochemical level argue for controlling admission glucose prior to surgery, if possible.

Intraoperative and Postoperative Hyperglycemia

Intraoperative or postoperative hyperglycemia is associated with increased mortality and morbidity. Doenst et al. found hyperglycemia (defined as glucose>360 mg/dl) occurring during cardiopulmonary bypass to be an independent risk factor for mortality. In addition, patients demonstrating hyperglycemia above this level during cardiopulmonary bypass carried an increased incidence of preoperative risk factors including reduced LVEF, CHF, cardiogenic shock, renal failure, previous cardiac surgery, or indication for emergency surgery [29]. Ghandi et al. similarly showed intraoperative hyperglycemia to be an independent risk factor for perioperative complications in a dose-dependent manner such that for every 20 mg/dl increase in blood glucose above 100 mg/dl patients suffered a 34% increase in perioperative complications [30]. Fish et al. determined a comparable relationship during the postoperative period finding that for every 30 mg/dl increase in serum glucose, hospital length of stay increased by 1 day. In addition, postoperative blood glucose exceeding 250 mg/dl was associated with a tenfold increase in complications, primarily cardiac or infectious [31]. Multiple subsequent studies corroborate postoperative hyperglycemia with adverse cardiovascular outcomes [32, 33].

Glycemic Control in the Perioperative Period

Glycemic Control in ICU Patients

Although the detrimental effects of hyperglycemia are well established, the optimal practice for perioperative glycemic control remains somewhat controversial. Results of large randomized controlled trials evaluating optimal glycemic target in critically ill patients is summarized in Table 29.2. In 2001, Van den Berghe et al. challenged the longstanding notion that hyperglycemia occurs as a tolerated component of the stress response. In that study, they demonstrated a 4% absolute mortality reduction in mechanically ventilated surgical ICU patients randomized to an intensive insulin regimen, targeting blood glucose level between 80 and 110 mg/dl, compared with "conventional" management, in which blood glucose was treated only when above 200 mg/dl [34]. This specific study formed the basis for the many major healthcare agency guidelines advising tight glucose control in the critically ill. However, the results of the Van den Berghe study have not been replicated, and, in fact, several large multicenter trials since have produced contradictory results [35–38]. In the NICE-SUGAR trial, mixed medical surgical ICU patients with an ICU length of stay anticipated to be >3 days were randomly assigned to intensive glucose control (BG 81–108 mg/dl) vs. conventional control (BG<180 mg/dL), The intensively

Table 29.2 Optimal glycemic target in critically ill patients (large randomized controlled trials)

Author (year)	Type of study (study population)	N (intervention/control)	Intervention target (mg/dl)	Control target (mg/dl)	Outcomes (intervention vs. control)	Quality of evidence
Leuven I	Randomized controlled trial (surgical ICU + mechanical ventilation)	765/783	80–110	180–200	Death during ICU: 4.6% vs. 8.0% ($p < 0.04$)	Moderate
Van den Berghe et al. (2001) [34]					In-hospital death: 7.2% vs. 10.9% ($p = 0.01$)	
Leuven II	Randomized controlled trial (medical ICU+ anticipated ICU LOS >3 days)	595/605	80–110	180–200	In-hospital death: 37.7% vs. 40.0%	High
Van den Berghe et al. (2006) [35]						
VISEP	Randomized controlled trial (severe sepsis)	247/289	80–110	180–200	Mean AM blood glucose: 112 vs. 151 ($p < 0.001$)	Moderate
Brunkhorst et al. (2008) [37]					28-day death: 24.7% vs. 26.0% ($p = 0.48$)	
					Hypoglycemia: 17.0% vs. 4.1% ($p < 0.001$)	
					Serious adverse events: 10.9% vs. 5.2% ($p = 0.01$)	
Glucontrol	Randomized controlled trial (medical-surgical ICU)	542/536	80–110	140–180	Hypoglycemia: 8.7% vs. 2.7% ($p < 0.0001$)	High
Preiser et al. (2009) [38]					ICU mortality: 15.3% vs. 17.2% (p. 410)	
NICE-SUGAR	Randomized controlled trial (mixed medical and surgical ICU +anticipated ICU LOS >3 days)	3154/3050	81–108	140–180	Death: 27.5% vs. 24.9% ($p = 0.02$)	High
Finfer et al. (2012) [36]					Hypoglycemia: 6.8% vs. 0.5% ($p < 0.001$)	
					ICU LOS: 6 vs. 6 ($p = 0.84$)	
					Hospital LOS: 17 vs 17 ($p = 0.86$)	
					Median number of days of mechanical ventilation 6.6 vs. 6.6 ($p = 0.56$)	

controlled cohort demonstrated an increase in mortality as well as severe hypoglycemic events, with no difference in ICU or hospital length of stay, days on mechanical ventilation, or initiation of renal replacement therapy [36]. The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study, similarly demonstrated an increased risk of adverse events related to hypoglycemia in critically ill septic patients treated with insulin targeting a blood sugar between 80 and 110 mg/dl vs. 180–200 mg/dl [37]. In the GluControl trial, mixed medical-surgical ICU patients treated with intensive insulin therapy (80–110 mg/dL) showed no clinical benefit but did demonstrate an increase in hypoglycemic events. Of note, this last study was stopped prematurely for study protocol violations, and was therefore underpowered [38]. Jacobi et al. recommends treatment of hyperglycemia >150 mg/dl with a maintenance target glucose <150 mg/dl and absolutely <180 mg/dl, with caution to avoid hypoglycemia, especially in certain vulnerable populations [39]. As it currently stands, the updated guidelines by the American Diabetic Association of Clinical Endocrinologists recommend targeting a blood glucose of 140–180 mg/dl in ICU patients [40].

Glycemic Control in Postoperative Cardiac Surgery Patients

Early glucose-insulin-potassium (GIK) solution trials in cardiac surgery patients showed a benefit of insulin therapy despite the occurrence of hyperglycemia in non-diabetics [41], suggesting a pleotropic and protective effect of insulin itself [42]. Lazar et al. went on to investigate the effect of glycemic control with GIK solutions by randomizing 141 diabetic patients undergoing CAB to either "tight" glycemic control with GIK (target glucose 125–200 mg/dl) vs. standard (<250 mg/dl) using intermittent SQ insulin before surgery to 12 h postop. GIK patients demonstrated lower blood glucose (mean 138 mg/dl) with an associated reduced incidence of postoperative atrial fibrillation, wound infections, hospital length of stay, 2-year survival, and recurrent ischemia [43].

The Portland Diabetic Project similarly established the benefit of glycemic control and insulin therapy by following 14,051 diabetic patients undergoing coronary bypass surgery treated either with SQ insulin (1987–1991 protocol) or continuous insulin infusion (1992–2001 protocol). In the continuous insulin infusion group, the glycemic target was periodically lowered according to protocol for goal 150–200 mg/dl during 1991–1998, 125–175 mg/dl during 1999–2001, and 100–150 mg/dl from 2001 on [44]. The group treated by continuous insulin infusion demonstrated improved glucose control as well as reduced mortality (2.5% vs. 5.3%), deep sternal wound infections, and hospital length of stay [45]. In 2007, D'Alessandro et al. further corroborated the benefit of glucose targeted insulin therapy by decreasing mortality in intensively treated diabetics. In this study, 300 diabetic patients undergoing CAB were risk-stratified by Euroscore. Patients exposed to glycemic control (initiation of intravenous insulin therapy for blood glucose >120 mg/dl) demonstrated reduced mortality compared with their Euroscore expected mortality, with the greatest reduction seen in moderate-high risk patients [46].

However, since the initial Van den Berghe trial, no study has shown improved mortality with insulin therapy that targets a blood glucose <110 mg/dl compared with moderate control (<180–200 mg/dl), although few studies suggest improved morbidity and cellular physiology [47, 48]. Even when "tight" control is relaxed to <140–160 mg/dl, few additional studies support an improvement in early mortality compared with targeting a blood glucose of simply less than 180 mg/dl [49, 50]. Improved morbidity has also been described with a glucose target <140–160 mg/dl vs. <180 mg/dl, though infrequently, and includes a diminution in postoperative cognitive dysfunction, postoperative atrial fibrillation, sternal wound infections, duration of mechanical ventilation, and degree of inotropic support [50–52].

Most evidence suggests equivalent outcomes among cardiac surgery patients treated with a moderate target (<180–200 mg/dl) vs a tighter one (<140–160 mg/dl) [53–60]. In 2007, Ghandi et al. established superiority of moderate glycemic control (defined as <200 mg/dl) vs. intensive control (80–100 mg/dl), as a result of an increase in mortality and stroke in patients treated with a lower blood glucose target [53]. Bhamidipati et al. investigated the effect of a target <140 mg/dl vs a target <180 mg/dl in patients undergoing isolated valve procedures, and showed equivalent mortality and rate of major complications [54]. That same year, those same investigators additionally examined patients undergoing isolated CAB, and demonstrated a superiority of <180 mg/dL over tighter as well as more liberal insulin regimens, with improvement in mortality as well as morbidity [55]. In 2015, Umpierrez et al. executed the GLUCOCABG trial, in which 303 patients undergoing coronary artery bypass were randomized to receive either intensive (100–140 mg/dl) or conservative (141–180 mg/dl) postoperative glycemic control. Although there was a statistically significant different in mean blood glucose among the two groups (132 vs. 154 mg/dl), there were no significant differences in any of the measured composite endpoints, including mortality, wound infection, pneumonia, bacteremia, respiratory failure, acute kidney injury, or major adverse cardiovascular events. Hypoglycemia did not occur at a statistically greater rate in the 100–140 mg/dl group [56]. Note that intensive therapy in the more recent studies no longer targets 80–110 mg/dl, but rather levels higher than that, so as not to expose patients to the morbid risk of hypoglycemia.

Interestingly, post-hoc analysis of the GLUCOCABG study showed that among nondiabetics, the 100–140 mg/dl insulin therapy group experienced improved clinical endpoints, suggesting the need for further investigation to support more intensive therapy aimed at the lower glucose targets in nondiabetics undergoing CAB [56]. Similarly, Greco et al. merged patient data from the Cardiothoracic Surgical Trials Network and University Health Consortium, and found that among patients undergoing cardiothoracic surgery (isolated valve, isolated CAB, or CAB/valve surgery), complications from hyperglycemic events were more common in nondiabetics, and furthermore, additional hospital costs associated with hyperglycemia were only seen in that patient group [61].

In cardiac surgery patients, glycemic control (and insulin therapy) consistently improves clinical outcomes and lessens morbidity, although the optimal target

remains controversial. Results of studies evaluating optimal glycemic target in post-operative cardiac surgery patients are summarized in Table 29.3. The exact target range has not been defined, nor has the issue of different targets for the diabetic vs the non-diabetic been resolved, although perhaps the non-diabetic population might benefit by tighter control. As it currently stands, the STS recommends a blood glucose targeted at <180 mg/dl in all patients, but stricter glycemic targets (<150 mg/dl) in high-risk patients, defined as those with a >3 day anticipated ICU length of stay, ventilator dependence, vasopressor use, and mechanical circulatory support [62].

Recommendations

Hyperglycemia in perioperative cardiac surgical patients is common, and has been linked to an increased rate of mortality and perioperative morbidity. Diabetics and patients with unrecognized impaired glucose metabolism suffer worse outcomes and should be identified preoperatively through screening by HbA1c levels as well as fasting blood glucose measurements.

- Perform preoperative screening utilizing HbA1c in all patients (evidence quality low; weak recommendation)
- Initiate a glycemic control protocol with continuous intravenous insulin therapy at the induction of anesthesia (evidence quality low; weak recommendation)
- Continue intravenous insulin therapy for all patients through the first night of surgery and transition to subcutaneous insulin on the first postoperative day, maintaining control for the first 3 days postoperatively (evidence quality moderate; weak recommendation)
- Target moderate- glycemic control (blood glucose 140–180 mg/dl) in most patients (evidence quality moderate; weak recommendation)
- Consider strict glycemic targets (blood glucose 100–140 mg/dl) in nondiabetics or high-risk patients (evidence quality low; weak recommendation)

Personal View of the Data

The ill effects of hyperglycemia on the cardiac surgery patient are well recognized at the biochemical, cellular, and patient based level. Although initial enthusiasm for control of blood glucose concentrations to levels between 80 and 110 mg/dl has waned, evidence supports the prevention of hyperglycemia above the range of 160–180 mg/dl. We believe all patients will benefit from preoperative screening and improved glucose control if indicated and time permits. Admission hyperglycemia should be treated prior to surgery, aiming for a level below 120 mg/dl. Intra- and postoperative blood sugar concentrations should initially be with intravenous

Table 29.3 Optimal glycemic target in postoperative cardiac surgical patients

Author (year)	Type of study (study population)	N (intervention/ control)	Intervention target (mg/dl)	Control target (mg/dl)	Outcomes (intervention vs. control)	Quality of evidence
Furnary et al. (2003) [44]	Prospective cohort study (diabetic patients undergoing any open-heart surgery)	2612 (1999–2001)/942 (1987–1991)	150–200 (1992–1994)	<200 (1987–1991) by subcutaneous insulin	Mean blood glucose: 177 mg/dl vs. 213 mg/dl ($p < 0.0001$)	Moderate
			125–175 (1999–2000) by continuous intravenous insulin		Death: 2.5% vs. 5.3% ($p < 0.0001$)	
Lazar et al. (2004) [43]	Randomized controlled trial (diabetic patients undergoing CAB)	72/69	125–200	<250	Mean blood glucose: 138 vs. 260 ($p < 0.0001$)	Moderate
					Atrial fibrillation: 16.6% vs. 42% ($p = 0.0017$)	
					LOS: 6.5 vs. 9.2 days ($p = 0.003$)	
					Recurrent ischemia: 5% vs. 19% ($p = 0.01$)	
					Wound infections: 1% vs. 10% ($p = 0.03$)	
Gandhi et al. (2007) [53]	Randomized controlled trial (on-pump cardiac surgery)	199/201	80–100	>200	Event (death, SWI, prolonged ventilation, cardiac arrhythmia, stroke, renal failure within 30 days of surgery): 44% vs. 46% (Risk Ratio = 1.0; CI = 0.8–1.2	Moderate
					Death: 4 vs. 0 ($p = 0.061$)	
					Stroke: 8 vs. 1 ($p = 0.020$)	
Leibowitz et al. (2010) [60]	Prospective cohort (diabetics or random blood glucose>150)	410/207	110–150	Standard of care	Mean blood glucose: 151 vs. 166 ($p < 0.0001$)	Low
					Infection: 11% vs. 5% ($p = 0.018$)	

Bhamidipati et al. (2011) [55]	Retrospective case-control (CAB)	134/2785	≤126	127–179	Mortality: 2.9% vs. 2.0% (p = 0.02) Major complications: 19.4% vs. 11.1% (p < 0.001)	Low
Song et al. (2012) [50]	Retrospective case-control (patients undergoing off-pump CAB)	453/251	110–150	>150	AKI: 3% vs. 8% (p = 0.004)	Low
Giakoumidakis et al. (2013) [49]	Randomized controlled trial	105/107	120–160	161–200	Mean blood glucose: 153.9 vs. 173.9 (p < 0.001) In-hospital mortality: 1 vs. 7 (p = 0.033)	Low
GLUCO-CAB Umpierrez et al. (2015) [56]	Randomized controlled trial (CAB)	151/151	100–140	141–180	Mean blood glucose: 132 vs. 154 (p < 0.001) Composite of complications: 42 vs. 52% (p = .87) Composite of complications (diabetics only): 24% vs. 55% (p = 0.008)	Moderate
Kurnaz et al. (2017) [51]	Randomized controlled trial (elective CAB)	20/20	80–120	80–180	POCD: 10 vs 11 (p = 0.047)	Very low

insulin and changed to subcutaneous insulin after the first postoperative day, when no longer critically ill, targeting blood sugars <160–180 mg/dl. Further research is necessary, however, to define glycemic targets in vulnerable populations, the optimal glucose metric for measurement, and glucose delivery protocol.

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