Hyperinsulinemic normoglycemia decreases glucose variability during cardiac surgery

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Abstract

Purpose Increased glucose variability may be associated with worse outcomes in critically ill patients. Hyperinsulinemic normoglycemia provides intensive glucose control during surgery and may reduce glucose variability. Our objective was to compare glycemic variability between two methods of glucose control in cardiac surgical patients: hyperinsulinemic normoglycemia vs standard insulin infusion. We also assessed whether the effect differed between patients with and without diabetes mellitus.

Methods We compared measures of glycemic variability, including the primary outcome, average real variability (ARV), and secondary outcomes, within-patient standard deviation (SD) and glucose lability index (GLI), in 252 patients who received hyperinsulinemic normoglycemia and 266 patients who received standard therapy. Data was randomly sampled from each patient treated with hyperinsulinemic normoglycemia, so patients in each group had a similar number of glucose measurements. The significance level for each hypothesis was 0.05, and 0.025 within diabetic status.

Results For nondiabetic patients, hyperinsulinemic normoglycemia reduced mean glucose measure-to-measure variability for ARV by an estimated $-0.23$ (97.5% CI $-0.30$, $-0.16$) mg/dl/min ($P < 0.001$) versus standard care. There was no difference in glycemic variability between groups for diabetic patients, with difference in means (97.5% CI) of $-0.10$ ($-0.20$, 0.02) mg/dl/min, $P = 0.07$. Mean SD was lower for hyperinsulinemic normoglycemia patients overall, with difference in means (95% CI) of $-19$ ($-22$, $-16$), $P < 0.001$, with a stronger effect in nondiabetics (interaction $P = 0.042$). GLI was also lower with hyperinsulinemic normoglycemia.

Conclusion Hyperinsulinemic normoglycemia decreases glucose variability for cardiac surgical patients with a stronger effect in nondiabetic patients.

Keywords Hyperinsulinemic normoglycemia · Glucose · Variability · Cardiac surgery

Introduction

Hyperglycemia is associated with higher morbidity and mortality in patients having cardiac surgery [1]. Why treatment of hyperglycemia has not consistently improved outcomes is unclear. It is possible that glucose-related factors such as glycemic variability, rather than elevated glucose concentrations, may worsen outcomes. Increased glycemic variability, defined as acute fluctuations in blood glucose concentrations, promotes multiple adverse cellular effects including activation of oxidative stress, endothelial dysfunction, protein glycation, and apoptosis [2–6]. This may explain the association between higher glycemic variability
and increased mortality in cardiac surgical [1] and critically ill patients [7]. Glycemic variability is even a stronger predictor of mortality than mean blood glucose concentration in critically ill patients [8].

Despite an association between glycemic variability and mortality [7, 8], the effect of various glucose management strategies on glycemic variability is largely unknown. The effect on perioperative glycemic variability may be especially important in cardiac surgical patients, who develop severe insulin resistance and hyperglycemia related to the stress of surgery and cardiopulmonary bypass, which is further exacerbated by dextrose-containing cardioplegia. Thus, an examination of the effect of intraoperative glycemic management strategies on glycemic variability is needed.

The hyperinsulinemic normoglycemia glucose management strategy involves provision of a fixed high-dose insulin infusion while titrating a concomitant variable exogenous glucose infusion aimed at normoglycemia. This technique has been used as an effective method to control blood glucose concentrations in patients undergoing coronary artery bypass graft surgery (CABG) [9, 10]. This technique has also been used to improve left ventricular contractility, though with unclear benefit [11, 12]. The effect of this technique on glucose variability is unknown [1]. The effect of diabetes on response to efforts to reduce glycemic variability is unknown.

The purpose of this investigation was thus to compare glycemic variability between cardiac surgical patients who received glucose management with either hyperinsulinemic normoglycemia or standard insulin infusions. Whether glycemic variability was similarly reduced in patients with diabetes mellitus compared to nondiabetic patients undergoing cardiac surgery was also examined.

Methods

With approval from the Cleveland Clinic Institutional Review Board and written informed consent, we evaluated 518 patients who were consecutively enrolled in a randomized clinical trial entitled “The Effect of Hyperinsulinemic Glucose Control on Outcomes Following Cardiac Surgery” (ClinicalTrials.gov identifier NCT00524472,andra Duncan, Principal Investigator, registered on August 31, 2007) at the Cleveland Clinic between 2008 and 2013. For the primary clinical trial, patients were randomized to either aggressive glucose control using a hyperinsulinemic normoglycemia technique (blood glucose target 80–110 mg/dl) versus standard insulin therapy (glucose target <150 mg/dl) and postoperative outcomes were compared between groups. This secondary analysis of the primary clinical investigation compared intraoperative glycemic variability between both groups.

Inclusion criteria for the primary clinical trial included patients aged 18–90 years scheduled for cardiac surgery including CABG and/or mitral, aortic, or tricuspid valve repair or replacement requiring cardiopulmonary bypass. Patients who required off-pump surgical procedures, had active infection, had elevated baseline serum troponin T concentrations (>0.1 ng/ml), or required hypothermic circulatory arrest were excluded.

Patients were randomly assigned (1:1 with concealed allocation) to intraoperative glucose management with hyperinsulinemic normoglycemia or standard care using a password-protected web-based system that was accessed by research personnel upon entrance to the operating room. Randomization to hyperinsulinemic normoglycemia or standard therapy was computer generated using the Plan procedure in SAS software and stratified by cardiac surgical procedure (CABG, valve repair/replacement, or combined procedures) and history of diabetes (type 1/type 2/diet-controlled vs none). Block size within each stratum ranged between 4 and 16 patients.

Anesthesia and surgery

Preoperative oral hypoglycemia agents were held in patients stopped diabetes at 12 h prior to surgery. Diabetic patients who required insulin received half of their usual dose of long-acting insulin on the morning of surgery. Anesthetic management in the operating room included use of American Society of Anesthesiology (ASA) standard monitors, brachial arterial catheter, and a central venous or pulmonary artery catheter. Anesthesia was induced with thiopental 3–5 mg/kg or etomidate 0.2–0.3 mg/kg. Suxamethonium or a nondepolarizing muscle relaxant facilitated tracheal intubation. Isoflurane, fentanyl, and/or midazolam were administered for maintenance of anesthesia. Additional non-depolarizing muscle relaxant was administered in incremental doses as clinically indicated. Surgery was performed through either a full midline sternotomy or a minimally invasive upper hemisternotomy. Routine strategies for heparinization, arterial and venous cannulation, and initiation and separation from cardiopulmonary bypass were followed. Myocardial protection was achieved in all patients using cold antegrade and/or retrograde Buckberg’s cardioplegia solution buffered in cold blood (1:4 ratio). Epinephrine was given after separation from cardiopulmonary bypass when the cardiac index was less than 2.0 l/min/m² despite preload optimization. Norepinephrine was given when myocardial performance was adequate (cardiac index ≥2.0 l/min/m²) but systolic blood pressure was <90 mmHg or systemic vascular resistance was <800 dynes sec/cm².
Research protocol

Because of the complexity of performing the hyperinsulinemic normoglycemia technique, intraoperative management of serum glucose concentrations was not blinded. Hyperinsulinemic normoglycemia consisted of an insulin infusion fixed at 5 mU/kg/min and administered with a concomitant variable glucose infusion (dextrose 20%) supplemented with potassium (40 mEq/l) and phosphate (30 mmol/l). Hyperinsulinemic normoglycemia was initiated in the operating room following measurement of baseline blood glucose and anesthetic induction. The glucose infusion was initiated at approximately 60 ml/h in nondiabetics and 30 ml/h in diabetics when the blood glucose concentration decreased below 110 mg/dl and then titrated to target glucose levels between 80 and 110 mg/dl. Intraoperative blood glucose concentrations were measured with a point-of-care glucose monitor (Accucheck, Roche Diagnostics, Switzerland) approximately every 5–10 min by research personnel whose sole responsibility was to manage the hyperinsulinemic normoglycemia technique. Hyperinsulinemic normoglycemia was initiated in the operating room following anesthetic induction and continued until sternal closure, when the insulin dose was decreased to 1 mU/kg/min. The variable dextrose infusion was weaned off slowly during the first initial postoperative hours in the intensive care unit (ICU) until the glucose concentration was maintained at >80 mg/dl with glucose supplementation. Blood glucose levels were collected also at 12, 24 and 48 h after arrival in the ICU to ensure good glucose control.

Patients who were randomized to the standard insulin infusion received intraoperative glucose management according to a conventional insulin protocol that involved initiation of a low-dose insulin infusion (1–3 units/h) when blood glucose was greater than 150 mg/dl during or after cardiopulmonary bypass. The insulin infusion was increased according to repeated blood glucose measurements, which were collected, analyzed, and reported from samples obtained for arterial blood gas analysis approximately every 30–60 min.

On arrival in the ICU, both randomized groups received the standard insulin infusion titrated to glucose concentrations with a target of <180 mg/dl on the day of surgery and <150 mg/dl on subsequent postoperative days.

Hypoglycemia was defined as blood glucose <40 mg/dl (2.2 mmol/l). Hypoglycemia was treated by administration of a bolus of 30–60 ml of 20% dextrose or 25–50 ml 50% dextrose.

Statistical methods

The primary outcome variable (for this secondary analysis) was glycemic variability calculated using average real variability (ARV). Secondary outcomes included the glycemic variability calculated using the glucose lability index (GLI) and within-patient standard deviation (SD).

Glucose variability measures

Our primary measure (for this secondary analysis) of within-patient glucose variability was generalized ARV [13], SD and GLI [14], which were a priori planned as secondary outcomes. ARV is calculated as the sum of the absolute value of all consecutive changes across measurements divided by the total time. GLI is calculated as the squared difference between consecutive glucose measures per unit of actual time between those samples. Because GLI can be affected by the frequency of glucose measurements [15], we divided it by the number of glucose readings (as with the ARV). SD was calculated as the square root of the average of the squared differences between individual glucose values and the mean. We also calculated the intraoperative time-weighted glucose concentration for each patient using the trapezoidal rule divided by total hours of measurement.

Patients treated with hyperinsulinemic normoglycemia had considerably more measurements per hour than patients who received standard treatment (mean ± SD of 5.6 ± 1.0 vs 1.4 ± 0.58). Thus, for our primary analysis, each variability measure was calculated on repeated random samples (1000 times) of glucose measurement data for each patient in the hyperinsulinemic normoglycemia group. The mean across samples was used as the data point for that patient in our primary analysis comparison to standard care. We chose the number of observations per hour to sample using random draws from a normal distribution with mean of 1.4 and SD of 0.58, mimicking the distribution of the number of measurements per hour in the standard group. We kept each patient’s first and last reading, then drew the rest of the samples with even spacing based on ranks of the data.

Patients randomized to either hyperinsulinemic normoglycemia or standard care were compared for balance on baseline characteristics and intraoperative factors using the absolute standardized difference, i.e., the difference in means or proportions divided by the pooled SD. Baseline variables with absolute standardized differences >0.2 were deemed imbalanced and adjusted for in all analyses comparing randomized groups on outcomes.

We first assessed the interaction between glucose control intervention and diabetic status (yes/no) on each glucose variability measure in separate linear regression models. If a significant interaction was observed (P < 0.15) for a particular outcome, the effect of the intervention on the primary and secondary outcomes would be assessed within diabetic and non-diabetic patients with a Bonferroni correction (i.e., P < 0.05/2). Otherwise, a two sample t-test was
used to assess the effect of the glucose intervention on outcome at the 0.05 significance level. SAS 9.2 statistical software (SAS Institute Inc, Cary, NC, USA) was used for all analyses.

**Results**

A total of 252 patients were randomized to hyperinsulinemic normoglycemia and 266 to standard care between 2008 and 2013. The randomized groups were well balanced on baseline variables (i.e., all absolute standardized differences <0.2). Sixty-nine patients (27%) in the hyperinsulinemic normoglycemia group and 74 (28%) in standard care had diabetes mellitus. Patient demographics, characteristics, and perioperative variables are shown in Table 1.

Comparing randomized groups on variability measures using raw and randomly sampled data

Table 2 displays the summary statistics of raw data and sampled data. Using all of the glucose measurement data.
(raw) from the hyperinsulinemic normoglycemia group, variability measured by ARV and GLI were higher, but SD was lower with hyperinsulinemic normoglycemia, likely due at least in part to the effect of differing number of glucose readings on the glucose variability measurements. Using the randomly sampled hyperinsulinemic normoglycemia data, hyperinsulinemic normoglycemia and standard patients had similar distribution of glucose readings per hour (1.4 ± 0.6 vs 1.4 ± 0.6). On average, the group means of the median interval between glucose readings for a patient were close on the randomly sampled data (hyperinsulinemic normoglycemia 37 ± 12 vs standard 47 ± 9 min), but not on the raw data, where glucose readings from hyperinsulinemic normoglycemia were only 11 ± 2.0 min apart. Intraoperative time-weighted average glucose in the sampled (121 ± 18 mg/dl) and raw (121 ± 19 mg/dl) intensive control data were very similar, on average. Without testing for interaction with diabetic status, mean ARV was lower in patients who received hyperinsulinemic normoglycemia compared with standard glucose therapy, with a mean difference of −0.19 (95% CI −0.24, −0.14) mg/dl/min, P < 0.001 (Table 3; Fig. 1).

### Interaction with diabetic status

The effect of hyperinsulinemic normoglycemia on the primary outcome of ARV depended on diabetes status (intervention-by-diabetes interaction of P < 0.019, Table 3; Fig. 2). For nondiabetic patients, hyperinsulinemic normoglycemia lowered mean ARV about 30% compared to standard, with a difference in means (97.5% CI) of −0.23 (−0.30, −0.16) mg/dl/min, P < 0.001, but there was no difference between the two groups for diabetic patients, with the difference in means (97.5% CI) of −0.10 (−0.20, 0.02) mg/dl/min, P = 0.07.

### Secondary outcomes

We found a quantitative (same direction) intervention-by-diabetic-interaction on the SD outcome (interaction P < 0.001); hyperinsulinemic normoglycemia had lower mean SD for both diabetics and nondiabetics (both P < 0.001), but the difference was larger for nondiabetics. There was no interaction with diabetic status for mean GLI (interaction P = 0.57). Ignoring diabetic status, both mean GLI and mean SD were lower with hyperinsulinemic normoglycemia than for standard glucose therapy, with a mean difference in GLI (95% CI) of −15 (−26, −4) (mg/dl^2)/min, P = 0.008, and the mean difference (95% CI) in SD of −19 (−22, −16) mg/dl, P < 0.001.

### Discussion

Although increased glycemic variability has been associated with worse outcomes in critically ill patients, little information is available to guide clinicians in how glycemic variability can be reduced. Our study investigates the glycemic variability between two methods of glucose control and is one of the first to report reduced glycemic variability with a hyperinsulinemic normoglycemia technique. Our investigation demonstrated that glycemic variability...
measured with ARV was reduced in patients who received the hyperinsulinemic normoglycemia technique, though most of the effect was derived from nondiabetic patients. Alternative measures of glycemic variability, such as GLI and SD, had consistent results and similarly found reduced glycemic variability. SD also found a stronger effect in nondiabetic patients. These results suggest that glycemic management with hyperinsulinemic normoglycemia may provide benefit not only by reducing hyperglycemia, but also by reducing glycemic variability.

Glycemic variability can be measured by several different methods, and different methods could have different results. As our primary outcome we used the ARV because

Table 3 Glucose variability measurements between hyperinsulinemic normoglycemia and standard insulin infusion (standard) groups

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hyperinsulinemic normoglycemia (N = 252)</th>
<th>Standard (N = 266)</th>
<th>Difference in means (CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average real variability (mg/dl/min)</td>
<td>Diabetes × intervention</td>
<td>0.57 ± 0.2</td>
<td>0.76 ± 0.4</td>
<td>−0.19 (−0.24, −0.14)</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>0.60 ± 0.24</td>
<td>0.70 ± 0.31</td>
<td>−0.10 (−0.20, 0.02)</td>
</tr>
<tr>
<td></td>
<td>No diabetes</td>
<td>0.56 ± 0.20</td>
<td>0.79 ± 0.38</td>
<td>−0.23 (−0.30, −0.16)</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycemic lability index (mg/dl²)/min</td>
<td>Diabetes × intervention</td>
<td>39 ± 78</td>
<td>54 ± 49</td>
<td>−15 (−26, −4)**</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>39 ± 31</td>
<td>49 ± 46</td>
<td>−10 (−34, 15)</td>
</tr>
<tr>
<td></td>
<td>No diabetes</td>
<td>39 ± 90</td>
<td>56 ± 50</td>
<td>−17 (−32, −2)</td>
</tr>
<tr>
<td>Standard deviation (mg/dl)</td>
<td>Diabetes × intervention</td>
<td>29 ± 12</td>
<td>48 ± 19</td>
<td>−19 (−22, −16)</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>32 ± 13</td>
<td>46 ± 22</td>
<td>−14 (−20, −8)</td>
</tr>
<tr>
<td></td>
<td>No diabetes</td>
<td>27 ± 11</td>
<td>48 ± 18</td>
<td>−21 (−25, −17)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD
If P < 0.15 for diabetes × intervention interaction, the effects stratified by diabetes status are primary [i.e., for ARV (average real variability) and standard deviation outcomes]

* Overall results from two-sample t-test with 95% CI; otherwise, from linear regression model with 97.5% CI

** Overall analysis was main result for glycemic lability index since the interaction with diabetes is non-significant

a Represents one missing data value

Fig. 1 Effect of hyperinsulinemic normoglycemia (HN) versus standard insulin infusion on average real variability (ARV) of glucose measurements during cardiac surgery. HN reduced ARV overall (P < 0.001). Interquartile range (IQR, box), median (horizontal line), high and low values within 1.5 IQR (whiskers), and mean (diamond) are shown. Standard standard insulin infusion, HN hyperinsulinemic normoglycemia

Fig. 2 Effect of hyperinsulinemic normoglycemia (HN) versus standard insulin infusion on average real variability (ARV) of glucose measurements during cardiac surgery by diabetic status. HN reduced ARV for nondiabetic patients (P < 0.001) but not for diabetics (P = 0.07), interaction P = 0.019. Interquartile range (IQR, box), median (horizontal line), high and low values within 1.5 IQR (whiskers), and mean (diamond) are shown

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it is intuitive for frequently measured data (simply averages the differences between all consecutive measurements), accounts for the total time of measurement, and does not square the differences (in contrast to the GLI). We used the generalized version of ARV, which does not require equally spaced measurements [13]. Adjusting for time between glucose measurements is critical; otherwise, unequal weight could be given to a brief time period of hyperglycemia that required multiple glucose measurements. GLI includes the correction for heterogeneity in the timing of glucose measurements as well, but squares the differences before summarizing; it has been more closely associated with hospital outcomes than other methods of capturing glucose variability [7]. SD is a commonly used measure of variability, but it does not take into account the distance between measurements, which is crucial in summarizing variability of frequently observed data [16].

There are several possible explanations why hyperinsulinemic normoglycemia decreased glycemic variability overall. First, reduced glycemic variability with hyperinsulinemic normoglycemia may have occurred because normoglycemia was targeted and this provided a narrower window of tolerated blood glucose concentrations. Second, the use of a high-dose insulin infusion may have also reduced glycemic variability because an aggressive high-dose insulin treatment, such as hyperinsulinemic normoglycemia, may be necessary to counter the insulin resistance which commonly occurs in patients having cardiac surgery. In contrast, the standard insulin infusion uses a lower dose insulin infusion which may have been insufficient to effectively reduce blood glucose concentrations. Third, use of a variable concomitant glucose infusion with hyperinsulinemic normoglycemia may have contributed to lower glycemic variability because it allows rapid titration of glucose concentrations. Finally, frequent blood glucose measurements, which are required with the hyperinsulinemic normoglycemia technique, allow for careful titration of blood glucose concentrations because of closer observation and faster treatment of glucose concentrations outside of the target range.

The optimal target glucose concentration to reduce morbidity and mortality in critically ill and surgical patients is currently unknown. The Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial determined that a glycemic target of normoglycemia (81–108 mg/dl) increased mortality in critically ill patients compared with a blood glucose target of 180 mg/dl or less [17]. This result contrasted with the earlier work of Van den Berghe and colleagues, who concluded that tight glucose control lowered morbidity and mortality in the ICU [18, 19]. Although frequent hypoglycemia may have contributed to the increase in adverse outcome in NICE-SUGAR, [20] another explanation for the divergent results may involve differences in glycemic variability between randomized groups. Of course, glycemic variability has a critical impact on outcomes, which was largely ignored in these large clinical trials because of the primary focus on glycemic control [1, 7, 8].

It is unclear why patients with diabetes did not receive a similar benefit of reduced glycemic variability with hyperinsulinemic normoglycemia. Because insulin resistance is a pathognomonic for type 2 diabetes mellitus, it is possible that a decreased responsiveness to insulin therapy in diabetic patients lowered the effectiveness of the high-dose insulin technique. We speculate hepatic and skeletal muscle uptake of glucose was lower in diabetic patients when receiving the hyperinsulinemic normoglycemic clamp, resulting in a smaller effect on glycemic variability.

Although hyperinsulinemic normoglycemia reduces sustained hyperglycemia and glycemic variability, use of this technique is not without risk. This technique is comprised of a high-dose insulin infusion which has potential to significantly increase risk of hypoglycemia. Hypoglycemia in our investigation, however, was rare due to frequent monitoring. Another important characteristic of hyperinsulinemic normoglycemia, however, is the labor-intensive nature of this technique. Our protocol involved having a research fellow assigned to measure blood glucose concentrations approximately every 10 min, which may not be practical in many situations and could limit the use of hyperinsulinemic normoglycemia even if proven helpful.

Our report has several strengths. It was a double-blind randomized clinical trial with a big sample size and it discusses a very unique topic with very scarce literature discussing similar topics. But also there are limitations to this investigation. This was a post hoc analysis of data from a clinical trial. In the raw data, the number of blood glucose measurements were significantly different between groups. Although we used a robust statistical method to randomly sample hyperinsulinemic normoglycemia patients and thus achieved a similar number of average readings and similar spacing compared to standard care patients, an ideal design would prospectively fix the spacing of the readings to be the same across all patients.

Conclusion

In cardiac surgery patients, the hyperinsulinemic normoglycemia technique for intraoperative glucose management lowered glycemic variability compared with standard insulin infusion. Most of the effect, however, is derived from nondiabetic patients. Though variability may also be reduced somewhat in diabetic patients, its effect is weaker and requires more study.
Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest. Dr. Abd-Elsayed performs consultancy work for Ultimaxx Health, Halyard and Innocol, which is not related to this work.

References