Iatrogenic hypoglycemia secondary to tight glucose control is an independent determinant for mortality and cardiac morbidity

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Abstract

Objective: Evaluation of the effects of tight glycemia control in critically ill patients should include temporal as well as punctual glycemia data. Methods: Insulin drip was used to target intensive care unit (ICU) glucose levels between 80 and 126 mg dl⁻¹ in a consecutive series of adult cardiac surgery patients. ICU hourly glycemia was prospectively recorded. Glycemia standard deviation, hyperglycemia index (area under the curve for glycemia > 126 mg dl⁻¹ divided by total hours in ICU), and hypoglycemic episodes were recorded and analyzed, together with outcomes. Results: A total of 596 patients were included. Hypoglycemia occurred in 21% of the patients. In-hospital mortality was 2.6%. There was a univariate correlation between mortality and glycemia standard deviation, and hypoglycemia occurrence. At multivariate analysis, hypoglycemia was a determinant for mortality (p = 0.002; odds ratio (OR) = 20.0), respiratory failure (p = 0.001; OR = 1.4), requirement of a tracheostomy (p = 0.001; OR = 21.6), and hemodynamic instability requiring intra-aortic balloon pump (IABP) (p = 0.01; OR = 1.5). To clarify the determinants of hypoglycemia, a second multivariate model was built. Diabetes (p = 0.001; OR = 23) and chronic renal failure (p = 0.01; OR = 25) were the sole determinants for hypoglycemia occurrence. Conclusion: Iatrogenic hypoglycemia secondary to ICU tight glycemia control correlates with hospital mortality, respiratory, and cardiac morbidity in patients undergoing cardiac surgery. ICU hyperglycemia index and glycemia temporal variability have no independent correlation with outcomes. Higher glycemia targets should be advised in the perioperative management of patients with diabetes and renal failure, as both conditions independently increase the risk of hypoglycemia occurrence.

Keywords: Hypoglycemia; Tight glucose control; Cardiac surgery; Mortality; Morbidity

1. Introduction

Hyperglycemia in critically ill patients or in the perioperative phases of major surgical procedures seems to be associated with increased mortality and morbidity [1,2]. For this reason, many researchers have proposed tight glucose control as an effective tool to prevent the deleterious effects of glucose unbalance [3].

There has been considerable recent controversy over the safety of tight glucose control that may lead to iatrogenic hypoglycemia. In this regard, at least two investigations were stopped in advance by data safety monitoring boards as a result of high incidence of severe hypoglycemic events and other serious adverse events [4,5].

In more selected groups of patients, such as the cardiac population, intra-operative insulin therapy for tight glucose control seems to increase the incidence of death and stroke [6].

Furthermore, it is well known that glucose profiles are characterized by important fluctuations even during continuous intravenous insulin infusion. Although many parameters have been proposed to properly represent glycemia excursions, literature data are mainly punctual and do not adequately summarize glycemia profile through time. Indeed, differences in blood glucose variability may lead to heterogeneous outcomes when using intensive insulin therapy [7,8].

The aim of the present study was to determine the association between intensive care unit (ICU) glycemia and outcomes in a population of ICU patients undergoing intensive insulin treatment (IIT) after being submitted to heart surgery.
A detailed comprehensive analysis was performed on different glycemic parameters. Our interest focused not only on punctual glycemia values but also on the impact of other glycemia data, including glycemia variability, presence and eventual duration of hyperglycemia (>126 mg dl\(^{-1}\)), and presence and frequency of hypoglycemia (<70 mg dl\(^{-1}\)).

2. Materials and methods

The present study reviews data of the first 30 months of experience with IIT in ICU critical patients submitted to cardiac surgery at the Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT).

An ICU protocol including insulin drip and 5% dextrose infusion has been routinely applied in all cardiac patients operated upon in our Institution since January 2006.

The protocol is a modification of the one proposed by Van den Berghe et al. [3]. Intra-operative management of blood glucose is achieved mainly with insulin bolus to maintain glycemia below 250 mg dl\(^{-1}\). A continuous infusion of 5% dextrose at 20 ml h\(^{-1}\) together with an insulin drip (regular insulin) is started at arrival in ICU.

The insulin drip infusion is started at a rate of 2 units h\(^{-1}\), if the glucose level at time of arrival in ICU is included between 120 and 220 mg dl\(^{-1}\) and at 4 units h\(^{-1}\) for glucose levels > than 220 mg dl\(^{-1}\). The rate is modified to target glucose levels between 80 and 126 mg dl\(^{-1}\) and is maintained till discharge from ICU. Blood glucose level is measured every hour with fingersticks (capillary blood) and/or undiluted whole venous/arterial blood (glucose analyzer). Glucose data are automatically recorded in a computerized chart together with other demographic, operative, and hospitalization information.

When blood glucose reaches the desired range (80—126 mg dl\(^{-1}\)), the insulin drip rate is left unchanged. Any time that blood glucose is included between 120 and 170 mg dl\(^{-1}\), the insulin drip is increased by 1 unit h\(^{-1}\). If glucose level is between 170 and 220 mg dl\(^{-1}\), the insulin drip rate is increased by 2 units h\(^{-1}\). An additional 5 units I.V. insulin bolus is given every time the blood glucose level is >220 mg dl\(^{-1}\).

Furthermore, the insulin drip rate is halved whenever the blood glucose level has decreased by over 50 mg dl\(^{-1}\) between two consecutive measurements. On the contrary, the insulin drip rate is increased by 2 units h\(^{-1}\) whenever the blood glucose level has increased by over 50 mg dl\(^{-1}\) between two consecutive measurements.

A 50 ml I.V. bolus of dextrose 50% in water (D50W) is given every time the blood glucose level is equal to or lower than 70 mg dl\(^{-1}\) and, for blood glucose levels lower than 60 mg dl\(^{-1}\), the insulin drip is discontinued.

After discharge from ICU, IIT is discontinued and standard treatment with subcutaneous insulin is used to achieve target glucose levels <220 mg dl\(^{-1}\).

Punctual and temporal glycemic data were analyzed. Several indexes to summarize temporal glucose variability were computed, including glucose standard deviation, percentage of time spent with glycemia >126 mg dl\(^{-1}\), hyperglycemic index (HGI) (area under the curve (AUC) for glycemia >126 mg dl\(^{-1}\) divided by total length of stay in ICU expressed in hours), and occurrence and frequency of hypoglycemia (<70 mg dl\(^{-1}\)).

Preoperative diagnosis of diabetes, hypertension, chronic obstructive pulmonary disease (COPD), and liver dysfunction were all based on previous clinical history confirmed by specialist consultation. Obesity was defined as BMI > 30 kg m\(^{-2}\). Cerebral stroke was defined as any new neurologic event documented at postoperative contrasted brain computed tomography (CT).

Acute renal failure was defined according to the Risk, Injury, and Failure; and Loss, and End-stage kidney disease (RIFLE) classification.

Respiratory failure was defined as prolonged intubation (>24 h) or re-intubation secondary to pulmonary causes.

Revision for bleeding was defined as any surgical revision (in the immediate postoperative phases or after discharge from ICU) secondary to profuse intrathoracic bleeding.

Sternal wound infection included superficial and deep sternotomy site infection.

Statistical analysis was performed to evaluate the determinants of in-hospital mortality and of the major morbidities, the determinants of hypoglycemia, and the variables that are associated with postoperative length of stay.

In particular, we used univariate and multivariate logistic regression to predict the occurrence of in-hospital morbidity/mortality in our population. The variables included in this analysis were the co-morbidities, the type of surgery, and the temporal glycemic summary variables described above.

To reduce artifacts from outliers, predictors as well as target variables were symmetrized in advance (e.g., log-transformation).

Multivariate analysis was performed by means of stepwise logistic regression. The stepwise search was performed using a backward strategy. With this method, the search starts by considering a full model with all the available variables and works by iteratively eliminating one variable per step until the model is able to adequately fit the data. Model selection is performed using the Akaike’s information criterion (AIC) index. Both crude models and models adjusted for age and gender were evaluated.

To evaluate the determinants of hypoglycemia, a chi-squared test was performed to check the association between the occurrence of hypoglycemic episodes and the co-morbidities.

Finally, to evaluate whether it was possible to find determinants of the length of postoperative hospitalization, we performed a multilinear stepwise regression considering the length of stay as outcome and co-morbidities, type of surgery, and glycemic variables as possible predictors.

3. Results

A total of 596 patients were included in the present study. Type of procedure performed included: 216 single valve, 47 multiple valves, 16 ascending aorta—aortic arch surgeries, 24 ventricular surgeries, 191 coronary bypass grafting, 78 coronary bypass grafting and valve surgeries, 15 heart transplantations, and nine minor cardiac surgery procedures without the use of cardiopulmonary bypass.
Table 1. Demographic and co-morbidity data in 596 patients undergoing ICU intensive insulin treatment.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>65.1 ± 12.3 (median 67, IQR: 58–74)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>198</td>
<td>33.2%</td>
</tr>
<tr>
<td>EF &lt; 40%</td>
<td>78</td>
<td>13.1%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>130</td>
<td>21.8%</td>
</tr>
<tr>
<td>Obesity</td>
<td>32</td>
<td>5.2%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>363</td>
<td>61%</td>
</tr>
<tr>
<td>COPD</td>
<td>54</td>
<td>9%</td>
</tr>
<tr>
<td>Creact. &gt; 2 mg dl⁻¹</td>
<td>31</td>
<td>5.2%</td>
</tr>
<tr>
<td>Dialysis</td>
<td>7</td>
<td>1%</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>25</td>
<td>4%</td>
</tr>
<tr>
<td>Previous AMI</td>
<td>299</td>
<td>50%</td>
</tr>
<tr>
<td>Periph. Vasc. Dis.</td>
<td>71</td>
<td>12%</td>
</tr>
<tr>
<td>Redo</td>
<td>29</td>
<td>5%</td>
</tr>
</tbody>
</table>

Demographic, major co-morbidity, morbidity, and mortality (in-hospital mortality or 30-day mortality) data are summarized in Tables 1 and 2.

Average length of stay in hospital was 10.4 ± 13 days (median: 7 days, interquartile range (IQR): 6–10 days, range: 1–169 days).

From the analysis of the ICU glycemia data, it emerged that mean glycemia was 130 ± 39.4 mg dl⁻¹ (20–500 mg dl⁻¹), median glycemia 124 mg dl⁻¹, mean standard deviation 31.0 (IQR: 106–147 mg dl⁻¹), range: 20–500 mg dl⁻¹), and mean HGI 13.7 ± 12.4 (0–91.3), median HGI 10.4.

A total of 123 patients (21%) had at least one episode of hypoglycemia (<70 mg dl⁻¹) with an average of 2.4 episodes per patient (from 1 to 17 episodes). Of these patients, 48 were males and 75 females (M/F = 0.6). Median age of patients developing at least one episode of hypoglycemia was 72 versus 68 years in the group without hypoglycemia (p < 0.01).

At univariate analysis, glycemia parameters were related to mortality (glycemia standard deviation and presence and frequency of hypoglycemia), respiratory failure (glycemia standard deviation and presence and frequency of hypoglycemia), requirement for a tracheostomy (presence and frequency of hypoglycemia), wound infection (glycemia standard deviation, HGI), surgical revision for bleeding (HGI), acute renal failure (HGI), postoperative requirement for intra-aortic balloon pump (IABP) (frequency of hypoglycemia), and requirement for postoperative support with extra-corporeal membrane oxygenator (HGI, glycemia standard deviation, and presence of hypoglycemia). Preoperative diagnosis of diabetes was related to wound infection occurrence only.

Determinants for mortality and morbidity, as resulting from the multivariate analysis, are summarized in Table 3 (adjusted for age and gender). Mortality was significantly associated with obesity (p = 0.003), liver dysfunction (p = 0.01), hypoglycemia occurrence (p = 0.002), and number of hypoglycemic episodes (p = 0.0001). As hypoglycemia seemed to play an important role in the occurrence of mortality, we identified independent determinants for hypoglycemia as well. Chronic renal failure (p = 0.01; odds ratio (OR) = 24.9) and diabetes (p = 0.001; OR = 22.8) were the sole determinants for ICU hypoglycemia occurrence.

Finally, Table 4 reports the determinants for length of postoperative hospitalization.

4. Discussion
Since the initial experience by Van den Bergh et al. was published [3], an increasing number of authors have focused their attention on the benefits of IIT in various clinical conditions including the perioperative phases after heart surgery [9,10].

More recently, there has been increasing controversy over the safety and efficacy of IIT, in particular over the risks of iatrogenic hypoglycemia [4,5].

In the second Leuven study, published by Van den Bergh et al. in 2006, hypoglycemia was more common in patients treated with IIT, and it was an independent predictor of death in multivariate analysis [11]. This study was the first to suggest the possible hazards of IIT.

Furthermore, the more recent NICE-SUGAR study showed that intensive glucose control increased mortality among ICU adults and that an 81–108 mg dl⁻¹ target was too tight and potentially dangerous [12].

Other authors have demonstrated that the occurrence of at least one glucose level <40 mg dl⁻¹ independently predicts mortality in patients receiving care in a multi-disciplinary adult ICU [13], and a mean glucose <70 mg dl⁻¹ is associated with a sixfold greater adjusted odds of death in adults hospitalized for acute myocardial infarction [14].

In a more selected cohort of patients, Gandhi et al. have shown that intra-operative IIT during cardiac surgery is associated with a higher incidence of death and stroke [6].

![Fig. 1. ICU glycemia box-plotting.](image-url)
Table 3. Determinants for mortality and morbidity by means of multivariate analysis. ORs adjusted for age and gender. CVA: cerebrovascular accident; ARF: acute renal failure; COPD: chronic obstructive pulmonary disease; and CRF: chronic renal failure.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Obese</th>
<th>Liver Dysf.</th>
<th>COPD</th>
<th>Multi valve</th>
<th>CRF</th>
<th>Hypogl.</th>
<th># Hypogl. episodes</th>
<th>Dialysis</th>
<th>Vent. surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td>OR = 23.7;</td>
<td>OR = 14.1;</td>
<td>p = 0.003;</td>
<td>p = 0.01;</td>
<td>OR = 20.0;</td>
<td>OR = 1.5;</td>
<td>OR = 2.8—195.7</td>
<td>CI = 2.8—195.7</td>
<td>p = 0.002;</td>
<td>p = 0.0001;</td>
</tr>
<tr>
<td></td>
<td>CI = 2.8—195.7</td>
<td>CI = 1.7—113.6</td>
<td>p = 0.01;</td>
<td>p = 0.003;</td>
<td>CI = 2.9—136.9</td>
<td>CI = 1.2—1.9</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Resp. failure</strong></td>
<td>OR = 4.2;</td>
<td>OR = 5.0;</td>
<td>OR = 4.1;</td>
<td>p = 0.005;</td>
<td>p = 0.003;</td>
<td>OR = 1.4;</td>
<td>OR = 1.5—113.6</td>
<td>CI = 1.5—113.6</td>
<td>CI = 1.7—4.1;</td>
<td>CI = 1.1—1.7</td>
</tr>
<tr>
<td></td>
<td>p = 0.005;</td>
<td>p = 0.003;</td>
<td>p = 0.0003;</td>
<td>p = 0.001;</td>
<td>CI = 1.7—14.8</td>
<td>CI = 1.1—1.7</td>
<td></td>
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<tr>
<td><strong>Tracheo</strong></td>
<td>OR = 13.0;</td>
<td>OR = 10.5;</td>
<td>OR = 77.1;</td>
<td>p = 0.006;</td>
<td>p = 0.0002;</td>
<td>OR = 1.3;</td>
<td>OR = 2.8—195.7</td>
<td>CI = 2.0—86.7</td>
<td>CI = 1.8—9.2</td>
<td>CI = 1.0—1.7</td>
</tr>
<tr>
<td></td>
<td>p = 0.006;</td>
<td>p = 0.008;</td>
<td>p = 0.0002;</td>
<td>p = 0.001;</td>
<td>CI = 1.7—14.8</td>
<td>CI = 1.1—1.7</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>CVA</strong></td>
<td>OR = 1.1;</td>
<td>OR = 1.1;</td>
<td>OR = 1.1;</td>
<td>OR = 1.8;</td>
<td>OR = 1.1;</td>
<td>OR = 1.8;</td>
<td>OR = 2.8—195.7</td>
<td>CI = 2.0—86.7</td>
<td>CI = 1.8—60.5</td>
<td>CI = 1.0—1.3</td>
</tr>
<tr>
<td></td>
<td>p = 0.007;</td>
<td>p = 0.007;</td>
<td>p = 0.0003;</td>
<td>p = 0.001;</td>
<td>CI = 1.8—60.5</td>
<td>CI = 1.1—1.7</td>
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<tr>
<td><strong>Wound Infection</strong></td>
<td>OR = 3.8;</td>
<td>OR = 3.8;</td>
<td>OR = 3.7;</td>
<td>OR = 3.7;</td>
<td>OR = 3.7;</td>
<td>OR = 3.7;</td>
<td>OR = 2.8—195.7</td>
<td>CI = 1.1—12.7</td>
<td>CI = 1.1—12.7</td>
<td>CI = 1.1—12.7</td>
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<td></td>
<td>p = 0.02;</td>
<td>p = 0.02;</td>
<td>p = 0.03;</td>
<td>p = 0.03;</td>
<td>p = 0.03;</td>
<td>p = 0.03;</td>
<td>CI = 1.1—12.7</td>
<td>CI = 1.1—12.7</td>
<td>CI = 1.1—12.7</td>
<td>CI = 1.1—12.7</td>
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<tr>
<td><strong>Post-op bleeding</strong></td>
<td>OR = 3.4;</td>
<td>OR = 3.4;</td>
<td>OR = 3.4;</td>
<td>OR = 3.4;</td>
<td>OR = 3.4;</td>
<td>OR = 3.4;</td>
<td>OR = 2.8—195.7</td>
<td>CI = 1.1—12.7</td>
<td>CI = 1.1—12.7</td>
<td>CI = 1.1—12.7</td>
</tr>
<tr>
<td></td>
<td>p = 0.01;</td>
<td>p = 0.01;</td>
<td>p = 0.03;</td>
<td>p = 0.03;</td>
<td>p = 0.03;</td>
<td>p = 0.03;</td>
<td>CI = 1.1—12.7</td>
<td>CI = 1.1—12.7</td>
<td>CI = 1.1—12.7</td>
<td>CI = 1.1—12.7</td>
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<tr>
<td><strong>ARF</strong></td>
<td>OR = 9.2;</td>
<td>OR = 12.9;</td>
<td>OR = 12.9;</td>
<td>OR = 12.9;</td>
<td>OR = 12.9;</td>
<td>OR = 12.9;</td>
<td>OR = 2.8—195.7</td>
<td>CI = 2.2—38.5</td>
<td>CI = 3.8—43.3</td>
<td>CI = 1.0—2.0</td>
</tr>
<tr>
<td></td>
<td>p = 0.002;</td>
<td>p = 0.0001;</td>
<td>p = 0.0001;</td>
<td>p = 0.0001;</td>
<td>p = 0.0001;</td>
<td>p = 0.0001;</td>
<td>CI = 2.2—38.5</td>
<td>CI = 3.8—43.3</td>
<td>CI = 1.0—2.0</td>
<td>CI = 4.3—82.9</td>
</tr>
<tr>
<td><strong>Post-op IABP</strong></td>
<td>OR = 1.5;</td>
<td>OR = 1.5;</td>
<td>OR = 1.5;</td>
<td>OR = 1.5;</td>
<td>OR = 1.5;</td>
<td>OR = 1.5;</td>
<td>OR = 2.8—195.7</td>
<td>CI = 2.2—38.5</td>
<td>CI = 3.8—43.3</td>
<td>CI = 1.0—2.0</td>
</tr>
<tr>
<td></td>
<td>p = 0.01;</td>
<td>p = 0.01;</td>
<td>p = 0.01;</td>
<td>p = 0.01;</td>
<td>p = 0.01;</td>
<td>p = 0.01;</td>
<td>CI = 2.2—38.5</td>
<td>CI = 3.8—43.3</td>
<td>CI = 1.0—2.0</td>
<td>CI = 4.3—82.9</td>
</tr>
</tbody>
</table>
Although most of the existing studies have evaluated the effects of IIT focusing on the absolute glucose levels, we believe that the clinical effects of tight glucose control should be interpreted using temporal blood glucose parameters and, in this way, considering simultaneously the combined and independent clinical impact of glycaemia sudden fluctuations (hyper- or hypoglycaemia), glycaemia temporal trends, and glycaemia variability during hospitalisation.

In a pediatric cardiac surgery population, Polito et al. hypothesized that larger disturbances in glycaemia metrics, glucose variability, and duration of hyperglycaemia would be associated with a greater incidence of morbidity events and a longer duration of hospitalization [15]. In the 72 h after surgery, average glucose $<110$ mg dl$^{-1}$ or $>143$ mg dl$^{-1}$, minimum glucose $<75$ mg dl$^{-1}$, and peak glucose level $>250$ mg dl$^{-1}$ reached the composite morbidity—mortality end point. Of interest, patients whose average early postoperative glucose level was $<109$ mg dl$^{-1}$ had sevenfold greater adjusted odds of reaching the morbidity—mortality end point [15].

In a study including over 7000 critically ill patients, Egi et al. have demonstrated that the standard deviation of glucose concentration is a significant independent predictor of ICU and hospital mortality [16].

More recently, Hermanides et al. have found a relationship between ICU mortality and glucose variability in a cohort of 5728 patients managed with IIT [17].

Although we are routinely using IIT since 2006 and we believe that glycaemia control plays a focal role in the ICU management of cardiac surgery patients, we are aware of the difficulties in defining an adequate glucose target and the risks of iatrogenic hyperglycaemia.

In the present study, we have achieved an aggressive glucose control thanks to IIT. This clearly emerges from punctual and temporal data. In fact, the median glucose level was 124 mg dl$^{-1}$ and the median HGI was 10.4 mg dl$^{-1}$ (i.e., 0.5 mmol l$^{-1}$), that is well within previously proposed targets [18].

As documented in our series, in spite of adequate IIT and achievement of glycaemic targets, hyperglycaemia occurred at a considerable rate of over 20%. It should be emphasized that, compared with other authors, we have used a higher threshold to define hypoglycaemia (i.e., $70$ mg dl$^{-1}$ or 3.9 mmol l$^{-1}$).

We have decided to use this cut-off because the lower limit of the normal fasting plasma glucose value is typically 70 mg dl$^{-1}$ and, in non-diabetic persons, the secretion of insulin decreases as glucose levels decline within the physiological range, and the release of counter-regulatory hormones, glucagon and epinephrine, increases when the glucose concentration falls to $65–70$ mg dl$^{-1}$ (3.6–3.9 mmol l$^{-1}$). Growth hormone and cortisol secretion also increase at similar plasma glucose concentrations. These hormonal responses begin well before the onset of symptoms of hypoglycaemia, which normally occur at glucose levels of 50–55 mg dl$^{-1}$ (2.8–3.0 mmol l$^{-1}$) [19,20].

In our experience, even a single episode of hypoglycaemia ($<70$ mg dl$^{-1}$) seems to impact significantly upon in-hospital mortality (OR = 20.0) and the higher is the number of hypoglycaemic events, the more significant is the OR for mortality (increasing 1.5 times per every extra episode of hypoglycaemia).

Interestingly, in our analysis, none of the other blood glucose punctual or temporal trends/variability data, including the markers of very poor blood glucose control (such as glucose standard deviation and HGI), seemed to impact independently upon mortality and major morbidity.

The second part of our study focused on identifying the determinants for hypoglycaemia. Krinsley and Grover have previously reported on the occurrence of hypoglycaemia ($<40$ mg dl$^{-1}$), its determinants, and its outcome in critically ill patients managed during two different historical periods (with and without IIT) [13]. The study included over 5000 ICU patients with a hypoglycaemia rate of 2%. Multivariate logistic regression analysis identified diabetes, septic shock, renal insufficiency, mechanical ventilation, severity of illness, and belonging to the IIT period as independent risk factors for the development of severe hypoglycaemia. Furthermore, hypoglycaemia was an independent predictor of mortality for the entire cohort (OR = 2.2) second only to mechanical ventilation (OR = 2.4).

Our findings confirm that diabetes and chronic renal failure are independent determinants for hypoglycaemia. It should be argued that the hypoglycaemia threshold is higher in patients with poorly controlled diabetes and, as a result, the deleterious effects of iatrogenic hypoglycaemia in the diabetic population are more evident and could be detected even at levels higher than 70 mg dl$^{-1}$.

The mechanism of hypoglycaemia in chronic kidney disease is less clear. It likely involves impaired gluconeogenesis, reduced renal clearance of insulin, and reduced renal glucose production.

As demonstrated in other studies, sepsis is a relatively common cause of hypoglycaemia [13,21]. Infection and sepsis were not independent determinants for hypoglycaemia in our analysis.

After having identified the determinants for mortality, we investigated any possible relationship between blood glucose levels and cardiac morbidity, focusing upon the postoperative requirement for mechanical hemodynamic support. In our series, there was a significant correlation between hypoglycaemia occurrence and requirement for postoperative forms of ventricular mechanical assistance such as postoperative IABP. The relationship with IABP use persisted after adjusting for age and gender. These findings suggest a possible relationship between occurrence of low glucose concentration and heart dysfunction. Although the relationship between hypoglycaemia occurrence and cardiac morbidity has been poorly investigated in the past, hypoglycaemia was shown to attenuate the sympathoadrenal and muscle sympathetic nerve activity outflow responses to simulated orthostatic stress and transient hypotension, and to decrease baroreflex sensitivity, that may lead to attenuation of vagal protection against sudden arrhythmic death [22].

### Table 4. Determinants for hospitalization length of stay by means of stepwise linear regression.

<table>
<thead>
<tr>
<th>Determinant</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>0.003</td>
</tr>
<tr>
<td># Hypoglycemia</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>

...
effects seem to last for at least 16 h, even after euglycemia is restored [22]. In addition, acute hypoglycemia has significant, albeit transient, effects on peripheral blood, enhancing hemostasis and increasing blood viscosity. Both effects may lead to intravascular stasis with subsequent reduction in vascular perfusion in patients with vascular disease. Acute hypoglycemia may therefore precipitate an acute vascular event or an arrhythmia.

In a more general perspective, in critically ill patients suffering from cardiogenic shock, hypoglycemia could be just a marker of disease severity that is often exacerbated by the decreased caloric intake.

Neural tissue does not depend on insulin for glucose uptake and thus greatly suffers whenever glycemia unbalances occur. For this reason, we tried to identify any possible relationship between neurological outcome and blood glucose parameters. Although the most feared non-fatal consequences of hypoglycemia include seizures and permanent cognitive dysfunction [13,21], in this series, we did not report any seizures’ episode.

In our experience, major neurological events such as cerebrovascular accidents were mainly related to patient’s age. Other markers of temporary neurological impairment that may be secondary to hypoglycemia, such as agitation and coma, were not systematically documented in the present series, and were not included in the analysis.

The relationship between mechanical ventilation and hypoglycemia has been previously proposed as a hypothesis by Krinsley [13]. In our experience, hypoglycemic episodes are strong independent determinants for tracheostomy (OR = 21.6) and respiratory failure requiring prolonged mechanical ventilation (OR = 1.4). Although it is difficult to find a cause–effect relationship, we could argue that the neurological consequences of hypoglycemia may indirectly impact upon patient respiratory function and delay weaning from mechanical ventilation, increasing the chances for tracheostomy.

The impact of blood glucose dynamics upon hospitalization length has been so far poorly investigated. In our analysis, the number of ICU hypoglycemic events had a significant impact upon total length of hospitalization. From a clinical perspective, this finding confirms that the euglycemia goal has a secondary importance and should always be coupled with a strict control of blood glucose fluctuations. Patients who have multiple episodes of hypoglycemia during their ICU stay may have slower post-operative recovery that significantly lengthens the hospitalization period.

5. Conclusion

IIT may result in iatrogenic hypoglycemia in spite of timely glucose monitoring. Although the morbidity and mortality benefits of IIT have been broadly demonstrated in the past, it is also necessary to evaluate how much the occurrence of hypoglycemia may mitigate the benefits of IIT.

Krisley and Grover have performed a sensitivity analysis showing that elimination of IIT benefits would have occurred had the rate of hypoglycemia been four times higher and the mortality attributable to hypoglycemia twice as high than that reported by them [13]. We were not able to perform a sensitivity analysis because all our patients were treated using IIT. It is indeed important to remark that, differently from Krinsley, we have used a higher threshold for hypoglycemia (i.e., 70 mg dl^{-1} vs 45 mg dl^{-1}) that, of course, presented with a 10 times higher rate (20% vs 2% approximately). Although the threshold for hypoglycemia is not well defined, we have clearly demonstrated that even blood glucose levels lower than 70 mg dl^{-1} have a strong impact upon mortality and cardiac morbidity after cardiac surgery procedures. In conclusion, we believe that the benefit–risk ratio of IIT should be re-evaluated in the light of this new acquisition.

References


Appendix A. Conference discussion

Dr M. Versteegh (Leiden, The Netherlands): Chairmen, Dr D’Ancona: Since the publications of Van den Berghe from Leuven in Belgium in 2001, an intensive insulin treatment is commonly used in many intensive care units all over the world. Our colleagues from Italy demonstrated clearly that this treatment is not without risk. Like many others, they show that the treatment can easily give hypoglycemia. Because the authors used a high threshold of 70 mg dl⁻¹ to define hypoglycemia, they find a high incidence of hypoglycemia in their study. They also find that hypoglycemia is associated with a significantly higher mortality and morbidity, regardless of whether there was one occurrence or a number of hypoglycemic episodes.

My question is this: In your experience, the negative effect of hypoglycemia seems much more obvious than published by the NICE-SUGAR group, in 2009 in the New England Journal of Medicine, although their study involved more than 6000 patients and they used a threshold of only 40 mg dl⁻¹. They found a higher mortality in the total group which had an intensive glucose treatment compared to the control group, but they state that there was no additional effect of severe hypoglycemia. There seems to be a difference in your findings. Do you have any explanation for this?

Dr D’Ancona: Well, the explanation is that maybe our patients were sicker. I’m not sure about the rate of diabetic patients in their study, but my idea is that having a good rate of diabetic patients, they may be even more sensitive to glycemia levels, so for them, even 70 can be very troublesome. That’s why the threshold goes up. Of course, it’s very difficult as I said to give a threshold for that, but I can tell you that, as you know, the hormonal changes happen with levels starting at 70 mg dl⁻¹. So I think that this is a good cut-off. That’s why we chose it. You see, we don’t have a comparison group, so I don’t know if in two similar groups of patients, without using intensive insulin treatment in a control group we would have had different results. This is a major limitation of my study. On the same point, we were not able to calibrate the exact cut-off for hypoglycemia. Of course, I think that the message is, as you were saying in the other trials, hypoglycemia is dangerous, and the second message is iatrogenic hypoglycemia is kind of crazy. I mean you don’t need to create it. So this is the take-home message. Concerning the limits and the level that you should use as a cut-off, at least from our numbers, it’s difficult to say. There are too few patients and no comparison group and I cannot say that. But the take-home message is: Be careful with intensive insulin treatment and maybe tolerate a higher glycemia level.