Perioperative Blood Glucose Levels <150 mg/dL are Associated With Improved 5-Year Survival in Patients Undergoing On-Pump Cardiac Surgery

A Prospective, Observational Cohort Study

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Abstract: Hyperglycemia is common during and after Coronary Artery Bypass Graft Surgery (CABGS) and has been shown to be associated with poor clinical outcomes. In this study, we hypothesized that a moderate perioperative mean blood glucose level of <150 mg/dL improves long-term survival in cardiac surgery patients. We conducted a prospective, observational cohort study in the heart center of the University Medical Center of Goettingen, Germany. Patients undergoing on-pump cardiac surgery were enrolled in this investigation. After evaluating perioperative blood glucose levels, patients were classified into 2 groups based on mean glucose levels: Glucose ≥150 mg/dL and Glucose <150 mg/dL. Patients were followed up for 5 years, and mortality within this period was recorded as the primary outcome parameter. Secondary outcome parameters included the length of ICU stay, the use of inotropic agents, the length of hospital stay, and the in-hospital mortality. A total of 455 consecutive patients who underwent cardiac surgery with cardiopulmonary bypass were enrolled in this investigation. A Kaplan–Meier survival analysis of the 5-year mortality risk revealed a higher mortality risk among patients with glucose ≥150 mg/dL. Glucose levels >150 mg/dL were associated with poor clinical outcomes. In-hospital mortality was significantly higher in patients with glucose ≥150 mg/dL compared with patients with glucose <150 mg/dL. Moreover, patients in the Glucose ≥150 mg/dL group required significantly higher doses of the inotropic agent Dobutamine (mg/d) compared with patients in the Glucose <150 mg/dL group (20.6 ± 62.3 and 10.5 ± 40.7, respectively; P=0.0104). Moreover, patients in the Glucose ≥150 mg/dL group showed a significantly longer hospital stay compared with patients in the Glucose <150 mg/dL group (28 ± 23 and 24 ± 19, respectively; P=0.0297). We conclude that perioperative blood glucose levels <150 mg/dL are associated with improved 5-year survival in patients undergoing cardiac surgery. More studies are warranted to explain this effect.

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INTRODUCTION

Hyperglycemia occurs frequently in both diabetic and non-diabetic patients during and after coronary artery bypass graft surgery (CABGS), especially when CABGS is performed on-pump.1 Hyperglycemia during cardiopulmonary bypass was shown to be an independent risk factor for death in patients undergoing cardiac surgery.2 A previous study revealed a proportional correlation between the blood glucose concentration (≥100 mg/dL) during surgery and the occurrence of postoperative complications.3 However, whether extremely tight intraoperative glucose control (80–110 mg/dL) can further reduce the rate of morbidity or mortality in patients undergoing cardiac surgery remains controversial.4 A randomized controlled study of critically ill patients, many of whom had high-risk cardiac surgery, found reduced morbidity and mortality rates in patients whose blood glucose was tightly controlled (80–110 mg/dL). In contrast, another prospective randomized clinical trial that compared intensive treatment (continuous insulin infusion during surgery for glucose levels between 80 and 100 mg/dL) with conventional treatment (insulin given only for a glucose concentration >200 mg/dL) revealed increased incidences of death.
and stroke in the intensive treatment group, raising concerns about the routine implementation of intensive treatment, and that intensive insulin therapy during cardiac surgery did not reduce perioperative death or morbidity.3

Based on these and other previous studies and according to the guidelines of the society of thoracic surgery2 and the American College of Cardiology Foundation/American Heart Association (ACC/F/AHA) Guideline for Coronary Artery Bypass Graft Surgery,1 a goal postoperative blood glucose level of approximately 150 mg/dL using continuous insulin therapy in patients who require ≥3 days in the intensive care unit (ICU) while avoiding hypoglycemia is recommended. To date, whether and to what extent these recommendations (targeting glucose levels <150 mg/dL) are associated with the long-term survival of patients undergoing on-pump cardiac surgery has been unclear. Therefore, this clinical investigation assesses the impact of blood glucose levels <150 mg/dL on 5-year mortality in patients undergoing cardiac surgery.

METHODS

Patients
Adult Caucasian patients who were admitted to the University Medical Center of Goettingen (UMG) and underwent cardiac surgery with cardiopulmonary bypass between January 2006 and January 2007 were included into this study, and 5-year follow-up was completed in February 2013. Patients with known neoplasms were excluded. This study conformed to the ethical principles of the Declaration of Helsinki, and the study protocol was approved by the institutional ethics committee of the University of Goettingen in Goettingen, Germany. The study was performed in accordance with relevant guidelines and regulations. The methods were performed in accordance with the approved guidelines. Written informed consent was obtained from either the patients or their legal representatives.

According to the standard operating procedures of the medical center, the intraoperative hyperglycemic target is <180 mg/dL and the postoperative blood glucose level target in the ICU is 150 mg/dL. These targets are usually achieved through either insulin bolus administration or continuous intravenous insulin therapy. Typically, patients in the ICU with blood glucose levels ≥150 mg/dL are treated with a standardized continuous insulin therapy approximating a glucose level <150 mg/dL. This therapy is titrated according to a standardized schema to achieve this goal; blood glucose levels are closely monitored at regular intervals to allow the insulin therapy to be adjusted according to the glucose level dynamic and to avoid hypoglycemia (blood glucose levels under 70 mg/dL), for example, continuous insulin therapy is stopped at blood glucose levels below 150 mg/dL.

Data Collection
Upon enrollment (day of surgery), current medication comorbidities were identified through anamnestic questionnaires of the patients or their legal representatives by examining the physicians’ notes and by consulting each patient’s family doctor. Blood glucose levels were measured perioperatively, beginning on the day of surgery, and throughout the entire ICU stay. The EuroSCORE,7 the Acute Physiology and Chronic Health Evaluation Score (APACHE II),8 and the Simplified Acute Physiology Score (SAPS II)9 were calculated at baseline to assess morbidity. The postoperative course, including the complete ICU stay, was assessed for relevant pulmonary and hemodynamic parameters. The pulmonary parameters comprised the arterial pH, lung compliance, pulmonary infiltrates, and the lung injury score. The hemodynamic measurements included the heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), mean pulmonary artery pressure (PAP), and pulmonary capillary wedge pressure (PCWP). The cardiac index (CI) and the systemic and pulmonary vascular resistance indices (SVRI and PVRI, respectively) were calculated from standard formulas. The postoperative use of catecholamine, amiodarone, cortisone, nitroglycerin, or vasopressin administration was recorded. The use of blood cell suspensions and blood products was also recorded over the observation period. The requirements for an intra-aortic balloon pump (IABP) and of extracorporeal membrane oxygenation (ECMO) were also assessed along with the lengths of hospital and ICU stays and the in-hospital mortality. Patients were followed up for 5 years to assess long-term mortality.

Outcome Measures
The 5-year mortality was recorded as the primary outcome parameter. Secondary outcome parameters included the in-hospital mortality, the length of ICU stay, the use of inotropic agents, and the length of hospital stay.

Statistical Analysis
The statistical analyses were performed using Statistica (version 10; StatSoft, Tulsa, OK). Continuous variables are presented as the mean ± standard deviation, and categorical variables are presented as an absolute number or percentage. Continuous variables were compared using the Mann–Whitney U test. Significance based on contingency tables was calculated using a 2-sided Fisher’s exact test or the χ² test as appropriate. The time-to-event data were compared using the log-rank test. To exclude the effect of potential confounders (age, sex, BMI, and morbidity scores [EuroSCORE, APACHE II, and SAPS II]) and covariates that varied at baseline with a P value <0.2 (eg, comorbidities, risk factors, and preoperative medications) on survival, we performed a multivariate Cox regression analysis to examine the survival times. Propensity-score matching was performed using the statistical computing software R (version 3.1.1) with the MatchIt package (version 2.4-21). Patients were matched based on age, sex, BMI, and the morbidity scores (EuroSCORE, APACHE II, and SAPS II) and covariates that varied at baseline with a P value <0.2 (eg, comorbidities, risk factors, and preoperative medications). Matched data were obtained for 110 patients in each group, with no significant differences between groups in any of the aforementioned variables. A P value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics
A total of 455 consecutive adult Caucasian patients who underwent cardiac surgery with cardiopulmonary bypass in the University Medical Center of Goettingen were enrolled in this study. The mean glucose level of each day was calculated (usually based on 4–6 glucose measurements each day), and the mean glucose level of the entire ICU stay was then recorded. Patients were classified into 2 groups according to their overall mean levels: Glucose ≥150 mg/dL and Glucose <150 mg/dL. One hundred ten patients were identified with a mean glucose level ≥150 mg/dL, and 345 patients had a mean glucose level <150 mg/dL (Table 1). The ages of the patients ranged from 28 to 91 years (median, 69 years) (Table 1). No significant differences were recorded in age, sex, EuroSCORE, or APACHE II score between the 2 groups (Table 1). The SAPS
II score was significantly higher among patients in the Glucose $\geq$150 mg/dL group compared with those in the Glucose <150 mg/dL group (26.1 $\pm$ 7.3 and 24.1 $\pm$ 7.4, respectively; $P = 0.0031$, Table 1). Similarly, patients in the Glucose $\geq$150 mg/dL group had higher body mass indices than did patients in the Glucose <150 mg/dL group (29 $\pm$ 5 and 28 $\pm$ 10, respectively; $P = 0.0115$). Regarding comorbidities at baseline, the frequencies of some preexisting diseases and risk factors were significantly higher in patients with glucose $\geq$150 mg/dL (ie, nicotine abuse, positive family history of coronary heart disease, insulin-dependent diabetes mellitus [IDDM], Table 1). The frequency of antidiabetic and antilipidemic agent use was significantly higher in patients in the Glucose $\geq$150 mg/dL group. The distribution of antidiabetic medications can be found in Table 2. The distribution of the urgency of surgery and associated surgical procedures did not significantly differ between the 2 groups (Table 1).

### OUTCOMES

#### Mortality Analysis

In all cases (100%), long-term follow-up (5 years) data were available for the initial survivors. If the patient/legal representative could not be reached by telephone or post, we confidently contacted the local registry office and asked them if the patient remained alive (was still registered). The overall mortality rate was 25.5% (n = 116). Kaplan–Meier survival analysis revealed a significantly higher 5-year mortality risk among patients in the Glucose $\geq$150 mg/dL group compared with patients in the Glucose <150 mg/dL group (35% and 22%, respectively; $P = 0.0043$, Figure 1). After performing propensity-score matching, the survival analysis results remained significant, with a small change ($P = 0.0339$, Figure 2). Similarly, analysis of the in-hospital mortality showed a significantly higher mortality among patients in the Glucose $\geq$150 mg/dL group ($P = 0.0030$, Table 3).

### TABLE 1. Patients Baseline Characteristics With Regard to Glucose Levels

| Variable                        | Glucose $\geq$150 mg/dL (n = 110) | Glucose <150 mg/dL (n = 345) | $P$ Value |
|---------------------------------|-----------------------------------|-------------------------------|-----------|
| Age ($\pm$ SD)                  | 69 $\pm$ 8                        | 67 $\pm$ 10                   | 0.1396    |
| Male/female (%)                 | 65.5/34.5                         | 65.0/35.0                     | 0.9195    |
| EuroSCORE ($\pm$ SD)            | 6.0 $\pm$ 3.6                     | 5.3 $\pm$ 3.9                 | 0.0465    |
| APACHE II ($\pm$ SD)            | 14.9 $\pm$ 6.1                    | 14.8 $\pm$ 6.7                | 0.7209    |
| SAPS II ($\pm$ SD)              | 26.1 $\pm$ 7.3                    | 24.1 $\pm$ 7.4                | 0.0031    |
| Body mass index (kg/m$^2$)      | 29 $\pm$ 5                        | 28 $\pm$ 10                   | 0.0115    |
| Comorbidities and risk factors  |                                   |                               |           |
| Nicotine abuse (%)              | 33                                | 37                            | 0.4366    |
| Hypertension (%)                | 78                                | 72                            | 0.2130    |
| Hypercholesterolemia (%)        | 52                                | 48                            | 0.4339    |
| Diabetes mellitus (%)           | 72                                | 19                            | $<0.0001$ |
| Positive family history of CHD (%) | 10                              | 18                            | 0.0353    |
| Renal disorder (%)              | 17                                | 13                            | 0.2321    |
| Peripheral disease (%)          | 10                                | 6                             | 0.2020    |
| Neurocerebral events (%)        | 13                                | 12                            | 0.8132    |
| Pulmonary hypertension (%)      | 5                                 | 9                             | 0.1330    |
| COPD (%)                        | 6                                 | 8                             | 0.4896    |
| Dialysis (%)                    | 1.0                               | 0.6                           | 0.7101    |
| Preoperative medications        |                                   |                               |           |
| $\beta$-blockers (%)            | 72                                | 63                            | 0.1091    |
| ACE inhibitors (%)              | 68                                | 58                            | 0.0565    |
| Antilipidemic agents (%)        | 71                                | 53                            | 0.0011    |
| Antidiabetic agents (%)         | 48                                | 10                            | $<0.0001$ |
| Urgency of surgery              |                                   |                               | 0.2474    |
| Elective (%)                    | 83                                | 83                            |           |
| Urgent (n = 41) (%)             | 12                                | 8                             |           |
| Emergency (%)                   | 5                                 | 9                             |           |
| Associated surgical procedures  |                                   |                               |           |
| CABG (%)                        | 75                                | 80                            | 0.2512    |
| Valve (%)                       | 55                                | 57                            | 0.7161    |
| Combined procedures (%)         | 21                                | 23                            | 0.6630    |

The data are presented as the mean $\pm$ SD or as a percentage. ACE inhibitors = angiotensin-converting-enzyme inhibitors; APACHE II = Acute Physiology and Chronic Health Evaluation Score; BMI = body mass index; CABG = coronary artery bypass graft surgery; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; SAPS = Simplified Acute Physiology Score.

### TABLE 2. Distribution of Antidiabetic Agents

| Oral | Insulin | Oral + Insulin |
|------|---------|----------------|
| %    | 48      | 60             | 8              |

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Multivariate Analysis

To exclude the effects of several confounders on the 5-year mortality and to determine whether a glucose level ≥150 mg/dL is an independent predictor for 5-year mortality, we performed a multivariate Cox regression analysis. This analysis included glucose levels ≥150 mg/dL, potential confounders (age ≥65, sex, BMI, and EuroSCORE, APACHE II and SAPS II scores) and covariates that varied at baseline with a P value <0.2 (diabetes mellitus, positive family history of coronary heart disease, pulmonary hypertension, preoperative medications (β-blockers, ACE inhibitors, antilipidemic agents, antidiabetic agents), Table 1). Multivariate Cox regression analysis revealed that a glucose level ≥150 mg/dL was an independent prognostic indicator of the 5-year mortality risk (hazard ratio, 2.10; 95% CI, 1.30–3.39; P = 0.0023; Table 3).

Perioperative and Postoperative Course

The incidence of severe hypoglycemia (blood glucose level ≤40 mg/dL) did not differ between the 2 groups; it was reported in 5 of 345 patients (1.4%) in the Glucose <150 mg/dL group and in 2 of 110 (1.8%) in the Glucose ≥150 mg/dL group (P = 0.6775; Table 4). Similarly, there was no significant difference in the incidence of moderate hypoglycemia between the 2 study groups; 42 of 345 patients (12.2%) in the Glucose <150 mg/dL group had moderate hypoglycemia (P = 0.2994).

An exploratory analysis of several organ-specific clinical endpoints over the perioperative phase revealed several significant differences between patients in the Glucose ≥mg/dL 150 group and patients in the Glucose <150 mg/dL group (Table 4).

With regard to pulmonary function, patients with high glucose levels had worse pulmonary compliance (43 ± 15 and 49 ± 24, respectively; P = 0.0191; Table 4). Patients in the Glucose ≥150 mg/dL group also had significantly more pulmonary infiltrates (quadrants) compared with patients in the Glucose <150 mg/dL group (1.4 ± 0.6 and 1.2 ± 0.6, respectively; P = 0.0215). Similarly, the lung injury score was higher in the Glucose ≥150 mg/dL group compared with the Glucose <150 mg/dL group (1.4 ± 0.5 and 1.3 ± 0.5, respectively; P = 0.0486, Table 4).

The analysis of hemodynamic variables revealed some statistical trends in several parameters with respect to glucose levels (Table 4), indicating more pronounced hemodynamic instability in patients in the Glucose ≥150 mg/dL group. Additionally, patients in the Glucose ≥150 mg/dL group required significantly higher doses of the inotropic agent dobutamine compared with patients in the Glucose <150 mg/dL group (26 ± 62.3 and 10.5 ± 40.7, respectively; P = 0.0104). Furthermore, patients in the Glucose ≥150 mg/dL group required significantly higher doses of the vasopressor agent vasopressin (0.26 ± 1.3 and 0.03 ± 0.30, respectively; P = 0.0320).

### Table 3. Multivariate Cox Regression Analysis

| Variable                        | Hazard Ratio | 95% CI       | P       |
|---------------------------------|--------------|--------------|---------|
| Age                             | 1.04         | 1.02–1.07    | 0.0004  |
| Sex, female                     | 0.91         | 0.61–1.38    | 0.6854  |
| EuroSCORE                       | 1.06         | 1.02–1.11    | 0.0027  |
| APACHE II                       | 1.03         | 1.00–1.06    | 0.0220  |
| SAPS II                         | 1.01         | 0.99–1.04    | 0.1221  |
| BMI                             | 1.01         | 1.00–1.03    | 0.0029  |
| Diabetes mellitus               | 1.28         | 0.76–2.16    | 0.3362  |
| Positive family history of coronary heart disease | 1.07 | 0.59–1.92 | 0.8090 |
| Pulmonary hypertension          | 1.58         | 0.88–2.85    | 0.1214  |
| β-blockers                      | 1.48         | 0.96–2.27    | 0.0702  |
| ACE inhibitors                  | 0.92         | 0.62–1.37    | 0.6984  |
| Antilipidemic agents            | 0.91         | 0.61–1.35    | 0.6608  |
| Antidiabetic agents             | 0.47         | 0.26–0.85    | 0.0122  |
| Glucose ≥150 mg/dL              | 2.10         | 1.30–3.39    | 0.0023  |

ACE inhibitors = angiotensin-converting-enzyme inhibitors; APACHE II = Acute Physiology and Chronic Health Evaluation Score; BMI = body mass index; SAPS = Simplified Acute Physiology Score.
Regarding the renal system, patients in the Glucose ≥150 mg/dL group showed significantly higher serum creatinine levels and higher serum urea levels compared with patients in the other group (1.4 ± 0.6 and 1.3 ± 0.8, respectively, for serum creatinine; \( P = 0.0231 \) and 30.4 ± 13.8 and 26.5 ± 13.1, respectively, for serum urea; \( P = 0.0068 \)).

Moreover, patients in the Glucose ≥mg/dL 150 group showed a significantly longer hospital stay compared with patients in the Glucose <150 mg/dL group (28 ± 23 and 24 ± 19, respectively; \( P = 0.0297 \), Table 4).

**DISCUSSION**

This prospective observational study evaluates whether mean perioperative glucose levels of <150 mg/dL in patients undergoing on-pump CABGS are associated with improved 5-year survival. Patients with mean blood glucose levels...
≥150 mg/dL had a significantly poorer 5-year survival rate than did those with blood glucose levels <150 mg/dL.

The observed beneficial effect of moderate glucose levels (<150 mg/dL) on 5-year survival is in accordance with previous studies showing that higher perioperative glucose levels are associated with worse outcome among patients undergoing on-pump cardiac surgery.2,4,10 The improved 5-year survival among patients with glucose levels <150 mg/dL could be attributed to long-lasting perioperative protective effects of lower glucose levels on various organ systems.1,2,4–14 A similar observation of the long-lasting persistent survival benefit of glycemic control was shown previously by Ingels et al although their work assessed the beneficial effect of tight glycemic control (90–110 mg/dL) on the clinical course of patients in a surgical intensive care unit10; tight glycemic control is no longer recommended because such extreme control has been shown to be associated with frequent hypoglycemic episodes with deleterious clinical consequences.5

Similarly, the observed higher in-hospital mortality among patients with glucose >150 mg/dL is consistent with previous observations showing that tight glycemic control is associated with lower in-hospital mortality.4,13 The observed significant longer length of stay among patients in the Glucose <150 mg/dL group compared with patients in the Glucose ≥150 mg/dL group is in accordance with previous studies showing that tight glycemic control is associated with a shorter ICU stay.2,5

A major strength of our study is the lower incidence of both severe and moderate hypoglycemia observed in this investigation (Table 4) compared with the higher incidence of hypoglycemia reported in intensive glycemic control cohorts in previous studies.2,4,16–18 This result indicates the safety of targeting a blood glucose level <150 mg/dL.

The observed beneficial effect of low glucose levels on organ function (pulmonary, cardiovascular, and renal) is consistent with previous investigations showing that tight glycemic control can reduce morbidity in critically ill patients.5,18 This beneficial effect of low glucose levels can be explained by the deleterious pathophysiological effects of hyperglycemia on several organ systems. Acute hyperglycemia has a deleterious effect on endothelial function by suppressing the formation of nitric oxide (NO) and impairing endothelium-dependent flow-mediated dilatation.19 Acute hyperglycemia also induces cardiomyocyte death through apoptosis or by exaggerating ischemia-reperfusion cellular injury.20,21 Additionally, hyperglycemia-induced abnormalities in hemostasis (increased platelet activation, adhesion, and aggregation)22 comprise altered plasma fibrinolytic activity and increased plasminogen activator inhibitor-1 (PAI-1) activity.23

Some limitations of our study must be discussed. A potential limitation is that preoperative plasma HbA1c concentrations were not measured. Because of this limitation, we cannot exclude a confounding effect of preoperative HbA1c on long-term survival. Measuring preoperative HbA1c concentrations may be helpful in assessing the adequacy of perioperative glycemic control and identifying patients at risk for postoperative hyperglycemia.14 However, HbA1c testing has several significant limitations, especially in the presence of high salicylate doses that potentially result under therapy with acetylsalicylic acid, a frequently used medication in this patient group.24,25 Additionally, we cannot rule out that improved aftercare treatment and a healthier lifestyle in the group of patients with glucose levels <150 mg/dL may have had a crucial impact on the long-term survival. Similarly, we cannot exclude the possibility that diabetic neuropathy had an impact on the long-term outcome of patients in the Glucose >150 mg/dL group. Furthermore, because no previous investigations have addressed the effect of moderate perioperative blood glucose levels on long-term outcomes in patients undergoing cardiac surgery, we were unable to conduct power calculations at the beginning of the study to estimate the sample size required to detect a given effect size with sufficient power. However, according to our observation of 35% mortality in the Glucose ≥150 mg/dL group compared with 22% mortality in the Glucose <150 mg/dL group, an ad hoc power analysis yielded a power of 0.85. Therefore, our investigated cohort of 455 patients undergoing cardiac surgery was sufficient to address our hypotheses.

Our results are in line with the stated beneficial effects of the recommended lower blood glucose levels in cardiac surgery patients according to the American Association of Clinical Endocrinologists and American Diabetes Association.26,27 According to our study, a target perioperative blood glucose level <150 mg/dL among patients with cardiac surgery is safe and worth considering in future studies. More studies are warranted to elucidate the potential beneficial effects of targeting moderate glucose levels (<150 mg/dL) in cardiac surgery patients.

CONCLUSIONS

In conclusion, the results of the present study suggest that perioperative blood glucose levels below 150 mg/dL are associated with improved long-term survival in patients undergoing on-pump cardiac surgery. More studies are warranted to explain this potential effect.

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