Proportion of time spent in blood glucose range 70 to 140 mg/dL is associated with increased survival in patients admitted to ICU after cardiac arrest

A multicenter observational study

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Abstract

The benefit of any specific target range of blood glucose (BG) for post-cardiac arrest (PCA) care remains unknown.

We conducted a multicenter retrospective study of prospectively collected data of all cardiac arrest patients admitted to the ICUs between 2014 and 2015. The main exposure was BG metrics during the first 24 hours, including time-weighted mean (TWM) BG, mean BG, admission BG and proportion of time spent in 4 BG ranges (≤70 mg/dL, 70–140 mg/dL, 140–180 mg/dL and >180 mg/dL). The primary outcome was hospital mortality. Multivariable logistic regression, Cox proportion hazard models and generalized estimating equation (GEE) models were built to evaluate the association between the different kinds of BG and hospital mortality.

2,028 PCA patients from 144 ICUs were included. 14,118 BG measurements during the first 24 hours were extracted. According to TWM-BG, 9 (0%) were classified into the ≤70 mg/dL range, 693 (34%) into the 70 to 140 mg/dL range, 603 (30%) into the 140 to 180 mg/dL range, and 723 (36%) into the >180 mg/dL range. Compared with BG 70 to 140 mg/dL range, BG 140 to 180 mg/dL range and >180 mg/dL range were associated with higher hospital mortality probability. Proportion of time spent in the 70 to 140 mg/dL range was associated with good outcome (odds ratio 0.984, CI [0.970, 0.998], P = .022, for per 5% increase in time), and >180 mg/dL range with poor outcome (odds ratio 1.019, CI [1.009, 1.028], P < .001, for per 5% increase in time). Results of the 3 kinds of statistical models were consistent.

The proportion of time spent in BG range 70 to 140 mg/dL is strongly associated with increased hospital survival in PCA patients. Hyperglycemia (>180 mg/dL) is common in PCA patients and is associated with increased hospital mortality.

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation, AUC = area under the curve, BG = blood glucose, CA = cardiac arrest, CPR = cardiopulmonary resuscitation, CRRT = continuous renal replacement therapy, CV = coefficient of variation, GEE = generalized estimating equation, GV = glycemic variability, IQR = interquartile range, IRB = institutional review board, NIH = National Institutes of Health, PCA = post-cardiac arrest, ROSC = return of spontaneous circulation, SD = standard deviation, SOFA = sequential organ failure assessment, TWM = time-weighted mean, VIF = variance inflation factor.

Keywords: blood glucose, cardiac arrest, hyperglycemia, hypoglycemia, prognosis
1. Introduction

Cardiac arrest (CA) is one of the major health problems, with a yearly incidence of about 50 to 110 per 100,000 people worldwide.[1-3] Despite initially successful cardiopulmonary resuscitation (CPR), a high proportion of patients who survive cardiac arrest die prior to hospital discharge or have severe neurologic injury.[4,5] After the return of spontaneous circulation (ROSC), the initial hours and days are defined as the post-cardiac arrest (PCA) syndrome, which often represents the extreme of critical illness and has a high risk of morbidity and mortality.[6] PCA care requires vigilant monitoring and intervention and must be tailored to the particular disease and dysfunction that affect each patient.[7,8]

Metabolic derangements following cardiac arrest, such as hyperglycemia and higher glyceric variability, may contribute to secondary brain injury and poor neurologic outcome.[9-12] Resuscitated patients usually require intensive care of blood glucose (BG).[13] However, the optimum BG concentration and interventional strategy to manage blood glucose in the PCA period are unknown.[14] There may be a U-shaped relationship between BG and mortality outcomes in PCA patients.[15,16,17] The approach to glucose management chosen for other critically ill patients may not be suitable for cardiac arrest patients.[18,19] The benefit of BG range 70 to 140 mg/dL is uncertain in adult PCA patients.

The main aim of the present study was to investigate the associations between different BG ranges and clinical outcomes in PCA patients. Our hypothesis was BG range 70 to 140 mg/dL could be associated with good hospital mortality outcomes in PCA patients.

2. Methods

2.1. Setting

This study used data stored in the high-resolution database, the eICU (eicu-crd.mit.edu), which comprises patients admitted between 2014 and 2015 at 208 hospitals located throughout the US. The elaborate description of eICU is available elsewhere.[20] The eICU was exempt from institutional review board (IRB) approval due to the retrospective design, lack of direct patient intervention, and the security schema, for which the re-identification risk was certified as meeting safe harbor standards by Privacert (Cambridge, MA) (Health Insurance Portability and Accountability Act Certification no. 1031219–2). Due to the HIPAA compliant de-identification in this database, our institutional IRB requirement was waived. After completing a National Institutes of Health (NIH) web-based training course (Protecting Human Research Participants), the author (certification number: 28795067) was approved to access to the database for research aims.

2.2. Study population

All patients in the eICU database were eligible for inclusion in the present investigation. If a patient had more than 1 ICU admission, only the first ICU stay was taken into consideration. We selected all adult patients whose admission diagnosis was cardiac arrest. Patients were excluded for the following reasons:

(1) Incomplete hospital mortality data
(2) ICU stay less than 24 hours
(3) Numbers of blood glucose measurements less than 2 during the first 24 hours after admission to ICU.

2.3. Clinical variables

Data on the following information were extracted: demographics, comorbidities, hospital admit source, sequential organ failure assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation (APACHE) IV score, physiological parameters that provided the highest APACHE IV score during the first 24 hours, use of vasopressors, insulin, glucocorticoid, mechanical ventilation, use of continuous renal replacement therapy (CRRT) and use of hypothermia.

All of the blood glucose (BG) tests, that is BG from laboratory and bedside, during the first 24 hours in the ICU were extracted. For every patient, we calculated maximum BG, minimum BG, mean BG, first BG after admitted to ICU (admission BG), time-weighted mean BG (TWM-BG), proportion of time spent in 4 BG ranges (<70 mg/dL, 70-140 mg/dL, 140-180 mg/dL, and >180 mg/dL) and coefficient of variation (CV), defined as the ratio of the standard deviation (SD) to the mean of BG during the first 24 hours (see supplemental material; http://links.lww.com/MD/E716, http://links.lww.com/MD/E717, http://links.lww.com/MD/E718, http://links.lww.com/MD/E719, http://links.lww.com/MD/E720, http://links.lww.com/MD/E721). TWM-BG was obtained as an area under the curve (AUC) by integrating BG over time divided by the whole time (24 hours). Patients were classified into 4 ranges: ≤70 mg/dL, 70 to 140 mg/dL, 140 to 180 mg/dL, and >180 mg/dL. Mild hypoglycemia was defined as BG ≤70 mg/dL, while severe hypoglycemia was defined as BG ≤40 mg/dL.

The first measured BG value represented the time from admission to the first measurement. BG remained constant at the levels observed in the previous measurement until the time point of the next measurement. We calculated time intervals between BG measurements and the proportion of time spent in different BG categories during the first 24 hours. Thus, during the first 24 hours, for each patient, time spent in each of the predefined BG categories ranged from 0% to 100%.

2.4. Outcomes

The primary outcome measure was hospital mortality. Secondary outcomes were ICU length of stay in overall and survival patients, ICU mortality, hospital length of stay in overall and survival patients, locations at hospital discharge.

2.5. Statistical analysis

Data were initially assessed for normality. Continuous variables are shown as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were reported as numbers and percentages. Group comparisons were made using χ² tests for equal proportion, analysis of variance for normally distributed variables, and Kruskal–Wallis tests otherwise. For missing values, the missing rate of variables was evaluated. Multiple imputations with “MICE” package of R software was performed for missing values.[21]

Given the retrospective nature of this study, multivariable logistic regression models were constructed using all available baseline information that related to patient demographics (sex and chronic comorbidities), hospital admit source, disease
severity (APACHE IV score) and treatments (use of vasopressors, insulin, glucocorticoid, mechanical ventilation, CRRT, and hypothermia) along with separate BG metrics. The models were constructed using backward stepwise selection, with variables that were significant ($P<.1$) included. Besides, the covariates were also determined by subject-matter knowledge, for example, past history of diabetes mellitus was not statistically significant, but was selected in the final models. Potential multicollinearity between different covariates was quantified by calculation of the variance inflation factor (VIF), which provided an index of how much the variance of an estimated regression coefficient is increased due to collinearity and VIF less than 5 was considered acceptable. The Hosmer–Lemeshow goodness-of-fit test was used to assess the calibration of the models. Sensitivity analysis was performed in patients with and without diabetes.

Generalized estimating equations (GEE) were used to account for potential correlation in outcomes among patients sampled within hospital clusters. Independence pattern (no association) were examined for within-hospital correlation. Covariates were selected similarly as those in the multivariable logistic regression models.

Hospital mortality was considered as a time-to-event variable. The event was death within hospital. Patients were censored when hospital discharged alive. The analysis truncated at 30 days. Duration of survivals in hospital were presented as Kaplan–Meier curves with log-rank test comparing different BG ranges. Cox regression model was fitted to test for an association between different BG metrics (TWM-BG ranges and proportion of time spent in different BG ranges) and hospital mortality after adjusting for potential confounders.

Data extraction was performed using PostgreSQL (version 10, www.postgresql.org). R software (version 3.5.1, www.r-project.org) was used for statistical analysis. A 2-sided $P$ value of $< .05$ was considered statistically significant.

3. Results

The eICU database contained 200,839 patient admissions. After exclusion, a total of 2028 patients from 144 hospitals were analyzed in our study (Supplemental Figure 1, http://links.lww.com/MD/E716), including 964 non-survivors and 1064 survivors, giving hospital mortality of 47.5%. ICU mortality was 37%. Non-survivors were slightly older, lower proportion of men and higher proportion of admitting from emergency department. Detailed information regarding the rate of missing values were displayed in Supplemental Figure 2, http://links.lww.com/MD/E717. Baseline characteristics and treatments of study patients between survivors and non-survivors were presented in Supplemental Table 1, http://links.lww.com/MD/E718.

A total of 14,118 measurements of blood glucose were extracted from 2028 PCA patients, 7 times per patient on average. Of the 14,118 measurements, 279 (2%) were equal or less than 70 mg/dL and 42 (0.3%) were equal or less than 40 mg/dL. TWM-BG for overall patients was 159 mg/dL, non-survivors had higher TWM-BG than survivors (170 vs 149, $P < .001$). The proportion of time spent in 70 to 140 mg/dL range was higher in survivors than non-survivors (38.4 vs 28.7, $P < .001$). Figure 1 shown the density distribution of the proportion of time spent in different BG ranges.

According to TWM-BG, 9 (0%) were classified into the $< 70$ mg/dL range group, 693 (34%) into the 70 to 140 mg/dL range group, 603 (30%) into the 140 to 180 mg/dL range group and 723 (36%) into the $> 180$ mg/dL range group. TWM-BG range $> 180$ mg/dL group was oldest, had the highest body mass index (BMI), the highest percentage of diabetes mellitus, the highest APACHE IV score, and the highest percentage of using insulin. TWM-BG range $> 180$ mg/dL group also had the lowest percentage of hypoglycemia (moderate or severe). Comparisons of baseline characteristics and treatments of different TWM-BG categories were displayed in Table 1. TWM-BG range 70 to 140 mg/dL group had the lowest ICU and hospital mortality and the highest proportion of discharging home. TWM-BG range 70 to 140 mg/dL group also had minimum hospital length of stay. Patient-centered outcomes were displayed in Table 2.

After adjusting for sex, ICU admit source, past history (diabetes mellitus, cancer), APACHE IV score, use of insulin, vasopressors, CRRT and hypothermia, patients with TWM-BG range in 140 to 180 mg/dL and $> 180$ mg/dL groups had higher odds ratio for hospital mortality in multivariable logistic regression and higher hazard ratio for hospital mortality in Cox proportional hazard model than 70 to 140 mg/dL group. Proportion of time spent in 70 to 140 mg/dL range was associated with lower odd ratio (OR 0.984, CI [0.970, 0.998], $P = .022$) and hazard ratio (HR 0.986, CI [0.977, 0.996], $P = .005$) for hospital mortality. The proportion of time spent in $> 180$ mg/dL range was associated with higher odds ratio and hazard ratio for hospital mortality (Table 3). With GEE model accounting for potential correlation in outcomes among patients sampled within hospital clusters, similar results were found (Fig. 2 and Supplemental Table 2–6, http://links.lww.com/MD/E719).

Sensitivity analysis showed time in BG 70 to 140 mg/dL was associated with low risk of death in patients without diabetes ($P = .002$) but not with mortality in patients with diabetes ($P = .294$), whereas time in BG range 140 to 180 mg/dL was associated with lower mortality in patients with diabetes ($P = .013$) but not with mortality in patient without diabetes ($P = .931$) (Supplemental Table 7, http://links.lww.com/MD/E720). Figure 3 displayed the Kaplan–Meier survival curves by TWM-BG categories, which showed that 70 to 140 mg/dL group was associated with the highest probability of survival (log-rank $P < .001$).
4. Discussion

This multicenter retrospective analysis of a large, heterogeneous cohort of PCA patients admitted in ICU supports the finding that the proportion of time spent in BG range 70 to 140 mg/dL is strongly associated with increased hospital survival. Hyperglycemia (>180 mg/dL) is common to PCA patients and is associated with higher odd ratio and hazard ratio for hospital mortality. Hypoglycemia is not statistically significant associated with hospital mortality probably due to low incidence.

Glycemic control and targets are contentious for PCA patients. Due to the scarcity of studies on the PCA period, resuscitation guidelines acknowledges that the optimum BG concentration and interventional strategy to manage BG in the PCA period are unknown. One RCT of 90 subjects showed no difference in day 30 mortality between strict (72–108 mg/dL) and moderate (108–144 mg/dL) BG management. However, in this RCT study, standard treatment protocol for OHCA patients had been targeted below 144 mg/dL, which cannot answer the question whether strict BG control is better than BG exceeding 144 mg/dL. One before-and-after observational study of 119 subjects showed reduced in-hospital mortality after implementation of a bundle of care that included defined BG range 5 to 8 mmol/L. However, the effect of BG management cannot be separated from the effects of other parts of the bundle. Both hyperglycemia and hypoglycemia were associated with poor neurologic outcome, suggesting a U-shaped relationship between BG and poor outcome in PCA patients. The nadir or optimal range are still not clear. Two retrospective studies demonstrated that BG concentrations of 116 to 143 mg/dL or 140 to 180 mg/dL were associated with increased survival and a favorable neurological outcome. Both hyperglycemia and hypoglycemia were associated with poor neurologic outcome, suggesting a U-shaped relationship between BG and poor outcome in PCA patients. The nadir or optimal range are still not clear. Two retrospective studies demonstrated that BG concentrations of 116 to 143 mg/dL or 140 to 180 mg/dL were associated with increased survival and a favorable neurological outcome.

| Variables | <70 (n = 9) | 70-140 (n = 603) | 140-180 (n = 603) | >180 (n = 723) | P value |
|-----------|------------|-----------------|-----------------|--------------|--------|
| Age, yr (median, [IQR]) | 59 (50, 72) | 62 (50, 73) | 63 (53, 74) | 66 (56, 75) | <.001 |
| Sex: male (n (%)) | 5 (56) | 426 (61) | 366 (61) | 412 (57) | .333 |
| BMI (median, [IQR]) | 25.9 (24.1, 27) | 25.6 (23.6, 32.8) | 28.6 (24.1, 33.5) | 30.2 (25.8, 35.9) | <.001 |
| ICU admit source, n (%) | 3 (33) | 173 (23) | 160 (27) | 199 (28) | .813 |

- Emergency Department
- Floor
- Direct Admit
- Operating Room
- Others

- Hypertension
- Diabetes mellitus
- Respiratory disease
- Heart failure
- Cirrhosis
- Chronic renal failure
- Cancer

- Admission vital sign (median, [IQR]):
  - Temperature, °C
  - Respiratory rate
  - HR, beats/min
  - MBP, mmHg
  - MBP, mmHg
  - Admission BG, mg/dL
  - Admission BG, mg/dL
  - Maximum BG, mg/dL
  - Minimum BG, mg/dL
  - Mean BG, mg/dL
  - TWM BG, mg/dL
  - CV (%)
  - BG <= 70 (% of patients)
  - BG <= 40 (% of patients)

- Severity of illness
  - APACHE IV score, (median, [IQR]):
  - SOFA (median, [IQR]):

- Treatments during 24 hours (n (%))
  - Mechanical ventilation
  - CRRT
  - Hypothermia
  - Vasopressors
  - Insulin
  - Glucocorticoid

APACHE=Acute Physiology and Chronic Health Evaluation, BG=blood glucose, BMI=body mass index, CRRT=continuous renal replacement therapy, CV=coefficient of variation, HR=heart rate, ICU=intensive care unit, IQR=interquartile range, MBP=mean blood pressure, MV=mechanical ventilation, SOFA=sequential organ failure assessment.
Hyperglycemia is common in the early phase of PCA syndrome. Global ischemia-reperfusion condition after OHCA, metabolic derangements, chronic prearrest comorbid conditions, exogenous epinephrine, hypothermia treatment might be associated with hyperglycemia after ROSC. The association between hyperglycemia after ROSC and worse clinical outcome in cardiac arrest patients is clear. Furthermore, a high glycemic variability (GV) is associated with increased mortality and poor neurologic outcome. GV might be associated with hyperglycemia after ROSC.

Tight glycemic control in critically ill including PCA patients is still controversial. The main harm of tight glucose control may be hypoglycemia, which is associated with increased mortality, morbidity and length of hospital stay. Overall, 159 (8%) patients in the present study had at least 1 episode of moderate hypoglycemia and 30 (1%) had severe hypoglycemia, which were lower than what had been observed in many of the other intensive care. In the present study, 723 (36%) PCA patients had TWM-BG > 180 mg/dL. The high percentage of hyperglycemia may reflect the principle of ‘first, do no harm’, which may be not benefit for our patients.

| Status at hospital discharge, n (%) | <=70 (n=9) | 70-140 (n=603) | 140-180 (n=603) | > 180 (n=723) | P value |
|-----------------------------------|-----------|--------------|---------------|--------------|---------|
| Death                             | 4 (44)    | 247 (36)     | 307 (51)      | 406 (66)     | <.001   |
| Discharged home                   | 1 (11)    | 223 (32)     | 142 (24)      | 128 (18)     |         |
| Discharged to nursing home        | 1 (11)    | 11 (2)       | 10 (2)        | 5 (1)        |         |
| Discharged to skilled nursing facility | 2 (22) | 67 (10)      | 46 (8)        | 79 (11)      |         |
| Discharged to rehabilitation      | 0 (0)     | 22 (3)       | 29 (5)        | 21 (3)       |         |
| Discharged to other places        | 1 (11)    | 123 (18)     | 69 (11)       | 84 (12)      |         |
| Status at ICU discharge, n (%)    | 4 (44)    | 184 (27)     | 244 (40)      | 325 (45)     | <.001   |
| Duration of stay, median (IQR)    |           |              |               |              |         |
| Hospital LOS, d                   | 5 (2, 13) | 6 (3, 12)    | 6 (3, 11)     | 6 (3, 11)    | .037    |
| Hospital LOS, survivors, d        | 13 (5, 21)| 8 (4, 15)    | 9 (5, 16)     | 10 (6, 17)   | .017    |
| Hospital LOS, deaths, d           | 2 (2, 3)  | 4 (2, 7)     | 3 (2, 6)      | 3 (2, 6)     | .179    |
| ICU LOS, d                        | 4 (3, 6)  | 4 (3, 7)     | 4 (3, 7)      | 4 (3, 7)     | .511    |
| ICU LOS, survivors, d             | 3 (2, 4)  | 4 (3, 6)     | 4 (3, 6)      | 4 (2, 6)     | .239    |
| ICU LOS, deaths, d                | 3 (2, 4)  | 4 (2, 6)     | 4 (3, 5)      | 3 (2, 5)     | .233    |

ICU=Intensive care unit, IQR=Interquartile range, LOS=Length of stay.

| Table 3 | Adjusted hospital mortality (logistic regression and Cox proportional hazards analysis) in patients with different BG variables. |
|---------|----------------------------------------------------------------------------------------------------------------------------------|
| BG variables | OR [95% CI] | P value | Logistic Regression Analysis | HR [95% CI] | P value | Cox Proportional Hazard Models |
| TWM-BG | | | | | | |
| 70-140 mg/dL | 1.00 [Reference] | | | | | |
| <=70 mg/dL | 1.00 [0.20, 4.67] | .995 | 1.00 [Reference] | 1.40 [0.52, 3.78] | .509 |
| 140-180 mg/dL | 1.53 [1.20, 1.96] | <.001 | 1.36 [1.15, 1.61] | <.001 |
| > 180 mg/dL | 1.47 [1.15, 1.89] | <.002 | 1.34 [1.13, 1.58] | .001 |
| Admission - BG | | | | | | |
| 70-140 mg/dL | 1.00 [Reference] | | | | | |
| <=70 mg/dL | 0.63 [0.30, 1.31] | .224 | 1.00 [Reference] | 0.75 [0.44, 1.28] | .294 |
| 140-180 mg/dL | 1.17 [0.87, 1.58] | .307 | 1.06 [0.86, 1.32] | .566 |
| > 180 mg/dL | 1.45 [1.14, 1.85] | .003 | 1.31 [1.11, 1.54] | .002 |
| Mean - BG | | | | | | |
| 70-140 mg/dL | 1.00 [Reference] | 1.00 [Reference] | | | | |
| <=70 mg/dL | 0.63 [0.12, 2.70] | .556 | 0.85 [0.27, 2.67] | .777 |
| 140-180 mg/dL | 1.62 [1.26, 2.08] | <.001 | 1.42 [1.20, 1.69] | <.001 |
| > 180 mg/dL | 1.80 [1.40, 2.30] | <.001 | 1.52 [1.29, 1.80] | <.001 |
| Proportion of time (%) spent in BG range (every 5%) | | | | | | |
| <=70 mg/dL | 0.941 [0.879, 1.004] | .073 | 0.969 [0.927, 1.014] | .179 |
| 70-140 mg/dL | 0.984 [0.970, 0.998] | .022 | 0.986 [0.977, 0.998] | .005 |
| 140-180 mg/dL | 0.999 [0.971, 1.008] | .250 | 0.992 [0.986, 1.003] | .245 |
| > 180 mg/dL | 1.019 [1.000, 1.029] | <.001 | 1.019 [1.000, 1.029] | <.001 |

BG=Blood glucose, TWM-BG=Time-weighted mean blood glucose.

Logistic regression models and Cox proportional hazards models were constructed using sex, ICU admittance source, history of diabetes mellitus, cancer, APACHE IV score, use of insulin, vasopressors, CRRT and hypothermia along with separate BG metrics. As for proportion of time (%) spent in BG ranges, <=70, 70 to 140, 140 to 180 and > 180 were considered separate variables in different logistic regression models and Cox proportional hazards models, that is, 4 models were created using the same covariates respectively.

APACHE=Acute Physiology and Chronic Health Evaluation, CRRT=Continuous renal replacement therapy, ICU=Intensive care unit.
insulin therapy studies with critically ill patients.\textsuperscript{[33–35]} Strict glucose control (72–108 mg/dL) leads to the higher incidence of hypoglycemia in OHCA survivors and moderate glucose control (below 180 mg/dL) was acceptable owing to the potentially detrimental effect of hypoglycemia arising from strict glucose control.\textsuperscript{[23,36]} In the present study, sensitivity analyses suggested time in BG range < = 70 mg/dL was not associated with mortality both in PCA patients with and without diabetes. The results may be attributed to the inadequately statistical power and the skew distribution of time in BG range < = 70 mg/dL (Supplemental Figure 2, http://links.lww.com/MD/E719).

Figure 2. (A) Adjusted odds ratio for hospital mortality with generalized estimating equation (GEE) model according to proportion of time (per 5% increase) spent in different time-weighted mean blood glucose ranges after multivariable adjustment. (B) Adjusted odds ratio for hospital mortality with GEE model according to time-weighted mean blood glucose ranges (the 70-140 mg/dL category as reference) after multivariable adjustment. The odds ratio and 95% confidence intervals (error bars) for each variable were calculated after multivariable adjustment for sex, ICU admit source, past history (diabetes mellitus, cancer), APACHE IV score, use of insulin, vasopressors, CRRT and hypothermia (Supplemental Tables 2–6, http://links.lww.com/MD/E719).

However, better glycemic control without a higher risk of hypoglycemia can be achieved. Closed-loop glucose control (Artificial Pancreas) consists of a continuous glucose monitor and an insulin pump, coupled with a control algorithm that directs insulin delivery on the basis of real-time sensor glucose measurements,\textsuperscript{[37]} which reduced the rate of hypoglycemia and may avoid the events of severe hypoglycemia.\textsuperscript{[38,39]} Andrew et al.

Figure 3. Kaplan-Meier survival curves by time-weighted mean blood glucose ranges (log-rank \( P < .001 \)).
demonstrated that in a population of medical and surgical cardiac patients treated with a validated insulin administration algorithm (e-protocol), a BG target of 80 to 110 mg/dL can be achieved with low rates of severe hypoglycemia and was associated with lower 30-day mortality compared with a 90 to 140 mg/dL BG target.\[40]\] Maybe it is time to rethink BG targets in critically ill patients including PCA patients in the setting of continuous BG monitor.\[41]\]

This study had several strengths. First, the data was extracted from multiple ICUs, making its findings highly generalizable. Second, there were 14,118 arterial BG measurements for 2028 patients during the first 24 h, which may reduce errors. Third, this study used different kinds of BG, including TWM-BG, mean BG, admission BG, and proportion of time spent in different BG ranges, which made the results robust. As a metric, proportion of time spent in different BG ranges captures both level and variability of BG. Fourth, we used multivariable logistic regression models, Cox proportional hazard models and GEE models. The findings were consistent, indicating that conclusions were not dependent on the chosen statistical approach.

There were several obvious limitations to this study. First, the study was retrospective in nature and was subject to the inherent limitations of the design. For instance, the time and numbers of BG for every patient were not same. Many potential confounding factors might not be included in the analysis, leading to biased results. Also, the study design only allowed us to show statistical associations and not causality between BG and hospital mortality. The results could be considered hypothesis generating only, rather than proof of causality. Second, initial rhythm, quality, and duration of cardiopulmonary resuscitation, which was an important prognostic factor, could not be assessed by the database. Third, we used the BG range 70 to 140 based on previously published studies\[16,17\], thus the exact BG levels associated with good outcomes are unknown. Fourth, we extracted BG measurements from laboratory and bedside, sampling was intermittent and included measurements made on point-of-care glucose meters, which may overestimate blood glucose concentration. It may explain the low incidence of hypoglycemia. Finally, we excluded the patients with only 1 BG measurement, and the reasons for few BG measurement were unknown. Among potential factors, few BG measurement could have been due to premature death or rapidly regained consciousness. In our study, few BG measurement may be due to premature death or rapidly regained awareness. In our study, few BG measurement could have been due to premature death or rapidly regained awareness. In our study, few BG measurement could have been due to premature death or rapidly regained awareness. In our study, few BG measurement could have been due to premature death or rapidly regained awareness.

5. Conclusions

In summary, proportion of time spent in BG range 70 to 140 mg/dL is strongly associated with increased hospital survival in PCA patients. Hyperglycemia (\(> 180\) mg/dL) is common in PCA patients and is associated with higher odd ratio and hazard ratio for hospital mortality. These results merit further investigation and prospective validation.

Author contributions

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References

[1] Berdowski J, Berg RA, Tijssen JG, et al. Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. Resuscitation 2010;81:1479–87.
[2] Andersen LW, Holmberg MJ, Berg KM, et al. In-hospital cardiac arrest: a Review. JAMA 2019;321:1200–10.
[3] Wissenberg M, Lippert FK, Følke F, et al. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. JAMA 2013;310:1377–84.
[4] Cronberg T, Lilja G, Horn J, et al. Neurologic function and health-related quality of life in Patients following targeted temperature management at 33 degrees C vs 36 degrees C after out-of-hospital cardiac arrest: a randomized clinical trial. JAMA neurology 2015;72:634–41.
[5] Sandrom C, D’Arrigo S, Callaway CW, et al. The rate of brain death and organ donation in patients resuscitated from cardiac arrest: a systematic review and meta-analysis. Intensive Care Med 2016;42:1661–71.
[6] Walker AC, Johnson NJ. Critical care of the post-cardiac arrest patient. Anesthesiology clinics 2018;36:419–28.
[7] Nabi D, Bernard S, Duffy SJ, et al. Post cardiac arrest syndrome: a review of therapeutic strategies. Circulation 2011;123:1428–35.
[8] Callaway CW, Donnino MW, Fink EL, et al. Part 8: post-cardiac arrest care: 2015 American heart association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015;132(Suppl 2):S645–82.
[9] Cueni-Vilozz N, Devigli A, Deolodder F, et al. Increased blood glucose variability during therapeutic hypothermia and outcome after cardiac arrest. Crit Care Med 2011;39:2225–31.
[10] Beiser DG, Carr GE, Edelson DP, et al. Derangements in blood glucose following initial resuscitation from in-hospital cardiac arrest: a report from the national registry of cardiopulmonary resuscitation. Resuscitation 2009;80:624–30.
[11] Borggrefe O, Woe MP, Nielsen N, et al. Dysglycemia, glycemic variability, and outcome after cardiac arrest and temperature management at 33 degrees C and 36 degrees C. Crit Care Med 2017;45:1337–43.
[12] Daviaud F, Dumas F, Demars N, et al. Blood glucose level and outcome after cardiac arrest: insights from a large registry in the hypothermia era. Intensive Care Med 2014;40:855–62.
[13] Girotra S, Chan PS, Bradley SM. Post-resuscitation care following out-of-hospital and in-hospital cardiac arrest. Heart (British Cardiac Society) 2015;101:1943–9.
[14] Losert H, Sterr F, Roine RO, et al. Strict normoglycaemic blood glucose levels in the therapeutic management of patients within 12 h after cardiac arrest might not be necessary. Resuscitation 2008;76:214–20.
[15] Padkin A. Glucose control after cardiac arrest. Resuscitation 2009;80:613–2.
[16] Kinsley JS, Preiser JC. Time in blood glucose range 70 to 140 mg/dL: > 80% is strongly associated with increased survival in non-diabetic critically ill adults. Crit Care 2015;19:179.
[17] Lanspa MJ, Kinsley JS, Hersh AM, et al. Percentage of time in range 70 to 139 mg/dL is associated with reduced mortality among critically ill patients receiving IV insulin infusion. Chest 2019;156:878–86.
[18] Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA 2008;300:933–44.
[19] Mark PE, Preiser JC. Toward understanding tight glycemic control in the ICU: a systematic review and meta-analysis. Chest 2010;137:544–51.
[20] Pollard TJ, Johnson AEW, Raffa JD, et al. The eICU collaborative research database, a freely available multi-center database for critical care research. Sci Data 2018;5:180178.
[21] Zhang Z. Decision tree modeling using R. Ann Transl Med 2016;4:195–275.
[22] Callaway CW, Soor J, Aibiki M, et al. Part 4: advanced life support: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care: 2015 American heart association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care: scientific statement. Circulation 2015;132(Suppl 1):S84–145.
[23] Oksanen T, Skrifvars MB, Varpula T, et al. Stricter versus moderate glucose control after resuscitation from ventricular fibrillation. Intensive Care Med 2007;33:2093–100.
Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation 2007;73:29–39.

Skrifvars MB, Pettila V, Rosenberg PH, et al. A multiple logistic regression analysis of in-hospital factors related to survival at 6 months in patients resuscitated from out-of-hospital ventricular fibrillation. Resuscitation 2003;59:319–28.

Kim SH, Park KN, Choe SP, et al. Time to reach target glucose level and outcome after cardiac arrest patients treated with therapeutic hypothermia. J Crit Care 2015;30:1204–9.

Vihonen H, Kuisma M, Salo A, et al. Mechanisms of early glucose regulation disturbance after out-of-hospital cardiopulmonary resuscitation: an explorative prospective study. PloS One 2019;14:e0214209.

Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet (London, England) 2009;373:1798–807.

Nurm J, Boyd J, Anttalainen N, et al. Early increase in blood glucose in patients resuscitated from out-of-hospital ventricular fibrillation predicts poor outcome. Diabetes care 2012;35:510–2.

Kim SH, Choi SP, Park KN, et al. Association of blood glucose at admission with outcomes in patients treated with therapeutic hypothermia after cardiac arrest. Am J Emerg Med 2014;32:900–4.

Mullner M, Sterz F, Binder M, et al. Blood glucose concentration after cardiopulmonary resuscitation influences functional neurological recovery in human cardiac arrest survivors. J Cereb Blood Flow Metab 1997;17:430–6.

Nirantharakumar K, Marshall T, Kennedy A, et al. Hypoglycaemia is associated with increased length of stay and mortality in people with diabetes who are hospitalized. Diabet Med 2012;29:e445–8.

Finfer S, Liu B, Chittock DR, et al. Hypoglycemia and risk of death in critically ill patients. N Engl J Med 2012;367:1108–18.

Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ 2009;180:821–7.

Yatabe T, Inoue S, Sakaguchi M, et al. The optimal target for acute glycemic control in critically ill patients: a network meta-analysis. Intensive Care Med 2017;43:16–28.

Nolan JP, Soar J, Cariou A, et al. European resuscitation council and European society of intensive care medicine guidelines for post-resuscitation care 2015. Resuscitation 2015;95:202–22.

Bally L, Thabit H, Hovorka R. Closed-loop for type 1 diabetes - an introduction and appraisal for the generalist. BMC medicine 2017;15:14.

Bally L, Thabit H, Hartnell S, et al. Closed-loop insulin delivery for glycemic control in noncritical care. N Engl J Med 2018;379:547–56.

Okabayashi T, Shima Y, Sumiyoshi T, et al. Intensive versus intermediate glucose control in surgical intensive care unit patients. Diabetes care 2014;37:1516–24.

Hersh AM, Hirshberg EL, Wilson EL, et al. Lower glucose target is associated with improved 30-day mortality in cardiac and cardiothoracic patients. Chest 2018;154:1044–51.

Krimsky JS. Is it time to rethink blood glucose targets in critically ill patients. Chest 2018;154:1004–5.