Hyperglycemia and Insulin Resistance in Cardiac Arrest Patients Treated With Moderate Hypothermia

Matthew D. Ettleson, Vanessa Arguello, Amisha Wallia, Lester Arguelles, Richard A. Bernstein, and Mark E. Molitch

Division of Endocrinology, Metabolism, and Molecular Medicine (M.D.E., A.W., L.A., M.E.M.), Department of Medicine, and Department of Neurology (R.A.B.), Northwestern University Feinberg School of Medicine, Chicago, Illinois 60611; and Department of Internal Medicine (V.A.), University of Illinois at Chicago/Advocate Christ Medical Center, Chicago, Illinois 60453

Context: It is unknown whether the hyperglycemia that follows cardiac arrest and during therapeutic hypothermia (TH) is due to the arrest or the TH, whether it is associated with adverse outcomes, or whether its treatment affects outcomes.

Objective: The objective of the study was to determine the effects of TH on the blood glucose (BG) levels in postcardiac arrest patients and the effects of hyperglycemia on mortality.

Design: This was a chart review of 62 patients undergoing TH after cardiac arrest between September 2005 and April 2008. BG levels from 72 hours before the arrest to 48 hours after TH and iv insulin infusion rates were analyzed and correlated with survival to discharge from hospital.

Setting: The study was conducted at a tertiary, university referral center.

Patients: Patients undergoing TH after cardiac arrest participated in the study.

Interventions: TH consisted of cooling as rapidly as possible to 33°C, holding that temperature for 24 hours, and then controlled rewarming to 37°C over 8 or 16 hours. Hyperglycemia was managed with iv insulin drip protocols.

Main Outcome Measure: The relationship of cardiac arrest and hypothermia to hyperglycemia, with a key secondary outcome being the relationship of hyperglycemia to survival to discharge, was measured.

Results: Analysis of glucose patterns showed no independent effect of TH on BG levels. Mean BG levels between cardiac arrest and the initiation of hypothermia were higher in nonsurvivors (253 ± 110 mg/dL, n = 48) than in survivors (192 ± 69 mg/dL, n = 24, P = .016). BG, insulin infusion rates, and insulin resistance during hypothermia, during rewarming, and 24–48 hours after hypothermia were not significantly different between the 2 groups.

Conclusions: In patients treated with TH, the TH had no independent effect on BG levels. Mortality was associated with increased BG levels after cardiac arrest but before initiation of TH or an insulin drip. Likely, it is the severity of stress from the cardiac arrest that causes the hyperglycemia in these patients. (J Clin Endocrinol Metab 99: E2010–E2014, 2014)

Therapeutic hypothermia (TH) improves neurologic outcomes after cardiac arrest (1–3). Glucose homeostasis is altered by TH and the systemic responses to whole-body ischemia including brain injury post cardiac arrest (4). Hyperglycemia has been associated with poor neurological outcomes for patients treated with TH, but it is unclear whether hyperglycemia directly contributes to deleterious outcomes or is simply a marker for overall

Abbreviations: BG, blood glucose; DM, diabetes mellitus; HR, hazard ratio; IR, insulin resistance; ROSC, return of spontaneous circulation; TH, therapeutic hypothermia.
poor health (5). Insulin resistance (IR) has also been observed in cardiac arrest patients treated with TH (6–8).

The primary goal of this study is to describe the effects of TH on blood glucose (BG) levels and IR in postcardiac arrest patients. A secondary goal is to determine whether an association exists between BG levels, IR, diabetes status, and mortality rate in postcardiac arrest patients undergoing TH.

Materials and Methods

Study population

Between September 2005 and April 2008, 65 patients were treated with TH after cardiac arrest (inpatient or outpatient arrest) at Northwestern Memorial Hospital under a research protocol with institutional review board approval (9). Inclusion criteria included the following: 18 years of age or older, cardiopulmonary resuscitation initiated within 15 minutes of arrest, return of spontaneous circulation (ROSC) within 60 minutes of arrest, systolic blood pressure greater than 90 mm Hg, and unable to follow commands and/or severely agitated upon restart of circulation. Exclusion criteria included the following: pregnancy, terminal illness, severe coagulopathy or pathological bleeding, do not resuscitate status, or noncardiac arrest-related encephalopathy. Written informed consent was obtained from the power of attorney or appropriate family member for TH. BG values and insulin treatment regimens of the 62 patients with complete data sets were ascertained retrospectively from the electronic medical records with additional approval of the Northwestern University Institutional Review Board (Supplemental Figure 1). Chart review determined whether patients were considered to have diabetes mellitus (DM) or not have diabetes mellitus (NonDM).

Therapeutic hypothermia protocol

Cardiac arrest patients were determined appropriate for TH by emergency, critical care, and neurology staffs based on criteria outlined above. Briefly, the TH protocol consisted of cooling as rapidly as possible to 33°C and then holding that temperature for 24 hours. Controlled rewarming to 37°C was then carried out over 8 or 16 hours, depending on the period of study (Supplemental Figure 2).

Insulin protocol

Intravenous insulin treatment of hyperglycemic patients used a previously developed protocol in which BG values are assessed hourly and infusion rates altered based on changes in BG (10). The target BG was 80–110 mg/dL, consistent with the American Diabetes Association guideline at that time (11).

Data collection

The prehypothermia period was defined as the 72 hours before the initiation of TH, including the cardiac arrest event if data were available (21 patients) and was further subdivided into prearrest and postarrest periods. The posthypothermia period started at the end of TH to 48 hours after TH and was subdivided into rewarming and postrewarming periods. BG values (chemistry and point of care) and insulin rates were recorded for all time periods in 4-hour blocks. BG levels and insulin rates were averaged within each time period and across all time periods to provide mean glucose levels and insulin rates for each patient. Thus, each patient contributed only one mean glucose value and one insulin rate for each time period to the overall averages, regardless of how many assessments were completed within each time period.

Insulin resistance was estimated by dividing the average insulin infusion rate by the average BG during each time period, as previously reported (12). Risk factors previously shown to be associated with worsening hyperglycemia, including type of cardiac arrest, time required for ROSC, and use of iv epinephrine, were also collected (13). Survival was defined as discharge from the hospital.

Statistical analyses

Means ± SD describe continuous baseline characteristics and percentages describe categorical baseline characteristics. Student’s t, Mann-Whitney, and χ² tests were used, as appropriate, to compare these variables between groups for all time periods. Kaplan-Meier curves were generated to compare survival probabilities for patients with peak glucose above and below the median peak glucose at the time of arrest. Cox proportional hazard models were used to estimate adjusted hazard ratios and 95% confidence intervals; the adjusting variables included gender, age, body mass index (BMI), history of diabetes mellitus, and time to ROSC. Statistical significance was accepted as a value of P < .05 (two sided). Statistical analyses were performed using GraphPad In-Stat and SAS version 9.3.

Results

Of the 62 patients analyzed [16 DM (26%); 46 NonDM (74%)], 52 (84%); 15 DM, 37 NonDM) received an insulin drip within 3 days of their cardiac arrest and 48 (77%; 13 DM, 35 NonDM) had the drip initiated after the start of hypothermia (Tables 1 and 2). All 62 patients had at least one BG level above the upper limit of the target range (glucose ≥ 110 mg/dL). The average BG levels after cardiac arrest but prior to TH, during TH, and 24–48 hours after TH were 227 ± 99.8, 159 ± 54.5, and 113 ± 25.5 mg/dL, respectively. Figure 1 illustrates the changes in BG observed before, during, and after TH in 21 patients who had inpatient cardiac arrests and had BG levels recorded for 48–72 hours before the cardiac arrest. There was a marked increase in the BG level after the cardiac arrest that decreased rapidly during hypothermia upon the administration of the insulin drip.

In the 52 patients who received an insulin drip, mean BG [128 ± 23 vs 150 ± 56 mg/dL (P = .079)] and mean insulin infusion rates [1.9 ± 1.8 vs 2.3 ± 2.7 U/h (P = .63)] trended higher in nonsurvivors compared with survivors; however, IR parameters were similar [0.014 ± 0.012 vs 0.013 ± 0.014 U/dL·h·mg (P = .91)]. Average BG levels were compared between survivors and nonsurvivors: between arrest and the start of TH (192 ± 68.7 vs 253 ± 112
mg/dL), during TH (146 ± 40.7 vs 166 ± 61.1 mg/dL), during the 8-hour rewarming (108 ± 22.9 vs 121 ± 55.8 mg/dL), 0–24 hours after TH (111 ± 16.5 vs 127 ± 63.2 mg/dL), and 24–48 hours after TH (114 ± 26.8 vs 112 ± 24.8 mg/dL). Only the average BG levels during the time between arrest and hypothermia were significantly different (P = .016). There were no statistically significant differences in the insulin infusion rates or IR between survivors and nonsurvivors at any time points. A similar comparison was made of average BG between DM and NonDM groups across the same time periods: between arrest and the start of TH [297 ± 123 vs 205 ± 81.0 mg/dL (P = .022)], at the time of the insulin drip initiation [281 ± 53.1 vs 210 ± 76.4 mg/dL (P < .001)], during TH (173 ± 59.1 vs 117 ± 46.6 mg/dL), 0–24 hours after TH (127 ± 55.3 vs 117 ± 46.6 mg/dL), and 24–48 hours after TH [131 ± 35.8 vs 106 ± 17.1 mg/dL (P = .033)]. There were no statistically significant differences in the insulin infusion rates or IR between DM and NonDM patients at any time points. DM patients were not at significantly increased risk of mortality among all patients [hazard ratio (HR) 1.3, 95% confidence interval 0.6–2.6] or those who completed hypothermia (HR 1.5, 95% confidence interval 0.7–3.5).

All patients who completed TH (n = 53) were stratified by median maximum BG at the time of arrest (above or below 220.5 mg/dL). Those individuals who had BG levels above the median were 2.4 times more likely to die during the hospital admission postarrest relative to those below the median, even after adjusting for age, gender, BMI, and
diabetes status ($P = .042$). When the time to ROSC was added to the model (with median ROSC values imputed for four missing values above the median and five missing values below the median), the HR was still significant at 2.3 ($P = .049$). For those above the median BG at arrest, the average survival time was 13 days compared with 25 days for those who had BG below 220.5 mg/dL.

**Discussion**

Hyperglycemia is commonly seen in patients after cardiac arrest and is associated with poor outcomes (6, 13, 14). The specific mechanism by which BG increases after cardiac arrest is not well understood (15, 16). TH did not appear to have an independent effect on glucose homeostasis in our study. Analysis of the glucose levels in the 21 patients with in-hospital cardiac arrest showed that the rise in BG occurred immediately after the arrest and prior to the institution of hypothermia, with no further increase associated with the hypothermia.

Previous studies have shown that hyperglycemia after cardiac arrest is associated with poor functional neurological recovery (17, 18). Our data revealed that increased BG levels (>220.5 mg/dL) immediately after cardiac arrest were associated with decreased survival, but BG levels after the initiation of insulin therapy were no longer associated with survival status. Although this lack of significance may be limited by small sample size, it suggests that the degree of hyperglycemia after cardiac arrest may not be the cause of increased mortality in these patients but rather may be a marker of the severity of stress caused by cardiac arrest. Many parameters used to create severity of illness scores (eg, Acute Physiology and Chronic Health Evaluation) are not available prior to or even immediately after arrest, precluding our development of such scores. The specific time periods for each patient and then pooling all the patients, the frequency of BG measurements has a smaller influence on the overall analysis. The measurement of IR as a ratio of infusion flow rate to BG provides an estimation only and has not been validated against the insulin clamp (12). Retrospective studies are also susceptible to confounding factors, such as age and BMI; however, adjusted hazard ratios were calculated when appropriate in an effort to minimize the confounding effect. Further analyses looking at cardiac arrest patients not treated with hypothermia may help elucidate this picture.

In conclusion, our study of BG, insulin infusion rates, and IR in cardiac arrest patients treated with moderate hypothermia revealed that TH did not appear to have an independent effect on glucose homeostasis and that only BG levels immediately after cardiac arrest and before insulin therapy and TH were associated with survival. We hypothesize that this value is a measure of the severity of stress caused by cardiac arrest and organ hypoperfusion and that it is the degrees of brain injury and cardiovascular instability (20) that are associated with the likelihood of survival. Although insulin therapy is standard in critically ill patients with hyperglycemia, its utility in this population will require further study, ideally with a larger sample size.

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M.E.M. takes responsibility for the contents of the article.

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![Figure 1. Blood glucose values in the 21 subjects who had in-hospital cardiac arrests, demonstrating the onset of hyperglycemia after cardiac arrest and before the onset of TH.](https://academic.oup.com/jcem/article-abstract/99/10/E2010/2836207)
contributed to the discussion; A.W. reviewed/edited the manuscript and contributed to the discussion; L.A. performed the statistical analyses, wrote the manuscript, and contributed to the discussion; R.A.B. reviewed/edited the manuscript; and M.E.M. reviewed/edited the manuscript and contributed to the discussion.

Address all correspondence and requests for reprints to: Mark E. Molitch, MD, Division of Endocrinology, Metabolism, and Molecular Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine, 645 North Michigan Avenue, Suite 530, Chicago, IL 60611. E-mail: molitch@northwestern.edu.

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References


