Short paper

Elevated prehospital point-of-care glucose is associated with worse neurologic outcome after out-of-hospital cardiac arrest ☆

Tiffany M. Abramson [a,*]**, Nichole Bosson** [b,c,d]**, Denise Whitfield** [b,c,d]**, Marianne Gausche-Hill** [b,c,d]**, James T. Niemann** [c,d]

[a] *Keck School of Medicine of the University of Southern California, Department of Emergency Medicine, Division of Emergency Medical Services, United States*
[b] *Los Angeles County Emergency Medical Services Agency, United States*
[c] *Harbor-UCLA Medical Center and the Lundquist Research Institute at Harbor-UCLA, United States*
[d] *The David Geffen School of Medicine at UCLA, United States*

Abstract

Objectives: Hyperglycemia is associated with poor outcomes in critically-ill patients. This has implications for prognostication of patients with out-of-hospital cardiac arrest (OHCA) and for post-resuscitation care. We assessed the association of hyperglycemia, on field point-of-care (POC) testing, with survival and neurologic outcome in patients with return of spontaneous circulation (ROSC) after OHCA.

Methods: This was a retrospective analysis of data in a regional cardiac care system from April 2011 through December 2017 of adult patients with OHCA and ROSC who had a field POC glucose. Patients were excluded if they were hypoglycemic (glucose <60 mg/dl) or received empiric dextrose. We compared hyperglycemic (glucose >250 mg/dL) with euglycemic (glucose 60–250 mg/dL) patients. Primary outcome was survival to hospital discharge (SHD). Secondary outcome was survival with good neurologic outcome (cerebral performance category 1 or 2 at discharge). We determined the adjusted odds ratios (AORs) for SHD and survival with good neurologic outcome.

Results: Of 9008 patients with OHCA and ROSC, 6995 patients were included; 1941 (28%) were hyperglycemic and 5054 (72%) were euglycemic. Hyperglycemic patients were more likely to be female, of non-White race, and have an initial non-shockable rhythm compared to euglycemic patients (p < 0.0001 for all). Hyperglycemic patients were less likely to have SHD compared to euglycemic survivors, 24.4% vs 32.9%, risk difference (RD) −8.5% (95 %CI −10.8%, −6.2%), p < 0.0001. Hyperglycemic survivors were also less likely to have good neurologic outcome compared to euglycemic survivors, 57.0% vs 64.6%, RD −7.6% (95 %CI −12.9%, −2.4%), p = 0.004. The AOR for SHD was 0.72 (95 %CI 0.62, 0.85), p < 0.0001 and for good neurologic outcome, 0.70 (95 %CI 0.57, 0.86), p = 0.0005.

Conclusion: In patients with OHCA, hyperglycemia on field POC glucose was associated with lower survival and worse neurologic outcome.

Keywords: Heart arrest, Emergency medical services, Prehospital, Hyperglycemia, Glucose, Neurologic outcome

Introduction

Sudden cardiac arrest is the third leading cause of death in the United States (US) with over 400,000 out-of-hospital cardiac arrests (OHCA) annually and approximately 10% survival to hospital discharge.[1–3] The morbidity associated with surviving OHCA is a leading cause of disability-adjusted life years.[4,5] Identifying prognostic markers and targets for post-resuscitation care are critical to improving outcomes.

Point-of-care (POC) glucose is frequently performed by emergency medical services (EMS) during resuscitation of patients in OHCA. However, there is scant evidence to support this practice. One study looking at OHCA with field POC glucose measurement found no difference in neurologic outcomes in patients with and without field treatment for hypoglycemia.[6] Even less is known about prehospital hyperglycemia in OHCA. Hyperglycemia is generally associated with poor outcomes in critically-ill patients, which is attributed to mechanisms including neuronal toxicity, neuroendocrine dysregulation and inflammation secondary to glucose toxicity, insulin resistance, and increased inflammatory cytokines.[7,8] After in-hospital cardiac arrest, hyperglycemia is associated with decreased survival and poor neurologic function.[9,10] This may also be true for patients with OHCA, which has implications for prognostication, field management, and post-resuscitation care. There is a need for rapidly available and objective measures that can help determine which patients may survive with good neurologic outcome versus those in whom further resuscitation efforts are futile. While there is no one measure to predict survival, identifying individual prognostic factors can support development of a tool to guide decision-making in field resuscitation.

Hyperglycemia is common after successful OHCA resuscitation.[11] However, most studies evaluating hyperglycemia and outcomes after OHCA are based on glucose measurements after hospital arrival, which may be confounded by release of stress hormones, prolonged downtime, medication administration, and delay to testing.[7] The objective of this study was to determine the association of hyperglycemia, determined by field POC glucose, and survival and neurologic outcome in patients with return of spontaneous circulation (ROSC) after OHCA.

Methods

Study design

This was a retrospective cohort study of data from a regional cardiac arrest registry including consecutive patients from April 2011 through December 2017 with OHCA treated by paramedics in Los Angeles County (LAC) and transported to a cardiac arrest receiving center. The study was reviewed and approved with waiver of informed consent by the Institutional Review Board of the University of Southern California (HS-18-00245).

Setting

Los Angeles County includes 88 cities spanning 4058 square miles with a population of 10 million.[12] The Los Angeles County Emergency Medical Services Agency (LAC-EMS) operates a regional cardiac arrest system that has been previously described and is closely coordinated with systemwide care standards and quality improvement.[13,14] EMS throughout LAC use uniform field treatment protocols, which at the time of the study included obtaining a POC glucose for non-shockable cardiac arrest, though it was common practice to obtain field POC in most patients with OHCA. Point-of-care glucose measurements are obtained using a portable glucometer and testing blood from an IV insertion or finger stick. EMS transports patients resuscitated from OHCA to one of 36 designated cardiac arrest receiving centers with 24/7 cardiac catheterization capabilities and targeted temperature management (TTM) policies.

Cardiac arrest receiving centers submit outcome data on all adult patients with ROSC after OHCA to a single registry maintained and verified by LAC-EMS.[15,16] Abstracted data elements include field ROSC, survival to hospital discharge (SHD), and neurologic outcome assessed with Cerebral Performance Category (CPC) extracted from the medical record. EMS provider agencies submit data on the field management of all patients to LAC-EMS, including point of care (POC) glucose testing, medications, and field outcome and disposition. These field data are merged with hospital outcome data based on a unique identifier for the EMS encounter.

Selection of participants

Consecutive adult patients (≥18 years) transported to a cardiac arrest receiving center with ROSC after non-traumatic OHCA were identified from April 2011 through December 2017 from the LAC-EMS registries. Patients were included if they had at least one field POC glucose measurement. Patients were excluded if they were hypoglycemic (glucose <60 mg/dL) or if they received empiric dextrose. We excluded hypoglycemic patients from the "normal" comparison group given the potential association with patient comorbidities and outcome, as well as the different prehospital management (i.e., dextrose and/or glucagon administration).

Measurements

Study variables included age, sex, race, field POC glucose, dextrose and/or glucagon administration by EMS, initial rhythm, witnessed arrest, bystander CPR, coronary angiography, percutaneous coronary intervention (PCI), TTM, field ROSC, and receiving center. The LAC cardiac arrest registry was used to determine SHD and CPC. The first documented POC glucose measurement was used for the analysis. Hypoglycemia was defined as glucose <60 mg/dL, euglycemia as 60–250 mg/dL and hyperglycemia as >250 mg/dL. The threshold of >250 mg/dl for hyperglycemia was selected a priori based on prior literature.[17,18] We further categorized elevated glucose levels as mild (>250–400 mg/dl), moderate (>400–600 mg/dl) and severe (>600 mg/dl).

Outcomes

Primary outcome was SHD for hyperglycemic patients compared with euglycemic patients. Secondary outcome was survival with good neurologic outcome, defined as CPC 1 or 2 at discharge.

Analysis

Data were extracted in Microsoft Excel (Microsoft Corporation, Redmond WA) and analyzed with SAS 9.4 (SAS Institute, Cary, NC). Age was reported as a median with interquartile range. Categorical data were calculated as frequencies with proportions, including elevated glucose levels. We determined the risk difference (RD) and 95% confidence interval for SHD and survival with good neurologic outcome in patients with hyperglycemia versus euglycemia. We calculated the adjusted odds ratios (AORs) for SHD and survival with good neurologic outcome with hyperglycemia compared with euglycemia, adjusted for age, sex, race, initial rhythm, witnessed arrest, bystander CPR, coronary angiography, PCI and TTM accounting for treatment center. In addition, we explored the impact of the level of hyperglycemia on the primary outcome of SHD by including the glucose level as a categorical variable in the model with euglycemia as the referent. Finally, given the LAC treatment protocol did not mandate POC glucose testing, we explored the possible selection bias in field POC glucose testing due to impact of patient and arrest characteristics, in particular initial rhythm, by comparing patients with and

without POC glucose documentation. Significance was set at alpha <0.05 for all. Missing data were excluded from the analyses.

Results

Of the 9008 patients with ROSC after OHCA, 2013 were excluded: 1493 had no documented field POC glucose, 420 had a glucose <60 mg/dl, and 100 were treated with empiric dextrose and/or glucagon. Of 6995 patients in the study cohort, 1941 (28%) were hyperglycemic and 5054 (72%) were euglycemic on field POC glucose. (Fig. 1) Patients with hyperglycemia were similar in age to euglycemic patients and had similar frequency of witnessed arrest and bystander CPR. Hyperglycemic patients were more likely to be female, non-White, and have an initial non-shockable rhythm and were less likely to receive TTM (p < 0.0001 for all) (Table 1).

On univariate analysis, SHD was lower for hyperglycemic patients compared with euglycemic patients, 24.4% versus 32.9%, RD −8.5% (95 %CI −10.8%, −6.2%), p < 0.0001. Of those who survived to discharge, good neurologic outcome was less frequent in hyperglycemic patients, 57.0% versus 64.6% of euglycemic patients, RD −7.6% (95 %CI −12.9%, −2.4%), p = 0.004 (Table 2). On multivariable analysis, the AORs for SHD and survival with good neurologic outcome with hyperglycemia compared with euglycemia on field POC glucose were 0.72 (95 %CI 0.62, 0.85), p < 0.0001 and 0.70 (95 %CI 0.57, 0.86), p = 0.0005 respectively. The complete logistic regression results are provided in Supplementary Tables 1 and 2. Table 3 shows the AOR for SHD by level of hyperglycemia.

We found no difference in patient gender, non-White race, witnessed arrest, or bystander CPR rates between those excluded due to lack of POC glucose documentation and our study cohort. Patients excluded were younger, median 67 years (IQR 56–79). Initial rhythm was missing for 423 patients (356 with POC glucose testing and 67 without). Among the 8585 patients with known rhythm, there was a slightly higher proportion of patients with initial shockable rhythm among those without documented POC glucose, 442/1426 (31%) compared to those in the study cohort 2015/7159 (28%), RD 1.9% (95 %CI 0.2, 3.7%), p = 0.03.

Discussion

We found that hyperglycemia on initial field POC glucose was associated with lower survival to hospital discharge and worse neurologic outcome in patients with ROSC after OHCA. These associations remained after adjusting for patient and arrest characteristics.

Previous studies have only utilized blood glucose measurements obtained in the emergency department or after hospital admission. To our knowledge, this is the first study to evaluate association of blood glucose measured during field resuscitation with survival and neurologic outcome after OHCA. Our findings add to and are in agreement with existing studies that found that high admission glucose levels and high median blood glucose levels over 24 h after ROSC were independently associated with poor neurologic outcomes and an increased risk of death.[8,19,20] Critically ill patients with newly diagnosed hyperglycemia had increased mortality, even when
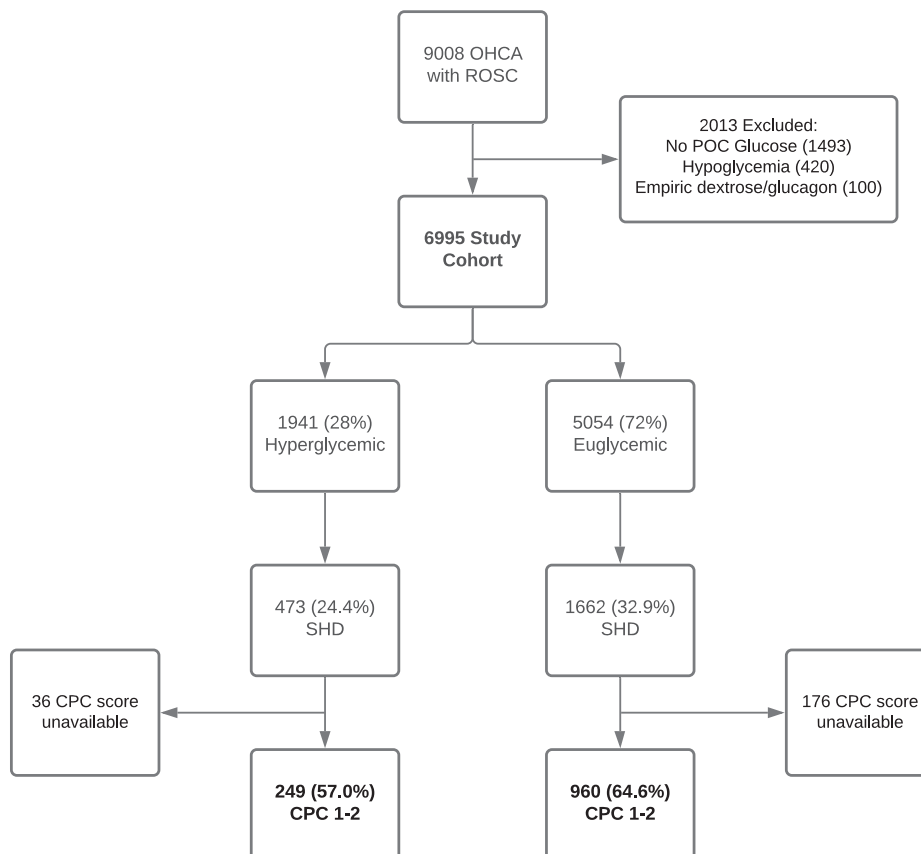

Fig. 1 – Study flow diagram.

Table 1 – Patient characteristics.

Characteristics	All patients (6995)		Hyperglycemic (1941)		Euglycemic (5054)		P value
	N	%	N	%	N	%	
Sex							
Male	4103	58.7	1055	54.4	3048	60.3	<0.0001
Female	2886	41.3	885	45.6	2001	39.6	
Unknown	6	0.1	1	0.1	5	0.1	
Age, median/IQR	69	58–81	70	58–81	69	57–81	ns
Race							<0.0001
Asian	851	12.2	242	12.5	609	12.0	
Black	965	13.8	268	13.8	697	13.8	
Hispanic	1642	23.5	581	29.9	1061	21.0	
Pacific Islander/Native Hawaiian	53	0.8	13	0.7	40	0.8	
White	3067	43.8	739	38.1	2328	46.1	
Other/unknown	417	6.0	98	5.0	319	6.3	
Initial Shockable Rhythm*	1909	27.3	399	20.6	1510	29.9	<0.0001
Witnessed arrest*	5513	78.8	1509	77.7	4004	79.2	0.3
Bystander CPR*	2849	40.7	775	39.9	2074	41.0	0.4
Coronary Angiography*	1137	16.3	290	14.9	847	16.8	0.09
Percutaneous Coronary Intervention	597	8.5	150	7.7	447	8.8	0.16
Targeted Temperature Management*	2488	35.6	612	31.5	1876	37.1	<0.0001
Level of Hyperglycemia							
>250 to 400 mg/dl			875	45.1			
>400 to 600 mg/dl			186	9.6			
>600 mg/dl			880	45.3			

* Unknowns: Initial shockable rhythm (337); Witnessed arrest (178); Bystander CPR (75); Coronary angiography (10); Targeted temperature management (67).

Table 2 – Patient outcomes.

	Hyperglycemic (1941)		Euglycemic (5054)		Risk difference (95 %CI)	P value
	N	%	N	%		
Survival to Hospital Discharge	473	24.4	1662	32.9	−8.5% (−10.8%, −6.2%)	<0.0001
CPC1-2*	249	57.0	960	64.6	−7.6% (−12.9%, −2.4%)	0.004

* Percent CPC1-2 in survivors for whom CPC known N = 437 for hyperglycemia (missing CPC in 36) and N = 1486 for euglycemia (missing CPC in 176).

Table 3 – Survival to hospital discharge by level of hyperglycemia.

	AOR* (95 %CI)	p value
Euglycemia (>60 to 250 mg/dl)	ref	ref
Mild (>250 to 400 mg/dl)	0.65 (0.54, 0.80)	p < 0.0001
Moderate (>400 to 600 mg/dl)	0.42 (0.27, 0.65)	p < 0.0001
Severe (>600 mg/dl)	0.88 (0.73, 1.06)	p = 0.19

* AOR = Adjusted odds ratio.

controlled for other comorbidities.[21] Our data suggest that initial field hyperglycemia after OHCA may be a prognostic marker for neurologic outcome.

Prior randomized controlled trials have evaluated tight glycemic control in critical illness and included divergent populations with different disease states and co-existing comorbidities. Such studies have failed to show that intensive treatment of hyperglycemia improves mortality or selected outcomes.[22,23] This may suggest that high glucose levels are a marker of the duration of arrest and resuscitation, and thus, more of an indicator of poor prognosis rather than directly causal.[24] Further, intensive glycemic control is associated with increased risk of severe hypoglycemia, other adverse events, and cessation of treatment.[22,23] However, Woo et al. found that in-hospital rapid control of blood glucose and shorter time to attain target blood glucose levels after OHCA were associated with favorable neurologic outcome.[25] There may be a level at which glycemic control is important. We did not find a clear dose relationship between level of hyperglycemia and worse outcome, however, moderate hyperglycemia appeared to be worse than mild hyperglycemia.

The findings of our study, in concordance with in-hospital cardiac arrest data, indicate that field POC glucose after OHCA may help drive immediate post-resuscitation care. Emphasis on high-quality CPR is critical particularly early in a resuscitation; once ROSC is achieved POC glucose can be included as part of a bundle of interventions to assess and stabilize the patient. Further, there is a lack of clear guidance on the duration of field resuscitation for OHCA to determine futility and a need for additional prognostic markers to guide decision-making. Given that field POC glucose testing is a rapid, safe, objective test, it may have potential as an early prognostic

marker to be incorporated as one factor in a tool to guide decision-making in field resuscitation.

Limitations

This was a retrospective analysis using registry data; we cannot determine whether hyperglycemia is causal or refletive of other unmeasured confounders associated with worse outcomes. Further, the data are subject to documentation errors or incomplete information. Missing data were assumed to be missing at random. In particular, not all OHCA received POC glucose testing and those patients were slightly more likely to have an initial shockable rhythm; although we cannot exclude the possibility of a selection bias, this was consistent with policy at the time. Given that all patients in the study achieved ROSC and were transported, we do not suspect systematic bias impacting our results. We are unable to assess temporality of the POC glucose check in relation to the patient achieving ROSC given that the times, when available, were documented by the paramedics in retrospect and, therefore, were not precise. The threshold of >250 mg/dl was selected in accordance with prior literature,[17,18] although other thresholds may have been chosen and could affect our results. We could not adjust for unknown confounders, including comorbidities such as diabetes mellitus, or elapsed time between cardiac arrest and EMS arrival. Despite regionalization of cardiac arrest centers and systemwide standards, there is variability in the use of TTM.[26] We attempted to control for both treating center and use of TTM in the regression analysis. Given the high false positive of STEMI on post-arrest ECGs,[27] we cannot accurately report the frequency of STEMI in the study cohort. These data are limited to patients transported to cardiac arrest receiving centers with ROSC and may not be inclusive of all surviving OHCA patients in LAC since patients without field ROSC who were transported to noncardiac arrest centers were not included in the registry. Finally, we were unable to evaluate longterm outcomes.

Conclusion

In this cohort of patients with OHCA treated in a regional cardiac system, hyperglycemia on field POC glucose measurement was associated with lower survival and worse neurologic outcome. Further studies are needed to fully understand how this finding can be integrated into OHCA management to be used as a prognostic indicator or to drive post-resuscitation care.

CRediT authorship contribution statement

James T. Niemann conceptualized the study and all authors contributed to the design and methodology. Nichole Bosson acquired the data and performed the formal analysis. Tiffany M. Abramson drafted the manuscript. All authors contributed substantially to the revision. Marianne Gausche-Hill identified funding for publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2022.100204.

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