

Perioperative Hyperglycemia: An Independent Risk Factor for Adverse Outcomes in Patients Undergoing Ascending Aorta Repair

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Abstract

Objective: Hyperglycemia is common in patients undergoing cardiac surgery and has been shown to be associated with worse outcomes. This study investigates if perioperative hyperglycemia has an impact on clinical outcomes on ascending aorta/arch repair surgery.

Methods: We retrospectively reviewed 1,582 cases of ascending aorta/arch repair at a single institution from 2003-2019. Patients were stratified according to level of preoperative and postoperative blood glucose. Chi-Square test and t-test were used for comparison of categorical variables and normally distributed variables between the groups. Multiple groups were compared by the Kruskal-Wallis test. Multivariate logistic regression analysis was used for analysis of the correlation between perioperative glucose and patient outcomes.

Results: In all, 7.3% of patients died in-hospital, 71.0% were discharged to home, and 21.6% discharged to long-term care/rehabilitation facilities. With elevating glucose level before and/or after surgery, in-hospital mortality increased. Higher preoperative (≥ 140 mg/dl) and/or postoperative (≥ 200 mg/dl) glucose measurements are independent predictors for in-hospital mortality (OR/1.98, 95% CI/1.14-3.42, $p = 0.015$ & OR/2.53, 95% CI/1.37-4.70, $p = 0.003$) after adjusting for demographic factors, diabetes mellitus, creatinine clearance and surgical variables. Additionally, high preoperative glucose levels are related to lower incidence of discharging home compared to lower preoperative glucose (OR = 0.68, 95% CI = 0.50-0.92, $p = 0.013$ and OR = 0.60, 95% CI = 0.42-0.87, $p = 0.007$).

Conclusion: High perioperative glucose is an independent risk factor for in-hospital mortality in patients undergoing ascending aorta repair. Further studies are necessary to confirm this finding and determine the causality.

Keywords

Ascending aorta and aortic arch repair, Deep hypothermic circulatory arrest, Hyperglycemia, Perioperative glucose, In-hospital mortality

Glossary of Terms

AKI: Acute Kidney Injury; ANOVA: Analysis of Variance; aORs: adjusted Odds Ratio; BMI: Body Mass Index; CABG: Coronary Artery Bypass Graft; CBP: Cardiopulmonary Bypass; CrCl: Creatinine Clearance; DHCA: Deep Hypothermic Circulatory Arrest; DM: Diabetes Mellitus; ICU: Intensive Care Unit; LOS: Length of Stay

Introduction

Hyperglycemia is reported in up to 60-90% of patients undergoing cardiac surgery [1]. This hyperglycemia is likely a metabolic consequence of surgical stress and anesthesia [1-4]. Previous studies have shown that perioperative hyperglycemia is related to poor outcomes in cardiac surgical patients [2-5]. All large studies to date have involved patients who underwent congenital heart surgery, non-selective surgery, or coronary artery bypass graft (CABG) [1]. There is a paucity of studies specifically focused on the ascending aorta and aortic arch repair. Patients undergoing ascending aorta and aortic arch repairs present the unique challenge of requiring cardiopulmonary bypass (CPB), often with the addition of deep hypothermic circulatory arrest (DHCA). Due to many of the factors of the surgery, including CPB, DHCA, and surgical stress, hyperglycemia is often noted perioperatively. Therefore, it is prudent to examine the impact of patients' blood glucose on clinical outcome in this patient population [1,5]. The objective of this study was to evaluate the predictive value of perioperative glucose on the in-hospital outcomes of patients who underwent ascending aorta and aortic arch repair surgery.

Materials and Methods

Patient population and data collection

All patients undergoing cardiac surgery at Memorial Hermann Heart & Vascular Institute between January 2003 and December 2019 were retrospectively reviewed. The database was established by collecting medical information through patient medical records and International Classification of Diseases-Ninth Revision-Clinical Modification (ICD-9-CM and ICD-10-CM) Volume 1 Diagnosis Codes, including demographic parameters, medical history, laboratory test results, medical treatment, procedural information, complications, and clinical outcomes.

From 2003-2019, a total of 1,760 patients underwent ascending aorta or aortic arch repair in our institution with one surgical team. In all, 1,582 patients were included in this study, while the remaining 178 were excluded due to incomplete data. Patients were analyzed according to their preoperative (< 110 mg/dl, 110-139 mg/dl, and \geq 140 mg/dl) and postoperative (< 140 mg/dl, 140-199 mg/dl, and \geq 200 mg/dl) blood glucose levels and placed into the appropriate category. The McGovern Medical School at UTHealth Houston Committee for the Protection of Human Subjects approved this retrospective study and consent was waived (IRB HSC-MS-18-0371, June 6, 2018). After data was queried and extracted through an electronic database, it was manually verified for accuracy by study assistants, and any missing information was obtained from alternate sources in the electronic medical record for all cases that were collected. This process provided an accurate and validated dataset for analysis.

Surgical procedures and glucose control

At our institution, hyperglycemia control is standardized with modified Atlanta Insulin Infusion Protocol intraoperatively among the cardiovascular anesthesiologist performing the anesthetic for the surgery. The consensus is to treat all intraoperative glucose values above 180 mg/dL with either a bolus of insulin and/or continuous insulin infusion. We targeted a blood glucose below 200 mg/dL and above 150 mg/dL based on frequent arterial blood gases. This was an institutional standardized management followed by each anesthesiologist. In the postoperative phase, blood glucose management follows the Atlanta Insulin Infusion Protocol in the intensive care unit (ICU), where an insulin drip is started and titrated accordingly, based on hourly glucose draws with oversight provided by a critical care physician.

Definitions

Preoperative glucose was defined in this study as fasting glucose in elective patients or the most proximal

random glucose in emergency/urgent surgical patients prior to entering the operating room. Postoperative glucose was defined as glucose tested immediately after arriving to ICU. In-hospital mortality was defined as death from all causes during intraoperative and postoperative hospitalization. Long-term care was defined as a transfer to long-term care/rehabilitation facility, skilled nursing facility, or hospice facility. In order to reduce the impact of multiple factors, causes, and diagnostic criteria of acute kidney injury (AKI), we choose a very extreme point of AKI that needed postoperative HD for oliguria, as defined as "AKI" in this study. Arrhythmia was defined as any new-onset cardiac arrhythmias documented after surgery. Respiratory insufficiency was defined as prolonged ventilator support > 24 hours, the development of acute respiratory distress syndrome, pulmonary edema, pneumonia, or re-intubation. Encephalopathy was confirmed by a neurologist in patients with abnormal level of consciousness manifested as confusion, delirium, agitation, seizures, or faulty cognition.

Statistical analysis

Categorical variables were reported as frequency (percentage), and continuous variables were expressed as mean \pm SD, or as median (interquartile range). Chi-Square test was used to compare categorical variables. To assess normally distributed and non-normally distributed continuous variables between two groups, independent samples t-test and Kruskal-Wallis test were applied, respectively. Multiple groups were compared using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test, as appropriate. Multivariate logistic regression analysis and adjusted odds ratios (aORs) were used to evaluate the predictive ability of perioperative glucose level on mortality and discharge disposition. A p-value < 0.05 was considered statistically significant. All analyses were performed with SPSS software version 22.0 (IBM Corp., Armonk, NY) and SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

A total of 1,582 patients were included in this 17-year study. The clinical characteristics of all enrolled patients are listed in [Table 1](#). The mean age was 57.6 \pm 14.9 years, 66.9% were males, the mean creatinine clearance rate (CrCl) was 93.7 \pm 44.4 ml/min, and 12.3% had diabetes mellitus (DM). Of all patients, 43.4% had Stanford type A dissection, 31.0% required emergency/urgent operation, 87.5% were performed with DHCA, and the mean operation time was 5.4 \pm 2.8 hours. The median (interquartile) ICU length of stay (LOS) was 7.2 days (4.0, 13.2) and median hospital LOS 12.0 (8.3, 19.0) days. In-hospital mortality occurred in 7.3% of patients, and 71.0% of patients were discharged home from the hospital.

Table 1: Characteristics of overall patients and patients stratified by preoperative and postoperative glucose respectively.

	Total Cases	Preoperative Glucose Level (mg/dl)			p-value	Postoperative Glucose Level (mg/dl)			p-value
		< 110	110-139	≥ 140 mg/dl		< 140	140-199	≥ 200 mg/dl	
Cases number (% total population)	1,582	978 (61.82%)	366 (23.14%)	238 (15.04%)		420 (26.55%)	947 (59.86%)	215 (13.59%)	
Age (years)	57.6 ± 14.9	56.4 ± 15.5	58.9 ± 13.9	60.1 ± 13.2	< 0.001	52.7 ± 16.0	59.0 ± 14.3	60.7 ± 13.0	< 0.001
Male	1,060 (66.9%)	652 (66.6%)	251 (68.4%)	157 (66.0%)	0.749	265 (62.9%)	646 (68.1%)	149 (69.3%)	0.132
BMI ^a	28.8 ± 6.5	28.1 ± 6.2	29.7 ± 6.5	30.5 ± 6.8	< 0.001	27.8 ± 5.8	29.1 ± 6.7	29.7 ± 6.1	0.001
CrCl ^b (ml/min)	93.7 ± 44.4	97.6 ± 45.9	91.0 ± 41.8	81.5 ± 39.5	< 0.001	97.6 ± 47.9	92.1 ± 43.0	92.9 ± 43.4	0.106
Baseline Medical Conditions									
DM	194 (12.3%)	78 (8.0%)	46 (12.6%)	70 (29.4%)	< 0.001	27 (6.4%)	118 (12.5%)	49 (22.8%)	< 0.001
HTN	1,129 (71.4%)	687 (70.2%)	261 (71.3%)	181 (76.1%)	0.206	291 (69.3%)	686 (72.4%)	152 (70.7%)	0.479
CAD	242 (15.3%)	144 (14.7%)	59 (16.1%)	39 (16.4%)	0.720	44 (10.5%)	150 (15.8%)	48 (22.3%)	< 0.001
COPD	263 (16.6%)	160 (16.4%)	72 (19.7%)	31 (13.0%)	0.094	67 (16.0%)	164 (17.3%)	32 (14.9%)	0.626
ESRD	80 (5.1%)	39 (4.0%)	21 (5.7%)	20 (8.4%)	0.016	18 (4.3%)	48 (5.1%)	14 (6.5%)	0.480
Surgical Variables									
Type A dissection	687 (43.4%)	304 (31.1%)	214 (58.5%)	169 (71.0%)	< 0.001	177 (42.1%)	399 (42.1%)	111 (51.6%)	0.033
Emergent/Urgent	491 (31.0%)	173 (17.7%)	172 (47.0%)	146 (61.3%)	< 0.001	129 (30.5%)	290 (30.6%)	73 (34.0%)	0.609
DHCA	1,385 (87.5%)	845 (86.4%)	328 (89.6%)	212 (89.1%)	0.209	358 (85.2%)	844 (89.1%)	183 (85.1%)	0.068
Operation time (hour)	5.4 ± 2.8	5.2 ± 2.4	5.7 ± 3.4	5.9 ± 3.1	< 0.001	5.4 ± 2.4	5.4 ± 2.9	5.7 ± 3.0	0.346
Pump time (minute)	156.5 ± 54.4	154.2 ± 56.4	160.4 ± 51.8	159.8 ± 49.6	0.112	160.1 ± 51.6	154.5 ± 54.6	158.5 ± 58.7	0.177
Clamp time (minute)	97.5 ± 40.4	96.7 ± 42.2	98.1 ± 38.1	100.0 ± 36.2	0.506	101.6 ± 41.2	95.7 ± 39.8	97.2 ± 41.1	0.044
Clinical Outcomes									
Ventilation Time (day)	1582	2 (1.3)	2 (1.6)	3 (2.7)	< 0.001	2 (1.4)	2 (1.4, 75)	2 (2.5)	0.023
Respiratory insufficiency ^c	445 (30.4%)	213 (23.0%)	130 (38.7%)	102 (50.2%)	< 0.001	120 (30.3%)	261 (29.4%)	64 (35.2%)	0.304
Arrhythmia ^c	577 (39.4%)	362 (39.1%)	124 (36.9%)	91 (44.8%)	0.180	136 (34.3%)	362 (40.8%)	79 (43.4%)	0.046
Acute kidney injury ^c	290 (19.8%)	148 (16.0%)	91 (27.1%)	51 (25.1%)	< 0.001	68 (17.2%)	172 (19.4%)	50 (27.5%)	0.014
Encephalopathy ^c	97 (6.6%)	49 (5.3%)	32 (9.5%)	16 (7.9%)	0.020	26 (6.6%)	56 (6.3%)	15 (8.2%)	0.632
Length of stay ^d	12.0 (8.3, 19.0)	11.3 (8.0, 17.2)	13.8 (9.0, 20.8)	14.8 (9.1, 20.8)	< 0.001	11.5 (8.0, 19.4)	12.3 (8.3, 18.7)	12.6 (8.5, 19.7)	0.445
ICU Length of stay ^d	7.2 (4.0, 13.2)	6.9 (3.8, 6.9)	8.0 (4.3, 8.0)	9.0 (5.1, 17.0)	< 0.001	6.9 (3.5, 11.8)	7.3 (4.0, 13.8)	8.2 (4.5, 13.9)	0.029
Discharge home	1125 (71.0%)	762 (77.9%)	234 (63.9%)	129 (54.2%)	< 0.001	320 (76.2%)	666 (70.3%)	139 (64.7%)	0.007
Discharge to long-term care	341 (21.6%)	165 (16.9%)	102 (27.9%)	74 (31.1%)	< 0.001	76 (18.1%)	222 (23.4%)	43 (20.0%)	0.072
In-hospital death	116 (7.3%)	51 (5.2%)	30 (8.2%)	35 (14.7%)	< 0.001	24 (5.7%)	59 (6.2%)	33 (15.3%)	< 0.001

Abbreviations: BMI: Body Mass Index; CAD: Coronary Artery Disease; CrCl: Creatinine Clearance; COPD: Chronic Obstructive Pulmonary Disease; DHCA: Deep Hypothermic Circulatory Arrest; DM: Diabetes Mellitus; ESRD: End Stage Renal Disease; OR: Operation

^aBMI is the weight in kilograms divided by the square of the height in meters; ^bCrCl was calculated using the Cockcroft-Gault equation: CrCl = $[(140 - \text{age}] \times \text{weight in kg} \times 0.85$ if female/ (serum creatinine $\times 72$); ^cStatistical analysis was performed in discharged patients (n = 1,466); ^dLOS was expressed as median (interquartile range).

The distribution of preoperative and postoperative glucose levels are shown in Figure 1. Postoperative glucose (161.7 ± 46.4 mg/dl) was higher than the preoperative glucose (111.3 ± 37.3 mg/dl) in this patient population ($p < 0.001$). The correlation between the two variables was assessed by Pearson correlation. The result showed that there was a small positive correlation between the blood glucose levels before and after the operation ($r = 0.116$, $p < 0.001$; Figure 2). The comparison of baseline characteristics among groups with different levels of preoperative glucose (< 110 mg/dl, 110 - 139 mg/dl, and ≥ 140 mg/dl) or postoperative glucose ($<$

140 mg/dl, 140 - 199 mg/dl, and ≥ 200 mg/dl) is shown in Table 1. Patients with higher perioperative glucose were older, had higher body mass index (BMI), lower creatinine clearance (CrCl), higher rates of preexisting DM, longer operation time, and higher frequency of emergency or urgent surgery.

Patients with higher preoperative glucose levels had higher rates of respiratory insufficiency, AKI, and encephalopathy in the postoperative phase. Patients with higher postoperative glucose were also more likely to experience AKI and develop arrhythmias. In looking

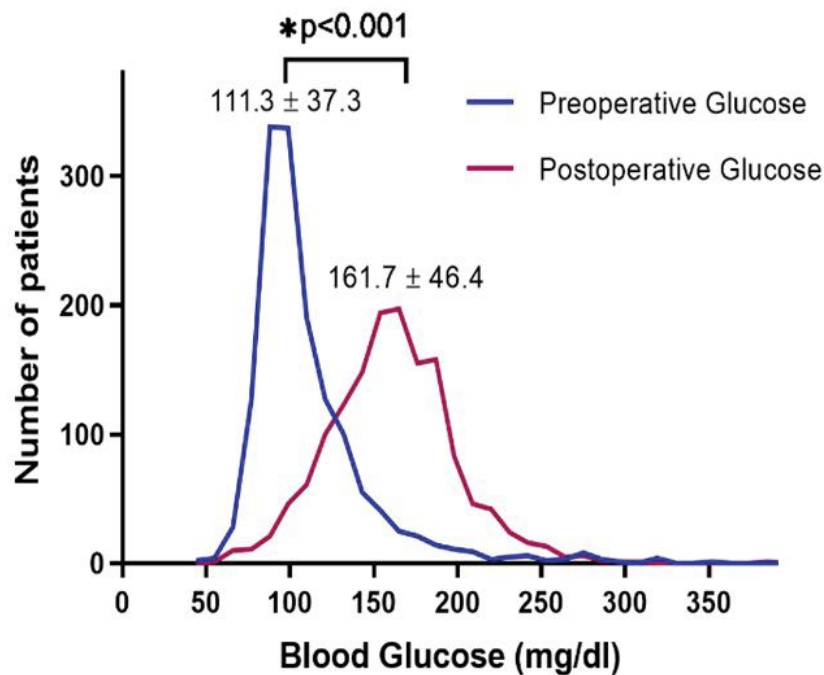


Figure 1: Distribution trend of average blood glucose perioperative.

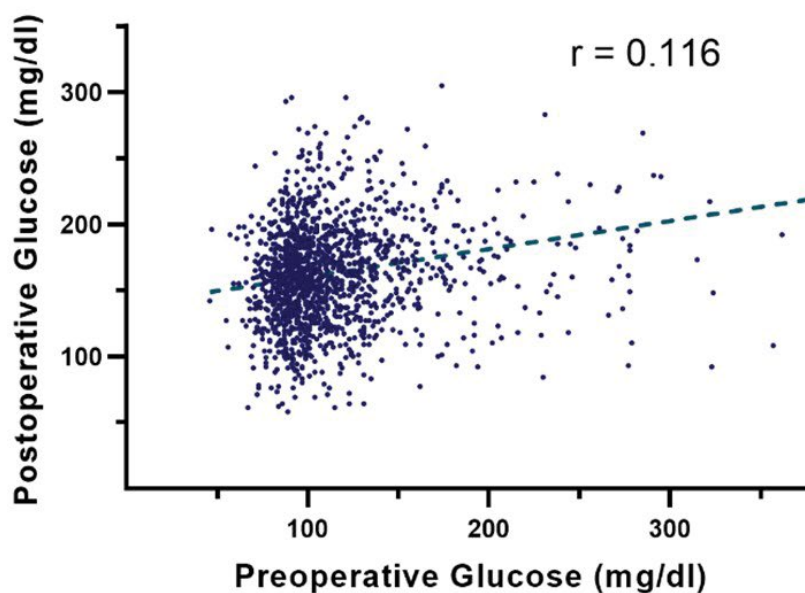


Figure 2: Potential weak correlation between preoperative and postoperative glucose levels ($r = 0.116$, $p < 0.001$).

at survival, patients with higher perioperative glucose levels had a higher risk of in-hospital death and lower rates of discharge to home.

The rates of discharged home and in-hospital death in different groups stratified by the combination of preoperative and postoperative glucose are summarized in Figure 3. Patients with preoperative glucose < 110 mg/dl and postoperative glucose < 140 mg/dl had the highest discharged home rate and lowest in-hospital mortality. As preoperative and postoperative glucose levels increased, in-hospital mortality increased and discharge to home rate decreased.

High preoperative (≥ 140 mg/dl) and postoperative (≥ 200 mg/dl) glucose are independent predictors for in-hospital mortality (preop OR = 1.98, 95% CI = 1.14-3.42, $p = 0.015$; postop OR = 2.53, 95% CI 1.37-4.70, $p = 0.003$) after adjusting for demographic factors (age, gender, BMI), diabetes mellitus history, creatinine clearance and surgical variables (emergency/urgent operation, DHCA, operation time, pump time and clamp time). Additionally, higher preoperative glucose levels (110-139 mg/dl and ≥ 140 mg/dl) are also related to lower incidence of discharging home compared to lower preoperative glucose < 110 mg/dl (preop OR = 0.68, 95% CI = 0.50-0.92, $p = 0.013$; postop OR = 0.60, 95% CI = 0.42-0.87, $p = 0.007$) (Figure 4). ICU LOS (9.0 days [5.1, 17.0]) and hospital LOS (14.8 days [9.1, 20.8]) were also statistically significant for patients with elevated

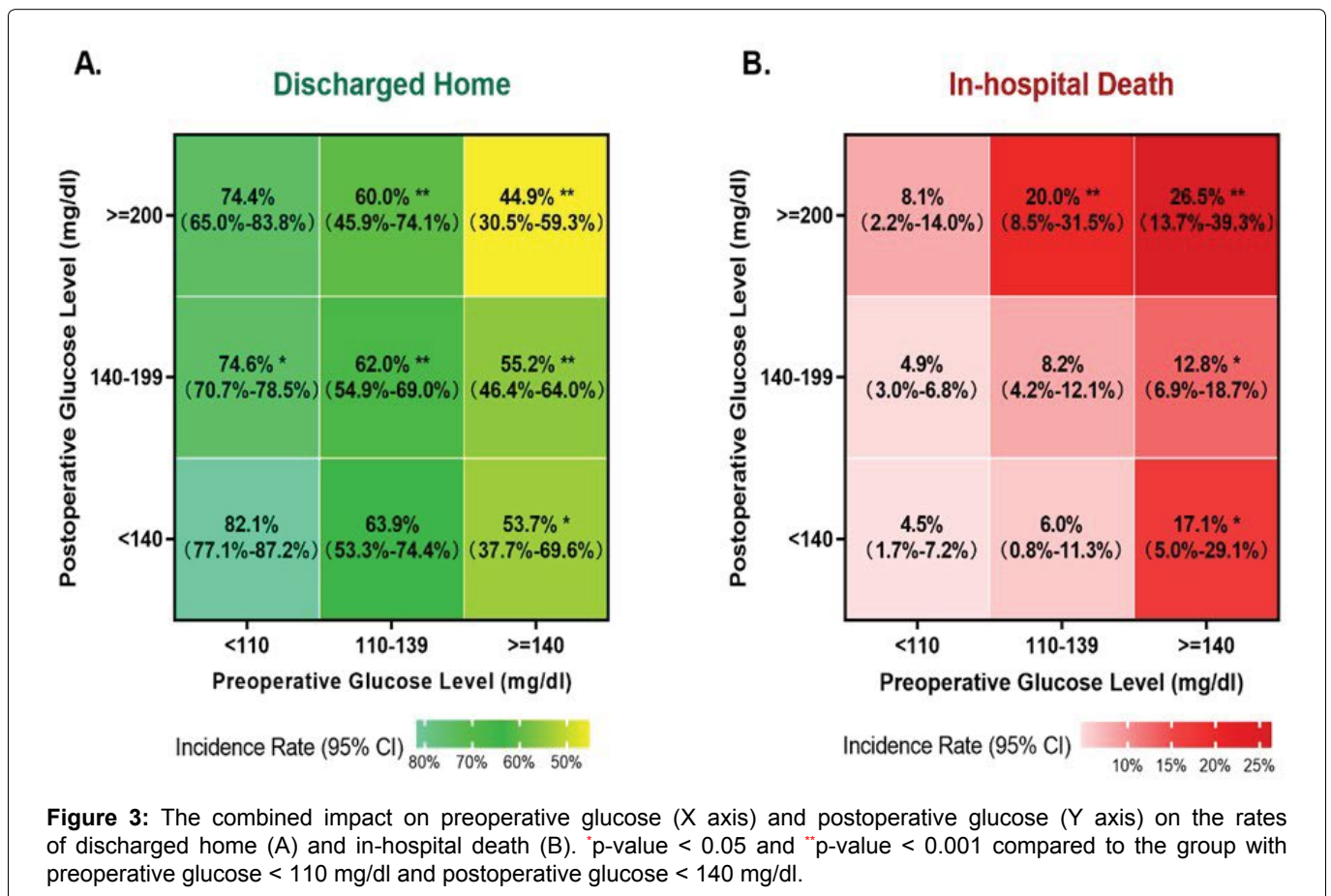
preoperative glucose > 140 mg/dL. ICU LOS and Hospital LOS were not statistically significant different for patients with elevated postoperative glucose.

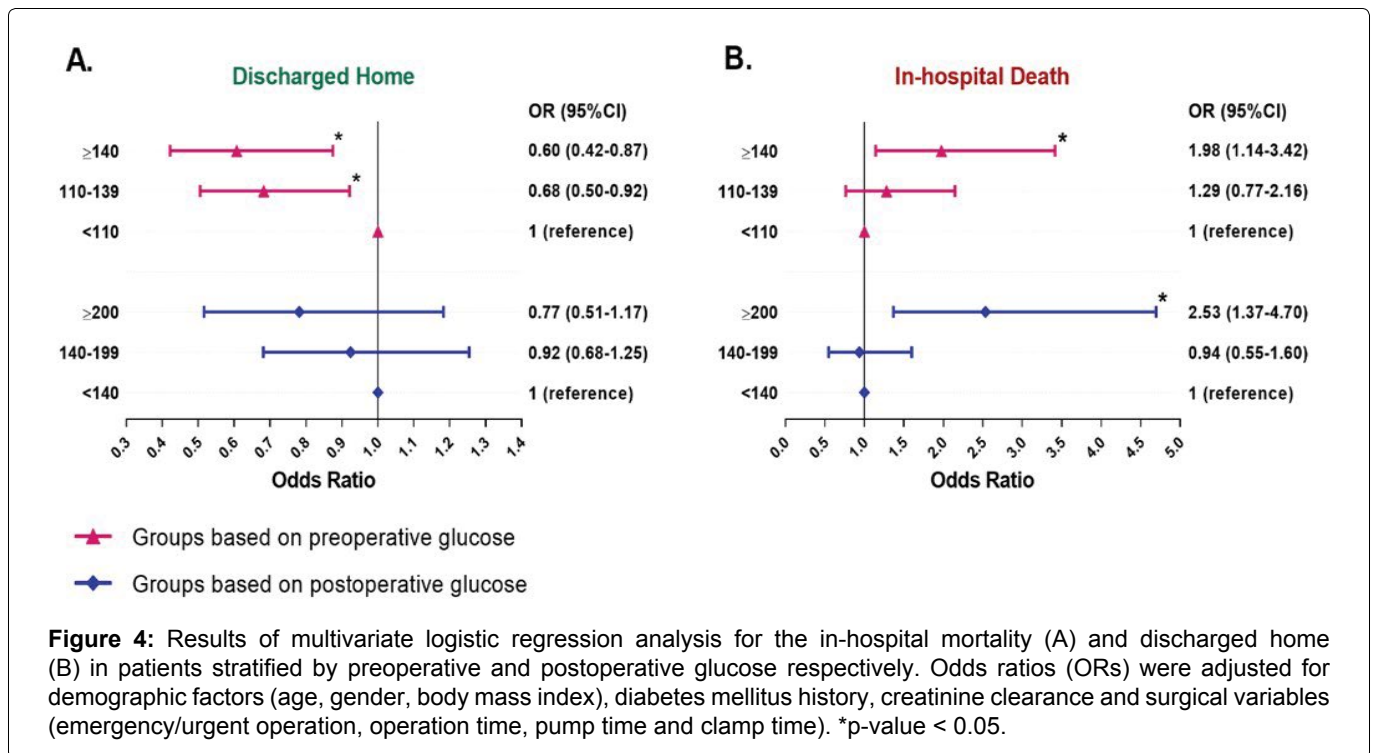
Discussion

Perioperative hyperglycemia was common in patients included in the study, despite standardized glycemic control management. In all, 16.3% of patients had preoperative glucose values higher than 140 mg/dl. Following surgery, 82.9% of patients had glucose values greater than 140 mg/dl, with 15.7% having values greater than 200 mg/dl.

Multiple factors determine the preoperative glucose of a patient, including comorbidities, the level of glucose control prior to hospitalization, disease severity, and home medications with DM patient [6] interestingly, this data suggests that it is unlikely that blood glucose after surgery is strongly associated with the preoperative glucose level. The study shows only a weak positive correlation between preoperative and postoperative blood glucose (Pearson's $r = 0.171$).

Postoperative glucose is primarily affected by surgical stress, operation time, surgery invasiveness, CPB, and DHCA [4,7-9]. Therefore, in addition to the clinical application of current and novel methods that have shown potential effectiveness [6,10], the advocacy of integrated management is critical to future glucose control.





Our data suggests that higher perioperative glucose is independently associated with higher rates of in-hospital mortality and lower rates of discharge to home, regardless of demographic factors, history of DM, creatinine clearance, or other surgical variables. This study is consistent with previous studies conducted in other types of cardiac surgery [2-4,11-14]. Thiele, et al. showed, via retrospective analysis, that admission blood glucose is correlated with increased morbidity and mortality among patients undergoing emergency CABG surgery [12]. In a retrospective analysis, Ascione, et al. showed that inadequate postoperative blood glucose control is a predictor of in-hospital mortality and morbidity [11].

There are several possible mechanisms that may explain this observation. First, hyperglycemia can enhance the glucose toxicity and oxidative stress reaction in the body, which can increase tissue damage and insulin resistance, a theory discussed by Li, et al. [14]. Second, high blood sugar may activate blood coagulation and promote osmotic diuresis, which, together, increase the risk of thromboembolism, ultimately leading to poor outcomes [15,16]. Additionally, hyperglycemia is associated with increased lipolysis and excess circulating free fatty acids, which are toxic to ischemic myocardium and may lead to damaged cell membranes in the myocardium, arrhythmias, calcium overload, increase myocardial oxygen demands and reduced contractility [15,17,18]. Other possible explanations include inflammation activation, the abolishment of intrinsic myocardial protective mechanisms, or increased infection [15,19,20]. From this evidence, it is reasonable to believe that hyperglycemia is not only a biomarker

of poor clinical outcomes but also, potentially, a strong contributor to poor clinical outcomes.

The current guidelines from the Society of Thoracic Surgeons recommends that diabetic patients maintain blood glucose concentrations ≤ 180 mg/dL before surgery and patients without diabetes have no recommended management [2]. In this study, we found that preoperative glucose ≥ 110 mg/dl is associated with longer ICU or hospital LOS, worse discharge status, and higher mortality (Table 1). After multivariate adjustment, preoperative glucose ≥ 110 mg/dl and preoperative glucose ≥ 140 mg/dl remained risk factors for in-hospital mortality-and these patients were less likely to be discharged to home (Figure 4). These results suggest that patients undergoing ascending aortic or aortic arch repair may benefit from more strict preoperative glucose control than currently recommended guidelines. Additionally, these results suggest that non-diabetic patients also need standardized blood glucose management prior to surgery.

Postoperative glucose in this study was measured immediately after surgery and, thus, it largely reflects intraoperative glucose management. A randomized trial by Gandhi, et al. evaluated the effects of intraoperative insulin in cardiac surgery patients, and their results showed no significant difference in primary outcomes between conventional group targeted to keep serum glucose < 200 mg/dl and intensive insulin therapy maintain serum glucose between 80 and 100 mg/dL [21]. However, we found that patients with postoperative glucose ≥ 200 mg/dl are more likely to have arrhythmia, AKI, LOS in ICU, in-hospital mortality and less likely to be discharged to home.

The strengths of this study include that it is a single center study, therefore, there is less variability of care between surgeons, anesthesiologists, and ICU care based on hospital volume. Additionally, this was a large study, with 1,582 patients, who underwent specifically ascending aorta and aortic arch repair surgery, many with deep hypothermic circulatory arrest.

One limitation is that it is a retrospective review, causing it to be subjected to selection bias. Another limitation is the inclusion of both diabetic and non-diabetic patients, as it is possible that these patients should be looked at in separate cohorts. Further analysis is likely required to determine the optimal glycemic goal in different patient populations and, more specifically, between patients who are diabetic vs. those with no history of DM. Additionally, this study spans 16 years and it is possible the surgical, anesthetic, and critical care techniques have changed over the course of this time, confounding our results.

With limited data from randomized control trials on the benefits of stringent intraoperative glucose control, the authors recommend maintaining blood glucose within a relatively loose range avoiding hypoglycemia [22]. While this study does not prove causality between perioperative hyperglycemia and clinical outcomes, our findings highlight the necessity to further examine the role of hyperglycemia in risk-adjusted outcomes and present an important potential opportunity to improve outcomes for patients undergoing ascending aorta and aortic arch repair surgery.

The ideal range for glycemic control remains unclear, and may differ across populations. However, given the results of this study, as well as prior studies that demonstrate a strong association with hyperglycemia and adverse events, the importance of perioperative glucose control, especially for patients with an extremely high level of glucose, should continue to be emphasized. Additionally, it is possible that guidelines should differentiate between different patient populations regarding blood glucose perioperatively.

Continuous blood glucose monitoring by using artificial endocrine pancreas intraoperatively is revealed by a spike in glucose levels immediately after DHCA on cardiopulmonary bypass [23]. Hopefully, continuous blood glucose monitoring can be used routinely in the perioperative period in order to help better control glucose levels and reduce complications associated with hyperglycemia.

Weakness on this study is we don't have completed information of Preoperative HbA1c levels so that we are unable to estimate how good glucose are controlled before the operation in knowing and unknowing patients with DM. Further studies are needed. However, this study is mainly analysis of stress induced

hyperglycemia, perioperative glucose control associated clinical outcome.

Conclusion

Among patients undergoing ascending aorta and aortic arch repair surgery, higher blood glucose levels before and after surgery are independent risk factors for in-hospital mortality, prolonged endotracheal intubation, multiple adverse clinical outcomes, and less likely to be discharged to home. Higher blood glucose is also associated with prolonged ICU LOS and hospital LOS. Further large-scale, well-designed prospective or clinical trials are required to elucidate the causality and confirm the optimal glycemic goal.

Funding

No funding was obtained for this study.

IRB Approval

HSC-MS-18-0371, on June 6, 2018.

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Citation: Bradley S, Markham T, Yan S, Mshvildadze M, Sandhu HK, et al. Perioperative Hyperglycemia: An Independent Risk Factor for Adverse Outcomes in Patients Undergoing Ascending Aorta Repair. *Transl Perioper Pain Med* 2023; 10(3):552-559

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Additional publication details

Journal short name: Transl Perioper Pain Med

Received Date: September 08, 2023

Accepted Date: November 14, 2023

Published Date: November 16, 2023