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Risk factors and impact of postoperative hyperglycemia in nondiabetic patients after cardiac surgery

A prospective study

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Abstract

Cardiac surgery induces a significant inflammatory hypermetabolic stress response, resulting in postoperative hyperglycemia in both preoperatively diabetic and nondiabetic patients. Such postoperative hyperglycemia has been associated with adverse outcomes in surgery and postsurgical recovery. Yet, while diabetes is a known risk factor for postoperative hyperglycemia, predictors of postoperative hyperglycemia among nondiabetics in the local Southeast Asian population remain unknown.

We aim to investigate the predictors and outcomes associated with hyperglycemia after cardiac surgery among nondiabetics in the local Southeast Asian population. We analyzed data from 1602 nondiabetic adult patients undergoing elective cardiac surgery, from 2008 to 2010 at the 2 main heart centers in Singapore.

Nondiabetic patients who developed postoperative hyperglycemia tended to be women, older, more obese, and hypertensive. Higher body mass index (BMI), age, aortic cross-clamp time, and blood transfusion were identified as independent risk factors of postoperative hyperglycemia. Postoperative hyperglycemia was also significantly associated with postoperative cardiac arrhythmias (26.9% vs 15.0%, $P < .001$), acute kidney injury (30.0% vs 20.1%, $P < .001$), longer intensive care unit (ICU) stay (46.7 ± 104.1 vs 37.2 ± 76.6 hours, $P = .044$) and longer hospitalization (11.5 ± 12.2 vs 9.6 ± 8.0 days, $P < .001$).

Our study identified aortic cross-clamp time and blood transfusion as independent risk factors of postoperative hyperglycemia after cardiac surgery in nondiabetics. Similar to other studies, higher BMI and age were independent risk factors for postoperative hyperglycemia. Postoperative hyperglycemia was also associated with adverse perioperative outcomes and should thereby be avoided by treating modifiable risk factors identified in this study including reducing blood transfusion and aortic cross-clamp time. Our findings contribute to early risk stratification of nondiabetic patients who are at increased risk of postoperative hyperglycemia.

Abbreviations: ADQI = acute dialysis quality initiative, AKIN = acute kidney injury network, AKI = acute kidney injury, ARF = acute renal failure, ACE = angiotensin converting enzyme, ACC = aortic cross-clamp, BMI = body mass index, CPB = cardiopulmonary bypass, CI = confidence interval, CABG = coronary artery bypass graft, DHEA = dehydroepiandrosterone, eGFR = estimated glomerular filtration rate, EuroSCORE = European System for Cardiac Operative Risk Evaluation, Hct = hematocrit, HDU = high dependency Unit, ICU = intensive care unit, IGF-1 = insulin-like growth factor 1, IRB = Institutional Review Board, LVEF = left ventricular ejection fraction, OR = odds ratio, SIRS = systemic inflammatory response syndrome.

Keywords: outcomes, postoperative hyperglycemia, predictors

1. Introduction

Cardiac surgery induces a significant endocrine and inflammatory hypermetabolic stress response in patients, resulting in postoperative hyperglycemia.[1,2] Such postoperative hyperglycemia has been associated with adverse postsurgical outcomes, increased risk of postoperative mortality, higher incidence of infection and renal failure, and increased risk of cardiovascular, respiratory, neurologic, and infectious morbidity.[1,3–5]

Risk factors predicting hyperglycemia in nondiabetics include black ethnicity, female sex, immunosuppression, higher body mass index (BMI), renal failure, hypertension, and hypercholesterolemia.[6–8] However, the perioperative predictors of hyperglycemia after cardiac surgery in nondiabetic patients in a South East Asian multiethnic population and outcomes of hyperglycaemia are unknown. Thus, we aim to study the predictors and outcomes of hyperglycemia after cardiac surgery in this population.

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2. Methods

2.1. Study Population

With SingHealth Centralised Institutional Review Board (CIRB) [IRB number 2008/137/D] approval and written informed consent from the patients before enrollment, a total of 3008 adult patients undergoing elective coronary artery bypass graft (CABG) cardiac surgery at the 2 main heart centers in Singapore were prospectively enrolled in this study. Of this, 1406 patients (46.7%) were excluded from the study as they had preoperative diabetes. Patients with a known history of diabetes, preoperative random plasma glucose >200 mg/dL or taking antidiabetic medications, or hemoglobin A1c (HbA1c) >6.5% were excluded a priori. Of the remaining 1602 nondiabetic patients included, 56.1% (n=898) developed postoperative hyperglycemia and 43.9% (n=704) were postoperatively normoglycemic (Fig. 1).

Postoperative hyperglycemia which is the primary outcome was defined as a blood glucose level of >10 mmol/L (approximately 180 mg/dL) within the first 48 perioperative hours.[8] The remaining patients who were included were considered normoglycemic for the purposes of this study.

Perioperative clinical practices and surgical management followed strict international standards. Anesthesia was induced with intravenous induction agents (propofol or etomidate) and maintained with a balanced anesthesia regime using low-dose fentanyl (10–20 $\mu g\,kg^{-1}$) in addition to volatile agents (primarily sevoflourane). Conventional cardiopulmonary bypass (CPB) circuits with heat exchangers, roller pumps, membrane oxygenators, arterial blood filters, venous reservoirs, and cardiotomy suction were utilized. Typically, 1300 to 1400 mL of prime was used in the CPB circuits. Perfusion targets include a hematocrit of >22%, mild-to-moderate hypothermia (32–35 °C), nonpulsatile flow rate of 2.2 to 2.4 $L\,min^{-1}\,m^{-2}$, mean arterial pressure of 50 to 70 mm Hg, glucose levels of below 10 mmol/L, and activated clotting times of >400 seconds. Cold blood cardioplegia was used to achieve myocardial protection. Aprotinin was not utilized in any patients.

All patients were kept to a tight baseline blood glucose control of within a range of 4 to 10 mmol/L, in accordance with hospital protocol and the "Society of Thoracic Surgeons Practice Guideline series: Blood Glucose Management During Adult Cardiac Surgery."[9] In line with hospital protocol, glycemic targets were strictly adhered to via insulin infusion and monitoring every 2 to 4 hours or more frequently if required, up to the first 48 hours.

Data extracted from the patients were chosen a priori and include patient characteristics, risk factors, surgical data, and postoperative outcomes up to 30 days postsurgery including intensive care unit (ICU) mortality, readmission to ICU, length of stay in ICU, length of stay in high dependency unit (HDU), new onset cardiac arrhythmia, cardiac failure, cardiac tamponade, postoperative infections, and length of hospitalization.

Perioperative outcomes were defined and categorized according to the ICD-10 coding (the 10th revision of the International Statistical Classification of Diseases and Related Health Problems) and noted from patient discharge summaries.

Acute kidney injury (AKI) was determined based on the acute kidney injury network (AKIN) criteria and defined as an absolute increase in serum creatinine of ≥26.4 mmol/L, and/or a ≥50% increase in the serum creatinine to the peak postoperative from the preoperative serum creatinine. The estimated glomerular filtration rate (eGFR) was calculated via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which has been previously validated in the local population.[10]

Acute renal failure (ARF) was defined according to the definition by the acute dialysis quality initiative (ADQI) RIFLE classification.[11] Accordingly, a threefold increase or ≥350 μmol/L increase in serum creatinine with an acute rise of ≥44 μmol/L, a decrease in >75% of GFR or urine output of <0.5 mL/kg/h for >24 hours or anuria for >12 hours was considered as ARF. Additionally, loss of kidney function, which required dialysis lasting longer than 4 weeks was also considered as ARF.

In accordance with the "Definitions of Terms of The Society of Thoracic Surgeons National Cardiac Surgery Database,"[12] an infection was considered present if a wound was opened with excision of tissue (I&D), there was a positive culture, or the patient was treated with antibiotics. This included infections that were sternum-superficial (skin, subcutaneous tissue), sternum-deep (muscle, mediastinum, bone), leg (incision site), IABP site, and septicemia (requires positive blood cultures).

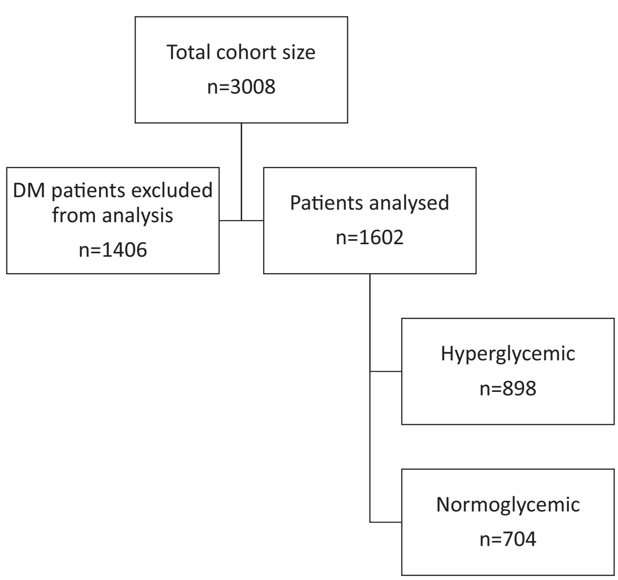

Figure 1. Flowchart of study cohort.

Table 1

Clinical characteristics and postoperative hyperglycemia after cardiac surgery.

Perioperative variables	All (n=1602)	Hyperglycemic (n=898)	Normoglycemic (n=704)	*P*-value
Preoperative variables				
Female	18.4 (295)	20.3 (182)	16.1 (113)	.031
Weight, kg	66.1±12.3	66.2±12.3	66.0±12.4	.753
Height, m	163.9±8.3	163.4±8.5	164.5±8.0	.008
BMI, kg/m^2	24.6±4.0	24.7±4.1	24.3±3.9	.031
Glucose, mmol/L	5.9±1.8	6.0±2.0	5.8±1.4	<.001
Age, y	58.1±11.6	59.6±10.8	56.2±12.3	<.001
Chinese	72.3 (1159)	71.2 (639)	73.9 (520)	.513
Malay	14.7 (235)	15.0 (135)	14.2 (100)	
Indian	7.2 (116)	8.0 (72)	6.2 (44)	
Others	5.7 (92)	5.8 (52)	5.7 (40)	
Anemia	20.7 (332)	22.5 (202)	18.5 (130)	.048
Atrial fibrillation	12.0 (192)	13.1 (118)	10.5 (74)	.108
Hypertension	63.4 (1016)	65.3 (586)	61.1 (430)	.085
Renal impairment	8.6 (138)	9.0 (81)	8.1 (57)	.513
Dialysis	2.2 (35)	1.9 (17)	2.6 (18)	.367
LVEF <30	6.2 (100)	6.8 (61)	5.5 (39)	.307
History of previous cardiac surgery	3.2 (51)	3.3 (30)	3.0 (21)	.686
Serum creatinine >200 μmol/L	2.3 (37)	1.9 (17)	2.8 (20)	.210
EuroSCORE (logistic)	3.6±5.0	4.0±5.8	3.1±3.7	<.001
Beta blockers	68.1 (1089)	69.2 (619)	66.9 (470)	.326
ACE inhibitors	42.1 (673)	43.7 (392)	40.0 (281)	.140
eGFR calculator	81.5±22.6	80.1±21.9	83.3±23.3	.006
Intraoperative variables				
Bypass time, min	112.3±60.0	119.3±62.5	103.5±55.4	<.001
Aortic cross-clamp time, min	66.4±42.9	103.5±55.4	71.6±45.0	<.001
Intraoperative blood transfusion	24.7 (395)	30.2 (271)	17.6 (124)	<.001
Highest intraoperative glucose	8.1±5.3	8.3±5.2	7.8±5.5	.051
Lowest intraoperative glucose	6.2±3.4	6.4±3.4	6.0±3.3	.060
Highest 24h glucose	10.4±2.2	11.7±1.9	8.6±1.0	<.001
Highest 48h glucose	8.4±2.1	8.9±2.3	7.7±1.2	<.001
Nadir Hct <22	20.9 (327)	24.4 (215)	16.4 (112)	<.001
Nadir Hct	24.9±4.1	25.5±4.2	24.4±4.0	<.001

Data are mean±SD or % (number).

ACE=angiotensin converting enzyme; BMI=body mass index;EuroSCORE=European System for Cardiac Operative Risk Evaluation;eGFR=estimated glomerular filtration rate; Hct=hematocrit; LVEF=left ventricular ejection fraction.

2.2. Statistical Analysis

All perioperative data were prospectively collected and collated in a secure central database. Full time personnel who were blinded to the study details analyzed the outcomes.

For continuous variables comparisons between patients with and without postoperative hyperglycemia were carried out using the student *t* test. Comparison of categorical variables were carried out via chi-squared analysis.

The association of the preoperative patient characteristics with postoperative hyperglycemia was then evaluated using logistic regression analysis. Significant patient characteristic and surgical risk factors were added to the model, and non-significant covariates were removed from the multivariate analysis in a stepwise manner. All statistical analyses were performed using IBM SPSS v.22.0 (SPSS IBM, NY); significance was judged at $P=.05$.

3. Results

The average age of patients included was 58.1±11.6 years and most patients were men (81.6%, n=1307) and hypertensive (63.4%, n=1016). Hyperglycemia occurs in 56.1% (n=898) of nondiabetic patients undergoing cardiac surgery (Fig. 1). They tended to be women, older, anemic, more obese, present with preoperative myocardial infarction, have a higher European System for Cardiac Operative Risk Evaluation (EuroSCORE) logistic, higher preoperative glucose levels, lower nadir hematocrit, and received intraoperative blood transfusion. These patients also had longer cardiopulmonary bypass (CPB) and aortic cross-clamp (ACC) times (Table 1).

On multivariate analysis, BMI (odds ratio [OR] 1.052, 95% confidence interval [CI] 1.025–1.080, $P<.001$), age (OR 1.028, 95% CI 1.019–1.038, $P<.001$), ACC time (OR 1.005, 95% CI 1.003–1.008, $P<.001$), and intraoperative blood transfusion (OR 1.708, 95% CI 1.323–2.206, $P<.001$), were identified as independent risk factors for postoperative hyperglycemia (Table 2).

Patients with postoperative hyperglycemia had a higher incidence of postoperative cardiac arrhythmias (26.9% vs 15.0%, $P<.001$) and acute kidney injury (30.0% vs 20.1%, $P<.001$). They also had longer ICU stays (46.7±104.1 vs 37.2±76.6 hours, $P=.044$), longer HDU stays (44.6±78.1 vs 38.0±36.4 hours, $P=.040$) and longer hospitalization (11.5±12.2 vs 9.6±8.0, $P<.001$) (Table 3).

Table 2

Multivariate logistic regression analysis of significant patient characteristics/variables and the incidence of postoperative hyperglycemia.

Factor	*P*-value	OR	95.0% CI Lower	95.0% CI Upper
BMI	<.001	1.052	1.025	1.080
Age	<.001	1.028	1.019	1.038
Aortic cross-clamp time	<.001	1.005	1.003	1.008
Blood transfusion	<.001	1.708	1.323	2.206
Lowest Hct	.065	0.973	0.945	1.002

BMI = body mass index, CI = confidence interval; OR = odds ratio.

4. Discussion

Hyperglycemia occurred in 56.1% of nondiabetic patients undergoing cardiac surgery in our cohort as compared with 39.7% seen in similar Western cohort studies.[8] We postulate that this is because patients of Asian origin have a higher insulin resistance at baseline as compared with those of Western origin. Other studies have shown that Asians, especially Asian Indians are predisposed to hyperglycemia as a result of higher insulin resistance.[13,14] This is due to genetic factors and behavioral factors such as diet, in turn likely causing Asian patients to develop an exaggerated hyperglycemic stress response to cardiac surgery,[15–17] accounting for the significantly higher rates of postoperative hyperglycemia among our Asian nondiabetics as compared with similar Western cohorts.

We identified age, increased BMI, increased aortic cross-clamp time, and intraoperative blood transfusion as independent risk factors for postoperative hyperglycemia in our Southeast Asian population.

Similar to other reported studies, increased age is associated with postoperative hyperglycemia after surgery. This is likely due to the decreased insulin sensitivity associated with aging, as a result of increased abdominal fat mass, mitochondrial dysfunction, lower insulin-like growth factor 1 (IGF-1) and dehydroepiandrosterone (DHEA) hormone levels and increased oxidative stress and inflammation.[18]

Despite Asians having a lower mean BMI than Western populations, BMI was still identified as an independent risk factor for postoperative hyperglycemia in our study (like similar Western population studies). We postulate that this is due to differences in fat distribution between the populations. There is an increased pro-inflammatory central adiposity and higher incidence of metabolic syndrome in Asians (unlike Western population) which could lead to an exaggerated hyperglycemic stress response and insulin resistance[19–21] in response to surgical stress despite the lower mean BMI amongst Asians.

Unlike previous studies, we demonstrate that longer ACC time is associated with postoperative hyperglycemia. Aortic cross clamping increases surgical stress and ischemic duration in patients, thus increasing release of stress hormones such as glucogenic catecholamines, glucagon, and cortisol into the circulation, as well as causing cortisol-induced insulin resistance by decreasing insulin receptors in hepatic and peripheral tissues,[22] leading to hyperglycemia. Although the mean ACC time in our population is similar to that in other Western population studies[8] we postulate that it was an independent risk factor in our study and not in those studies due to the exaggerated surgical stress response in our Asian population.

Hyperglycemia has been associated with longer CPB time due to the insulin resistance that accompanies surgical intervention, resulting in poorer patient outcomes.[23] Although we found that CPB time was higher in hyperglycemic patients ($P < .001$) on univariate analysis, CPB time was not a statistically significant predictor of hyperglycemia on multivariate analysis. In contrast, ACC time was identified as a significant predictor of hyperglycemia in our study (OR 1.005, 95% CI 1.003–1.008, $P < .001$). Both CPB time and ACC time have been shown to induce an inflammatory response and predispose patient to hyperglycemia via increasing plasma concentration of MPO and IL-8 inflammatory cytokines.[24] However, in addition, longer ACC time (and not CPB time) has been shown to further induce an inflammatory response by increasing plasma concentrations of MCP-1, leukocyte counts, and lowering concentration of regulated on activation, normal T cell expressed and secreted.[24] We postulate that in this way, longer ACC time (and not CPB time) is an independent risk factor for postoperative hyperglycemia.

Intraoperative blood transfusion was also identified as an independent risk factor of postoperative hyperglycemia. In addition to an ongoing systemic inflammatory response induced by cardiac surgery, allogenic blood transfusions further aggravate the systemic inflammatory response by increasing the levels

Table 3

Clinical outcomes and postoperative hyperglycemia after cardiac surgery.

Perioperative variables	All (n = 1602)	Hyperglycemic (n = 898)	Normoglycemic (n = 704)	*P*-value
Outcomes and complications				
Cardiac arrhythmia	21.6 (346)	26.9 (241)	15.0 (105)	<.001
Cardiac failure	0.3 (5)	0.4 (4)	0.1 (1)	.391
Cardiac tamponade	1.2 (16)	1.4 (11)	0.9 (5)	.610
Postoperative infection	1.4 (23)	1.3 (12)	1.6 (11)	.833
AKI	25.7 (410)	30.0 (269)	20.1 (141)	<.001
Acute renal failure	1.3 (20)	1.7 (15)	0.7 (5)	.084
ICU mortality	1.7 (27)	2.2 (20)	1.0 (7)	.057
Readmission to ICU	3.5 (55)	3.8 (34)	3.0 (21)	.366
Length of stay in ICU, d	42.5 ± 93.1	46.7 ± 104.1	37.2 ± 76.6	.044
Length of stay in HDU, d	41.7 ± 63.4	44.6 ± 78.1	38.0 ± 36.4	.040
Length of hospitalisation, days	10.6 ± 10.6	11.5 ± 12.2	9.6 ± 8.0	<.001

Data are mean ± SD or % (number).

AKI = acute kidney injury; HDU = high dependency unit; ICU = intensive care unit.

of circulating inflammatory mediators.[25] Furthermore, transfusion of blood products cause a systemic inflammatory response syndrome (SIRS),[25] which increases insulin resistance and secretion of stress hormones, causing stress hyperglycemia.[26]

Previous studies have shown that blood transfusion in thalassemia patients causes acute increases in serum ferritin and hemoglobin which contribute to an increase in insulin resistance.[27] We postulate that this could partly account for the development of postoperative hyperglycemia among our patients who received blood transfusions, given the relatively high prevalence of thalassemia in Asian populations.

However, nadir hematocrit was not identified as an independent risk factor of postoperative hyperglycemia, unlike other Western cohort studies.[28] A low nadir hematocrit has been suggested to cause excessive hemodilution and a subsequent increase in sympathetic autonomic response, which in turn further increases the release diabetogenic hormones such as cortisol, catecholamines, and glucagon, and inhibits insulin secretion, thus increasing the risk of postoperative hyperglycemia in patients with low nadir hematocrit.[28] We postulate that the liberal blood transfusion to maintain a relatively high nadir hematocrit protects against this hyperglycemic effects of low nadir hematocrit in our patient cohort. However, this liberal blood transfusion itself predisposes our patients to postoperative hyperglycemia due to the inflammatory effects of blood transfusion as described earlier.[25,26] As such, blood transfusion, and not nadir hematocrit, was found to be independently associated with postoperative hyperglycemia in our cohort.

Hyperglycemia after cardiac surgery is also associated with poor cardiac, renal, and hospitalization outcomes as described above. Postsurgical hyperglycemia increases production of reactive oxygen species targeting the I_{Kr} ion channel, thus causing QTc interval prolongation and cardiac arrhythmias,[29] as observed here. Acute postoperative hyperglycemia also causes acute kidney injury (AKI) by inducing neutrophil, monocyte, mitochondrial and renal endothelial dysfunction, as well as proinflammatory cytokine production.[30] Atherosclerosis is another complication of hyperglycemia, causing multiorgan system damage,[31] which could result in the longer ICU stay, HDU stay, and hospitalization length associated with postoperative hyperglycemia here.

A limitation of our study was the time period of data which was collected, which was from 2008 to 2010 and sample size analysis was not performed. However, we believe that the sample size is significant and key associations are likely to be unchanged and still relevant. Furthermore, the same factors that predispose patients to develop hyperglycemia may also contribute to the poorer outcomes in those patients. Thus, it cannot be determined, from this study, whether it is the postoperative hyperglycemia itself or its risk factors that cause an increased rate of complications after cardiac surgery. Nonetheless, these findings support the need for tight glycemic control in patients undergoing cardiac surgery.

The risk factors identified also enable better prediction of patients who are likely to get postoperative hyperglycemia, enabling better glycemic control, and clinical management of these patients. The identification of clinical and perioperative predictors of postoperative hyperglycemia, specific to Southeast Asian patients will enable clinicians to refine the risk profile specific to the Southeast Asian population and bring personalized risk stratification closer to reality.

Furthermore, our study shows that postoperative hyperglycemia is indeed associated with poorer outcomes in the local population, further supporting the need to predict at-risk patients and more closely control and manage they glycemic levels.

In conclusion, higher BMI, age, longer aortic cross-clamp time, and intraoperative blood transfusion are independent risk factors of postoperative hyperglycemia after cardiac surgery, which is in turn associated with increased risk of adverse outcomes, including postoperative cardiac arrhythmia, AKI, and length of stay. Postoperative hyperglycemia should thereby be avoided by treating modifiable risk factors identified in this study including reducing blood transfusion and aortic cross-clamp time.

Author contributions

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Writing – review & editing: Vikaesh Moorthy, Ming Ann Sim, Lian Kah Ti, Sophia Tsong Huey Chew.

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