Original Article

Variations of Perioperative Cardiac Surgery Blood Glucose and Glycemic Variability in Diabetes and Non-Diabetes

Wacharin Sindhvananda, MD, PhD[1], Muanchanok Surit, MD[2]

[1] Department of Anesthesiology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

[2] Department of Anesthesiology, Faculty of Medicine, Naresuan University, Phitsanulok, Thailand

Background: Not only perioperative high blood glucose but also glycemic variability (GV) is significantly associated with mortality in cardiac surgery. Perioperative hyperglycemia in diabetes (DM) patients is well-known, however, there is less information in non-diabetes (non-DM) patients.

Objective: The present study objectives were to show the variations of perioperative blood glucose, to compare the characteristics, frequency, and severity of hyperglycemia, and to compare GV between non-DM and DM undergoing cardiac surgery.

Materials and Methods: A prospective observational study was conducted between January 2016 and July 2018. Cardiac-surgery patients, age 20 to 80 years, undergoing cardiopulmonary bypass (CPB) were recruited. The differentiation between the DM and the non-DM was based on standard diagnosis. Perioperative blood glucose was measured every 30 minutes by POCT-glucose and controlled by insulin based on the institutional protocol. GV measures were standard deviation (SD), coefficient of variance (CV), and mean absolute glucose (MAG). Characteristics of blood glucose changes were demonstrated, which were related to events or surgical procedure. Comparison of blood glucose, GV, and events of hyperglycemia were carried out using Student t-test or chi-square test as appropriate.

Results: Perioperative hyperglycemia were 60% in DM and 30% in non-DM. Hyperglycemia started at the beginning of the operation in DM and in late CPB in non-DM. Inotropes or vasopressors was associated with sharp shooting increases of blood glucose. Hyperglycemia with more severity was commonly found during the early postoperative period in both DM and non-DM. The GV of DM was higher than in non-DM. The average MAG were 31.98 and 28.05 mg/dl/hour in DM and non-DM, which was the only measure that could significantly differentiate DM and non-DM.

Conclusion: Perioperative hyperglycemia in cardiac surgery occurred in both non-DM and DM despite the treatment by insulin infusion. Inotropes or vasopressors infusion was significantly related to a sudden hyperglycemia. MAG might be a better monitor of GV than SD and CV during cardiac surgery.

Trial registration: Thai Clinical Trials Registry, TCTR 20190411005

Keywords: Hyperglycemia, Glycemic variability, Mean absolute glucose, Cardiac surgery

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Surgical stress and anesthesia lead to glucose metabolic disturbances. Perioperative hyperglycemia has been reported in up to 80% in cardiac surgery[1]. Perioperative hyperglycemia is related to mitochondrial injury, endothelial dysfunction, immune dysregulation, and superoxide generation[2]. As a result, perioperative hyperglycemia is significantly associated with mortality in cardiac surgery[3]. Due to the known impairment of glucose regulation, perioperative hyperglycemia in diabetes (DM) is well known and under close surveillance. On the contrary, perioperative hyperglycemia is not as well known in non-diabetes (non-DM). There are only a few reports demonstrating the magnitude of hyperglycemia in non-DM during surgery[4,5]. Consequently, perioperative hyperglycemia in non-DM should be studied further and be more documented.

Correspondence to:

Sindhvananda W.

Department of Anesthesiology, Faculty of Medicine, Chulalongkorn University, Pathumwan, Bangkok 10330, Thailand.

Phone: +66-86-7858710, **Fax**: +66-2-6494000 ext. 81515

Email: wacharins@hotmail.com

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In cardiac surgery, many surgical factors are associated with the rising of blood glucose. Tight control by insulin infusion has been claimed to be an effective method to control hyperglycemia. Therefore, insulin regimen was carefully established by individual institutions following a recent target of blood glucose (140 to 180 mg/dl) during cardiac surgery[2,6]. However, because of the tight blood glucose control, more events of hypoglycemia, up to 20% in DM, had been reported[7]. Additionally, questions remain on how the tight blood glucose control affects the non-DM.

Recently, the glycemic variability (GV) has been looked at. GV is more significantly related to postoperative morbidity and mortality than high blood glucose[8,9]. To get good post-cardiac surgery outcomes, the target blood glucose level together with GV should be examined. Because most of the previous studies focused only blood glucose level, there has been less information regarding GV in cardiac surgery.

Based on the above information, the three objectives of the present study were to demonstrate the variations of blood glucose during cardiac surgery in non-DM and DM, to compare characteristics, frequency, and severity of hyperglycemia, and to compare GV between non-DM and DM undergoing cardiac surgery.

Materials and Methods

Patients recruitment and study protocol

After getting Naresuan University Institutional Review Board (NU-IRB, No.569/58) approval, a prospective observational study was conducted in patients who were set for open heart surgery undergoing cardiopulmonary bypass (CPB) at Naresuan University Hospital between January 2016 and July 2018. The clinical trial registration number was TCTR 20190411005. Inclusion criteria were patients between the age of 20 and 80 years and undergoing elective valvular heart surgery (VH) or coronary artery bypass graft (CABG). Exclusion criteria were DM type I, previous inotropes or vasopressors infusion, on intra-aortic balloon pump (IABP), and having a recent steroid administration. After informing and discussion regarding the research issues, written informed consents were requested and signed from all the recruit participants.

The enrolled sample were divided into DM and non-DM group. To reduce bias, criteria to include in the DM group were strictly as follows, 1) history of non-insulin dependent DM (NIDDM) diagnosis, 2) previous diabetic control with diet or oral hypoglycemic medications, 3) random blood glucose greater than 200 mg/dl, or 4) HbA1c greater than 6.5%. The recruit samples that did not meet the above DM criteria would be allocated in the non-DM group. Because previous reported events of perioperative hyperglycemia of DM and non-DM were 60% to 70% and 30% to 40%, respectively[1-5], the calculated sample size was 28 in each group (P1=65%, P2=30%, type I error=0.8, type II error=0.2).

Anesthetic management

Patients received their usual cardiac medications early morning on the day of the surgery. On the day of the surgery, patients were given midazolam 0.02 mg/kg and fentanyl 1 mcg/kg. A five-lead electrocardiogram (EKG), pulse oximetry, and non-invasive blood pressure monitoring were initiated. Then, an arterial catheter was inserted, under local anesthesia, into the radial artery for invasive blood pressure monitoring. General anesthesia induction consisted of fentanyl 5 to 10 mcg/kg, midazolam 0.2 to 0.4 mg/kg, and pancuronium 0.1 to 0.15 mg/kg. Additionally, propofol 0.5 to 1 mg/kg was administered as appropriated. After the trachea was intubated, a right internal jugular multi-lumen central venous catheter was inserted. Anesthesia was maintained using sevoflurane 1% to 2% and its concentration was later adjusted as required by the clinical conditions. Neuromuscular blockade was achieved by an additional dose as required.

Fluid and blood glucose monitoring

The intravenous fluid for volume replacement was Acetar. A dextrose solution at 5% of 40 ml/hour was started once insulin was administered. There was no steroid administration during the operation; however, if it became necessary, then the given case was excluded from the study. The solvent used for inotropic and vasopressors was saline 0.9%. The intraoperative blood glucose was monitored by point of care testing (POCT) using Dextrostrix (Accucheck Performa®) every 30 minutes. The initial sampling was at the completion of the radial arterial cannulation. The postoperative blood glucose in the intensive care unit (ICU) was monitored by POCT-glucose every 60 to 120 minutes for 24 hours.

Glycemic control and Insulin protocol

For DM, oral hypoglycemic medications could be taken on the morning day of surgery. The insulin infusion was started as the initial blood glucose

value from POCT-glucose increased above 180 mg/dl using rapid insulin (RI) infusion of two units per hour. None of the insulin infusion was used if the initial blood glucose was less than 180 mg/dl. The insulin protocol used for the consecutive blood glucose monitoring were as follows, the consecutive blood glucose 140 to 180, 180 to 250, and more than 250 mg/dl, started RI of one, two and three units per hour, respectively. Additionally, five units of RI was injected intravenously when the blood glucose increased above 200 mg/dl and the RI infusion was stopped once blood glucose was below 120 mg/dl. Hypoglycemia (blood glucose of less than 70 mg/dl) was treated with 50% dextrose 5 ml.

For non-DM, control of blood glucose started when the blood glucose increased above 180 mg/dl. Two and three units per hour of RI infusion was injected once blood glucose was 180 to 250 and above 250 mg/dl, respectively. An additional five units of RI intravenously was given if the blood glucose increased above 200 mg/dl.

Glycemic variability

GV means the variation in the blood glucose level[10,11]. There are various methods to measure GV. For the present study, intraoperative GV referred to 1) standard deviation (SD) that was calculated from all the intraoperative blood glucose sampling, 2) coefficient of variance (CV) that was SD divided by the mean value, and 3) mean absolute glucose (MAG) that was the summation of absolute values of differences consecutive intraoperative blood glucose sampling divided by time duration of the first and the last sampling. MAG is calculated using at least seven samplings and usually observed per hour[12]. The intraoperative GV measures in the present study were derived from the blood glucose sampling at 30, 60, 120, 150, 180, 240, 270, and 300 minutes from the beginning of surgery. The intraoperative MAG (mg/dl/hour) was derived by the summed difference of two consecutive samplings divided by five (hours).

Intra and postoperative variables

Type of operation, durations of operation, and type of inotropes or vasopressors were documented. POCT-glucose were recorded and summarized according to time period of skin incision to CPB, during CPB, starting inotropes or vasopressors infusion and 24-hour postoperative period. Events of hypoglycemia (less than 70 mg/dl) and hyperglycemia (more than 180 mg/dl) were documented.

Outcome data and missing data

Values of blood glucose by POCT-glucose were the study outcome. Patients whose POCT-glucose samples were missing at any time of sampling were excluded.

Confounding factor

Demographic data (age, gender, body mass index [BMI]), preoperative assessment data (underlying disease and the American Society of Anesthesiologists [ASA] status), and type and duration of operation were recorded and statistically analyzed.

Statistical analysis

All data were evaluated using the software of SPSS for analyzing and extracting the p-value for the collected data. The data were expressed as numbers, percentage, mean, and 95% confidence interval. Comparison of mean and numbers were carried out using Student t-test (independence t-test for between groups, pair t-test for in group) and chi-square test, respectively. A probability value less than 0.05 was considered statistically significant.

Results

During the period of the present study, 85 patients met the inclusion criteria but 19 patients met exclusion criteria. The most common reason to exclude was previous inotropes or vasopressors infusion. Incomplete blood glucose data was found in six patients (three of DM, and three of non-DM). These patients were excluded. Finally, 60 patients (30 of DM and 30 of non-DM) were enrolled in the present study.

The demographic and preoperative data showed no significant difference between DM and non-DM groups with respect to the age, BMI, ASA status, and type of operation. Hypertension (HT) and the duration of operation were found to have significant difference, which DM group having more HT and longer duration of operation (Table 1).

Trends of intraoperative blood glucose that revealed continuous increase from the intraoperative period until the postoperative period were observed in both DM and non-DM group (Figure 1). Most of the high blood glucose values, which were approximately 200 mg/dl, occurred in the postoperative period (Table 2, 3). The characteristics of the intraoperative blood glucose that increased in DM were slightly different from the non-DM. Regard to most of DM, the increase of blood glucose occurred from the start of the surgery and the incidence of hyperglycemia

Table 1. Demographic and perioperative data of DM and non-DM

	DM (n=30) n (%)	Non-DM (n=30) n (%)	p-value
Age (year); mean (95% CI)	63.13 (59.4 to 66.9)	58.80 (54.2 to 63.4)	0.234
BMI (kg/m^2); mean (95% CI)	23.41 (22 to 24.9)	21.85 (20.6 to 23.1)	0.157
HbA1c (%); mean (95% CI)	7.00 (6.83 to 7.17)	4.92 (4.67 to 5.17)	0.001
Underlying disease; n (%)			
Hypertension	30 (100)	21 (70.0)	0.001
Dyslipidemia	21 (70.0)	9 (30.0)	0.559
Stroke	3 (10.0)	3 (10.0)	0.777
ASA physical status; n (%)			0.359
ASA 2	0 (0.0)	1 (3.3)	
ASA 3	30 (100)	29 (96.7)	
Type of operation; n (%)			0.266
CABG	16 (53.3)	8 (26.7)	
CABG with valve surgery	4 (13.3)	2 (6.7)	
Single valve surgery	9 (27.0)	19 (63.3)	
Multiple valve surgery	1 (3.3)	1 (3.3)	
Duration of operation (hours); mean (95% CI)	5.28 (4.84 to 5.72)	4.37 (3.96 to 4.78)	0.004
Inotropes/vasopressors			0.977
Dopamine	30 (100)	30 (100)	
Epinephrine	5 (20.8)	5 (20.8)	
Dobutamine	3 (10.0)	2 (6.7)	
Norepinephrine	2 (6.67)	1 (3.3)	
Milrinone	2 (6.67)	3 (10.0)	

CI=confidence interval; DM=diabetes; BMI=body mass index; ASA=American Society of Anesthesiologists; CABG=coronary artery bypass graft

Table 2. Blood glucose values (mg/dl) of DM and non-DM by perioperative events

Events	DM (n=30) Mean (95% CI)	Non-DM (n=30) Mean (95% CI)	p-value
Skin incision to CPB	122.27 (106 to 138)	91.47 (85.4 to 97.5)	0.001*
During CPB	131.00 (120 to 142)[a]	119.03 (111 to 127)[a]	0.093
Inotropes/vasopressors infusion	190.00 (177 to 203)[b]	169.54 (155 to 185)[b]	0.105
24-hour postoperative period	190.89 (163 to 219)[c]	193.95 (184 to 204)[c]	0.894

CI=confidence interval; DM=diabetes; CPB=cardiopulmonary bypass

* Statistically significant between DM and non-DM, [a] Statistically significant between before and during CPB, [b] Statistically significant between during CPB and inotropes/vasopressors infusion, [c] Statistically significant between inotropes/vasopressors infusion and 24-hour postoperative period

Table 3. Numbers of hyperglycemic event regarding the time of sampling

Sampling at (minute)	0	30	60	90	120	150	180	210	240	270	300
Events	Before CPB; n (%)		CPB; n (%)			Inotropes/vasopressors infusion; n (%)				Post-surgery; n (%)	
DM	4 (13.3)	5 (16.7)	2 (6.7)	3 (10.0)	7 (23.3)	12 (40.0)	18 (60.0)	17 (56.7)	17 (56.7)	14 (46.7)	11 (36.7)
Non-DM	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.7)	5 (16.7)	5 (16.7)	5 (16.7)	8 (26.7)	6 (20.0)	5 (16.7)

DM=diabetes; CPB=cardiopulmonary bypass

Table 4. Intraoperative glycemic variability

GV measures	DM (n=30) Mean (95% CI)	Non-DM (n=30) Mean (95% CI)	p-value
SD (mg/dl)	47.14 (41.4 to 52.9)	39.57 (33.8 to 45.3)	0.074
CV (%)	29.34 (25.7 to 33)	27.70 (25.2 to 30.2)	0.470
MAG (mg/dl/hour)	31.98 (27.6 to 36.4)	28.05 (25 to 31.1)	0.001*

CI=confidence interval; DM=diabetes; SD=standard deviation; CV=coefficient of variance; MAG=mean absolute glucose

* Statistically significant

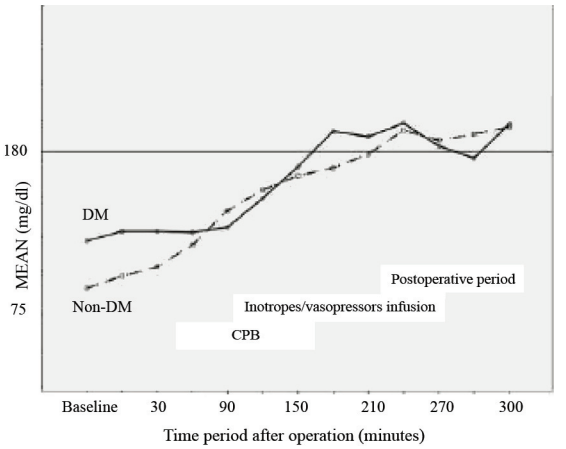

Figure 1. Perioperative trend of blood glucose values between DM and Non-DM.

The begin of CPB range was at 30 to 50 minutes after starting surgery. The average and standard deviation CPB time were 2.02 and 0.44 hours.

(before CPB) was 13% to 17% (Table 3). For the non-DM, their blood glucose commonly increased in late period of CPB (Table 3). A sudden and large increase in blood glucose was revealed after the inotropes or vasopressors infusions in both DM and non-DM groups (Table 2).

There was no event of hypoglycemia in the DM or in the non-DM groups in the present study. Events of once hyperglycemia (greater than 180 mg/dl) were found in 18 of 30 (60%) in the DM group and 8 of 30 (26.67%) in the non-DM group. Based on the standard target of blood glucose (140 to 180 mg/dl), numbers of successful control as the target throughout perioperative period were two (6.67%) and five (16.67%) patients in DM and non-DM, respectively, and without statistically significant difference.

For intraoperative GV, SD, and CV of DM were higher values than that of non-DM with no statistical significance. The average MAG of DM was higher value than that of non-DM with statistical significance (Table 4).

Discussion

Cardiac surgery is highly related to hyperglycemia. Like the previous studies[1,4,5,12], events of perioperative hyperglycemia in the present study were found in up to 60% of DM and 30% of non-DM in cardiac surgery. That meant perioperative hyperglycemia has probably occurred despite the invasive blood glucose control. The cause of hyperglycemia in cardiac surgery is not limited only by the nature of insulin-uptake impairment as being in DM. Surgical stress plays a role that leads to release of a great extent of cortisol and catecholamines. These stress hormones induce insulin resistance[13]. However, there are much more important causes that brings about events of serious hyperglycemia in the cardiac surgery than other surgeries. First, hypothermia leads to impairment of insulin secretion, activation of catecholamines release, and hypokalaemia[14,15]. Second, heparin increases the total free fatty acids that leads to insulin resistance[16,17]. Finally, CPB initiates the non-pulsatile flow. Decreases of insulin secretion occurs because of hypoperfusion of the pancreas[15]. As a result, awareness of hyperglycemia during cardiac surgery is necessary for both DM and non-DM.

In the present study, a sudden and significant increase of blood glucose was demonstrated in both DM and non-DM. A cause of the increase of blood glucose was most likely be infusion of inotropes or vasopressors. As it is known, adrenergic drugs interfere with glucose metabolism[1] and inhibition insulin secretion[13,18]. To apply the present study results, more frequent blood glucose monitoring should be considered once infusion of inotropes or vasopressors was taken.

Characteristics of hyperglycemia (above 180 mg/dl) were different between DM and non-DM. Regarding DM, hyperglycemia most likely began when the operation started, which was probably because of their previous abnormal glucose metabolism. The present study revealed an incidence of hyperglycemia of 13% to 17% before CPB

despite the insulin infusion, which an ineffective preoperative blood glucose control might probably be the explanation.

The characteristic of hyperglycemia of non-DM revealed in the present study should be taken into consideration. As in normal practice, the delay of giving insulin infusion for non-DM in case of blood glucose within 140 to 180 mg/dl was probably decided due to concern of hypoglycemia. The hidden point of this concern is that the self-regulation of glucose homeostasis of non-DM still works. As a result, it seems to be sensible that insulin should be delivered when there is an occurrence of hyperglycemia (greater than 180 mg/dl). Furthermore, the glucose disturbance affected by adrenergic drugs is usually underestimated. Moreover, uncertainty cardiovascular status during weaning off CPB could happen. Therefore, increasing dose of inotropic or adrenergic drugs might be taken once poor myocardium contraction existed. As a result, a practical point learned from the present study results is to be reminded to get a much more intensive control of blood glucose for non-DM once adrenergic drugs are infused.

Perioperative hyperglycemia occurred despite providing tight glucose control. Theoretical causes[2] might be 1) inadequate treatment of insulin intra-operatively, 2) large dynamic increases of inotropes or vasopressors, 3) hypokalemia, 4) stress and pain postoperatively, and 5) dextrose solution was administered along with inotrope or vasopressors. Intraoperative inadequacy of treatment was most likely a major cause in the present study. Based on a previous study, Duggan et al strongly recommended aggressive treatment of intraoperative hyperglycemia[2]. The Duggan methods are more frequent monitoring of blood glucose and double dose of insulin infusion if the blood glucose was not lower after treatment by more than 30 mg/dl than the previous glucose value. However, it should be noted that the aggressive treatment by insulin was documented based on DM condition.

Variation of blood glucose has recently looked-at due to its effect of microcirculatory disturbance[19]. Acute glucose swings lead to increases of oxidative stress that cause deleterious cellular injury, especially for the myocardial cell[20]. Recently, GV (maximum-minimum values greater than 4 mmol or greater than 72 mg/dl) was reported as being associated with postoperative atrial fibrillation (POAF)[21]. However, GV during cardiac surgery has not been widely studied. There is no specification on which GV indexes should be used in cardiac surgery. In addition, there has been no study of relationship between GV and poor outcomes after cardiac surgery. The present study was a pilot study to reveal GV in cardiac surgery. As expected, GV of DM was higher than non-DM. Based on previous studies (non-cardiac surgery condition)[22,23], a high variation of blood glucose was diagnosed by SD greater than 30 mg/dl and CV greater than 20%. Based on the present study results, a high variation of blood glucose was found in both DM and non-DM during cardiac surgery. Kotagal et al[5] demonstrated a higher odd ratio of perioperative cardiac adverse outcomes in non-DM than that of DM. It might imply that the acceptable level of GV in non-DM should be lower than that of DM. As previous discussion, further studies regarding GV and control of GV during cardiac surgery should be taken into consideration.

In contrast to SD, MAG is a fine measure tool to detect blood glucose change. MAG refers to real blood glucose difference between the former and the present blood glucose, which is not the difference from the mean as calculating for SD. The essential recommendation to calculate MAG is at least summation of six differences (or seven times of blood glucose monitor)[10]. The present study used nine times of blood glucose monitor (at 30, 60, 90, 120, 150, 180, 240, 270, and 300 minutes) to apply in the formula of MAG then divided by five (hour). Based on previous studies, MAG was proven to be more reliable to monitor variation of blood glucose in diabetic patients than SD, CV, and mean amplitude of glycemic excursion (MAGE)[10,24]. Interestingly, the present study demonstrated the higher values of MAG in DM with statistical significant difference comparing to that of non-DM. Based on a basic assumption, GV of DM should be truly more than that of non-DM. Based on the present study results, MAG could statistically differentiate DM from non-DM. Therefore, it might assume that to monitor intraoperative blood glucose variation MAG was advantageous over SD and CV.

For generalization, the present study demonstrated different characteristics of hyperglycemia between DM and non-DM. For non-DM, aggressive insulin treatment as in DM might possibly lead to hypoglycemia or potential harm and inflammation in previously insulin-naive patients[5]. The application from the present study results were 1) provide aggressive insulin treatment in DM[2,25], and 2) start insulin infusion whenever adrenergic drugs are infused in non-DM even though blood glucose is 140 to 180 mg/dl.

The advantage of the present study was the

priority study demonstrating perioperative blood glucose variation over time in form of line graph and revealing the values of intraoperative GV of both DM and non-DM. However, the present study had some limitations. First, sample size of 30 each was too small for using GV (SD, CV, MAG) that were derived from the present study as the reference values. Second, the present study did not use continuous glucose monitoring (CGM). As known, CGM records capillary blood glucose every five minutes; thus, it is preferred to use for calculation of GV[24]. Third, the present study used blood glucose monitoring from POCT-glucose as it was a standard blood glucose monitoring during cardiac surgery. Glucose values from POCT-glucose might have some deviation from glucose value from blood sampling. Last, the significant differences of characteristics of DM (more numbers of HT and longer duration) might have some degree of confounding to the result interpretations.

Conclusion

Perioperative hyperglycemia in cardiac surgery was found in DM as well as in non-DM despite treatments delivered by insulin infusion. For DM, hyperglycemia occurred at the beginning of the operation. For non-DM, hyperglycemia occurred late or when weaning off CPB. Inotropes or vasopressors infusion was a significant cause of hyperglycemia. MAG might be a better monitor of GV during cardiac surgery. Further studies of blood glucose variation in cardiac surgery by using MAG as an index should be considered.

What is already known on this topic?

Cardiac surgery is known for causing a severity of hyperglycemia, especially in diabetic patients. CPB in general is subjected to be a main cause of hyperglycemia. The increase of perioperative blood glucose needs tight control by insulin infusion to reduce perioperative complications.

What this study adds?

Perioperative hyperglycemia can be found in non-diabetes. Not CPB in general but inotropes or vasopressors infusion specified in this study is the main cause of hyperglycemia. The nature of GV during perioperative cardiac surgery of DM and non-DM were firstly demonstrated in this study. MAG was a GV index that could statistically differentiate DM from non-DM. Thus, MAG might be a better GV index to use in monitoring perioperative blood glucose. As there has been no study of GV in cardiac surgery, future studies of GV in cardiac surgery should focus and consider using MAG.

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Ethics approval and consent to participate

Ethics approval of the present study was given by the Ethical Committee, Faculty of Medicine, Naresuan University, No.569/58. All patients in this study gave written informed consent.

Availability of data and material

The datasets used or analyzed during the current study are available from the corresponding authors on reasonable request.

Authors' contributions

All authors read and approved the final manuscript.

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Conflicts of interest

The authors declare no conflict of interest.

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