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Correlation of blood glucose variability based on CGMS monitoring during cardiopulmonary bypass and postoperative delirium in patients with rheumatic heart disease valve replacement

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Abstract: *To investigate the relationship between blood glucose variability based on continuous glucose monitoring system (CGMS) monitoring and postoperative delirium (POD) in patients with rheumatic heart disease undergoing valve replacement during cardiopulmonary bypass. From July 2021 to July 2022, we conducted real-time dynamic blood glucose monitoring after admission to the operating room in 122 patients undergoing valve replacement for rheumatic heart disease. CGMS were used to record indicators related to blood glucose variation, including CV, GluAve, GluSD and MAGE, and MMSE was also used for evaluation one day before surgery. To rule out preoperative cognitive impairment. At postoperative days 1, 2, and 3, the CAM-ICU scale was used to assess patients' unconsciousness. Finally, binary logistic regression analysis was used to study the relationship between intraoperative blood glucose changes and POD. The age of patients with POD was significantly older than that of patients without POD, and the occurrence of POD was related to the duration of extracorporeal circulation and the value of the blood glucose variation index (CV, GluAve, GluSD, MAGE). By binary logistic regression analysis, we found that age, CPB cycle time and blood glucose variability were independent risk factors for postoperative delirium (POD) (P <0.05). In addition, we also found that the area under ROC curve of CV, GluAve, GluSD and MAGE were 0.684, 0.830, 0.820 and 0.802, respectively, which indicated that these indexes could predict the occurrence of postoperative delirium (POD). GluAve had the strongest prediction effect on POD (sensitivity 85.7%, specificity 81.5%). Blood glucose variability based on CGMS monitoring during cardiopulmonary bypass in patients with rheumatic heart disease valve replacement is associated with the occurrence of postoperative delirium. Longer duration of CPB and increased intraoperative blood glucose variability are independent risk factors for POD in patients with rheumatic heart disease valve replacement. Continuous monitoring of intraoperative blood glucose by CGMS can provide real-time guidance for early intervention of blood glucose fluctuations to reduce the incidence of postoperative POD.*

Keywords: *blood glucose variability; postoperative delirium; cardiopulmonary bypass; valve replacement*

1. Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) DSM-5, postoperative delirium is a neurological disorder characterized by altered mental status[1],It mostly refers to the delirium state that occurs within 7 days after the end of the operation. Postoperative delirium is characterized by acute impairments of attention, consciousness, and cognition and is one of the common complications after cardiac surgery[2].The occurrence of POD may not only cause physical and mental harm to patients and their families, but also may affect the confidence of other patients to seek medical treatment, which is not conducive to the development of medical career. At present, the incidence of POD in patients after cardiac surgery is more than that of other surgeries, and the incidence rate is about 18%~42%[3] .Cardiac surgery is a well-deserved major surgical operation, the operation time is long, the trauma is large, patients often need cardiopulmonary bypass, some studies have shown that the incidence of delirium after undergoing cardiopulmonary bypass (CBP) is 27%, which is at a relatively high incidence level[4].Cardiopulmonary bypass significantly changes normal physiology, and various indexes change greatly, and whether intraoperative blood glucose values, as

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the result of various hormones and multi-factor influences, are related to the occurrence of postoperative delirium remains to be demonstrated. Six observational studies consistently found that hyperglycemia was associated with POD and/or POCD and not with diabetes mellitus (DM) (the prevalence of DM in these studies was 22.5-30%)[5].Hyperglycemia is an important factor in increased mortality in intensive care units and in critically ill patients undergoing cardiac surgery[6], Hyperglycemia can also cause the release of a large number of pro-inflammatory cytokines, leading to coagulation dysfunction and abnormal vascular response[7].However, the correlation between perioperative blood glucose levels and POD is still controversial, especially the correlation between intraoperative blood glucose variability (GV) and POD is rarely reported in the literature at home and abroad. This study planned to include 122 patients who underwent valve replacement for rheumatic heart disease as the research object, and to explore the relationship between blood glucose variability monitored by CGMS and postoperative delirium during cardiopulmonary bypass in patients undergoing valve replacement for rheumatic heart disease, and to verify whether intraoperative blood glucose variability is related to the occurrence of postoperative POD in patients, so as to provide new clinical evidence for early prediction and early prevention of POD.

2. Material and methods

2.1 Study design

A total of 122 patients who underwent valve replacement for rheumatic heart disease in our hospital from July 2021 to July 2022 were selected, including 58 males and 64 females. Age 18-74 years, average age 53.2 years. Inclusion Criteria: (1) Age≥ 18 years; (2) proposed valve replacement; (3) The patient voluntarily joins and signs the informed consent form. Exclusion Criteria: (1) Psychiatric-related illness before surgery; (2) the patient has audio-visual impairment; (3) History of previous head disease or head trauma; (4) preoperative delirium; (6) the assessment is not complete; (7) Diabetes mellitus or impaired glucose tolerance before surgery; (8) intraoperative use of diuretics; (9) Severe liver and kidney disease (Child score greater than 9 points or grade C; serum creatinine >177umol/L); (10) The score of the Preoperative Mini-Mental State Examination (MMSE) was too low (17 points for illiterate <, 20 points for primary school <, and 24 points < for secondary school).

2.2 Anesthetic Management

All patients were treated with endotracheal intubation general anesthesia, radial artery and dorsalis pedis artery puncture and catheterization for ambulatory blood pressure monitoring, elbow vein and femoral vein puncture to establish fluid channel, during the anesthesia process, we first injected midazolam with a dosage of about 0.04mg/kg mg/kg, then etomidate with a dosage of about 0.30mg/kg mg/kg, then sufentanil with a dosage of about 0.50ug/kg mg/kg, and finally rocuronium bromide with a dosage of about 1.00mg/ kg mg/kg. After the endotracheal intubation is completed, the patient is mechanically ventilated, and the tidal volume is set to about 6~8mL/kg to keep the PETCO2 level at 35~45mmHg. Intraoperatively, propofol 6.00~8.00mg/kg/h, remifentanil 0.10~0.20ug/kg/h, and dexmedetomidine 0.20~0.70ug/kg/h were administered. Postoperatively, in order to ensure the safety and comfort of patients, we used intravenous self-controlled (PCIA) analgesia, which was composed of sufentanil 3 μg/kg, butorphanol tartrate infusion 5 mg and trolisetron 10 mg plus normal saline, a total of 150 ml, 3 ml/h, and all patients were assessed for pain using the standard numeric score (VAS) after surgery, so that all patients had a VAS score of ≤ 3.

2.3 Observation indicators and evaluation criteria

1) Blood glucose variability: After entering the operating room, the subjects used CGMS to monitor their blood glucose levels in real time, and the induction system of CGMS will detect blood glucose values every 5 minutes, and finally form a continuous image of blood glucose changes, so that we can obtain the patient's blood glucose changes during the operation, and its measured values include the coefficient of variation (CV), as well as the mean blood glucose value (GluAve), blood glucose standard deviation (GluSD) and Mean Amplitude of Plasma Glucose -Excursions (MAGE)

2) Postoperative delirium: 1 day before surgery, we perform a preoperative Mini-Mental State Assessment (MMSE). After surgery, we will first administer the Richmond agitation sedation score to the patient, and for patients with RASS ≥-3, we will further use the Confusion Assessment Method

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Intensive Care Unit (CAM-ICU scale) to assess whether delirium occurs after surgery.

2.4 Sample Size and Statistical Analysis

Review of the literature, the incidence of delirium after cardiopulmonary bypass (CBP) was approximately 27%, the RR value was 2.15, and when $\alpha = 0.05$, $1-\beta = 0.8$, the estimated total sample size of PASS 15 was 102 patients, and a total of 122 patients were included considering the 20% loss to follow-up rate. The data were analyzed using IBM SPSS Statistics for Windows version 26.0 (IBM Corp, Armonk, NY, USA) statistical software. Continuous data were presented as mean ± standard deviation ($x \pm s$) and t-test for comparison between groups, while non-normally distributed continuous data were presented as median (M) and interquartile range (IQR), and Mann-Whitney U test was used for comparison between groups. Count data were expressed as frequency or percentage, and chi-square ($\chi 2$) test was used for comparison between groups. Multivariate logistic regression analysis was performed to screen out the independent risk factors of POD. The predictive effect of blood glucose variability related indicators on POD was determined by plotting the receiver operating characteristic (ROC) curve, and the area under the ROC curve (AUC) was calculated. $P < 0.05$ was statistically significant.

3. Results

Among the 122 patients, a total of 18 patients did not complete the follow-up (death, withdrawal, incomplete data, etc.), and a total of 104 cases were included, including 27 patients with POD and 77 patients without POD, with a POD incidence rate of 26.0%.

1) Comparison of perioperative conditions between POD group and non-POD group (including preoperative baseline, operation duration, CPB duration, blood loss, etc.)

Among the 104 patients, there were 27 patients with postoperative delirium (POD group) and 77 patients without postoperative delirium (non-POD group), and there were no significant differences in perioperative indexes between the two groups, including gender composition, height, BMI, operation duration, intraoperative fluid infusion, blood loss and urine output, preoperative and intraoperative hemoglobin (HB) value, lactate value, blood group composition, and preoperative MMSE value, among which the duration of CPB was related to the occurrence of POD (P <0.05).

Table 1: Comparison of general data between the two groups

	Non-PODgroup (n=77)	PODgroup (n=27)	$t/\chi 2$ value	P value
Age (years)	53.1±11.042	58.1±8.3	-2.166	0.033
Sex(Male/Female)	35/42	17/10	2.451	0.117
height(cm)	160.5±7.0	162.5±6.7	-1.314	0.192
BMI(kg/m²)	23.3±3.5	22.1±3.3	1.665	0.099
Duration of surgery(min)	263.8±47.7	255.4±39.1	0.828	0.366
CPB duration(min)	108.7±28.4	133.1±28.1	-3.851	0.000
Intraoperative-infusion volume(ml)	458.4±161.7	475.9±106.9	-0.522	0.603
bleeding(ml)	555.8±190.9	492.6±225.2	1.413	0.161
Urine output(ml)	842.2±395.1	861.1±336.1	-0.222	0.825
Preoperative HB value(g/L)	135.8±20.1	135.1±12.8	0.183	0.855
Intraoperative HB value(g/L)	104.3±14.1	99.5±10.3	1.630	0.106
Preoperative lactate value(mmol/L)	1.3±0.6	1.4±0.5	-0.954	0.342
Intraoperative-lactate value(mmol/L)	2.0±0.8	2.3±0.8	-1.246	0.216
Blood type(A/B/O/AB)	(22/14/35/6)	(5/8/12/2)	2.025	0.567
Preoperative MMSE score	27.88±0.9	27.85±0.9	0.148	0.883

2) The coefficient of variation of blood glucose in the non-POD group was compared with that in the POD group

The blood glucose variability related indexes CV, GluAve, GluSD and MAGE in the POD group were significantly higher than those in the non-POD group, with $P < 0.05$, and the difference was statistically significant. (See Table 2)

Table 2: Comparison of intraoperative blood glucose variability between the two groups

	Non-POD group(n=77)	POD group(n=27)	*t* value	*P* value
CV(%)	28.26±2.94	30.48±3.84	-2.741	0.009
GluAve	8.029±0.827	9.400±1.059	-6.874	0.000
GluSD	2.365±0.310	2.774±0.360	-5.655	0.000
MAGE	2.746±0.659	3.500±0.592	-5.249	0.000

3) Multivariate logistic regression analysis was performed to analyze the risk factors for POD

Multivariate logistic regression analysis was performed on several indicators of P <0.05 in univariate regression analysis, and the results showed that age, CPB duration, and blood glucose variability were independent risk factors for postoperative delirium, P < 0.05, and the difference was statistically significant.(See Table 3)

Table 3: Multivariate Logistic regression analysis

factors	β	SE	Wald	OR	95%CI	*P* value
age	0.304	0.146	4.371	1.356	1.019~1.803	0.037
CV(%)	1.030	0.372	7.680	2.802	1.352~5.807	0.006
GluAve	1.101	0.215	26.205	3.007	1.973~4.584	0.000
GluSD	1.431	0.357	16.071	4.182	2.078~8.419	0.000
MAGE	1.517	0.374	16.417	4.559	2.189~9.498	0.000
CPB time	0.829	0.285	8.491	2.292	1.312~4.003	0.004

4) Analysis of the predictive value of glycemic variability related indicators on the occurrence of POD

The areas under the ROC curve of CV, GluAve, GluSD and MAGE were 0.684, 0.830, 0.820 and 0.802, respectively, suggesting that CV, GluAve, GluSD and MAGE could predict POD, and GluAve had the strongest predictive effect on POD (sensitivity 85.7% and specificity 81.5%).(See Table 4)

Table 4: The predictive value of blood glucose variability related indexes on the occurrence of POD was analyzed

factors	AUC	95%CI	P value	Diagnostic cut-offs	Sensitivity	Specificity
CV	0.684	0.553~0.815	0.005	0.295	71.4%	63.0%
GluAve	0.830	0.723~0.937	0.000	8.75	85.7%	81.5%
GluSD	0.820	0.730~0.911	0.000	2.39	67.5%	88.9%
MAGE	0.802	0.714~0.889	0.000	2.85	64.9%	88.9%

4. Discussion

Studies have shown that persistently high blood sugar levels may lead to cognitive dysfunction[8,9].Severe perioperative hyperglycemia impairs postoperative immune function by decreasing basophil count, T cell activation, and decreasing monocyte function[10].In patients undergoing cardiac surgery and other critically ill patients, postoperative hyperglycemia is associated with an increased risk of complications[11].Amy M. Shanks[12] et al. believe that hyperglycemia reduces the body's immune response and ability to fight bacterial infections.The occurrence of delirium in diabetic patients may be related to the damage of endothelial cells in the brain by high blood sugar levels in the body, causing thickening of the basement membrane of cerebral microvessels, stenosis of cerebral blood vessels and changes in perfusion, resulting in impairment of attention, memory and frontal lobe function[3].According to the paper by Georgia Davis[13]hospitalized patients, up to 40% of critically ill patients and 32% of general patients develop hyperglycemia, with and in the first 24 hours after surgery, 25.2% of patients have blood glucose elevated to BG> 140 mg/dL, of which 7.4% have blood glucose above BG> 180 mg/dL. By 48 hours and 72 hours postoperatively, 31.5% and 34.6% of patients had BG> 140 mg/dL, respectively.

Cheng[14]showed that increased glycemic variability is an independent risk factor for ICU delirium in patients after liver transplantation. In patients undergoing major noncardiac surgery, intraoperative blood glucose levels above 8.3 mmol/L were associated with a significantly increased risk of postoperative infection[12].Patients with a preoperative HbA1c of 5.9% or greater may require careful

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perioperative glycemic control to facilitate surgery or recovery[15].From the above, it can be seen that factors such as surgery have a greater impact on blood sugar levels. However, the incidence of postoperative delirium was higher after major cardiac surgery undergoing cardiopulmonary bypass, so we performed a correlation analysis between blood glucose variability during cardiopulmonary bypass and the occurrence of postoperative delirium to understand whether blood glucose changes were associated with the occurrence of postoperative delirium.

At present, endocrinology departments commonly use continuous glucose monitoring systems (CGMS) to monitor patients' blood glucose in real time, regulate the use of hypoglycemic drugs, and maintain blood glucose in diabetic patients within the appropriate range.Wu [16]showed that the use of a real-time ambulatory glucose monitoring system to monitor blood glucose changes in patients receiving intensive insulin pump therapy can detect blood glucose abnormalities more accurately than traditional manual blood glucose measurement methods, thereby greatly improving the detection rate of blood glucose abnormalities. In general, glycemic variability (GV) refers to intraday GV or daily GV, but it can also be exponential months to years of follow-up GV, blood glucose values measured by glucose self-monitoring (SMBG) or continuous glucose monitoring (CGM) are often used to assess intraday or daily GV, while fasting blood glucose (FPG) and HbA1c can also be used to assess GV. Although GV generally refers to changes in overall blood glucose, including hyperglycemia and hypoglycemia, GV is also used to refer to postprandial blood glucose fluctuations, particularly in patients with T2DM[17] .

In recent years, there have been numerous studies on the impact of glycemic variability (GV) on disease and prognosis, and in the future, the monitoring and control of glycemic variability in high-risk patients may have important clinical implications, such as intensive perioperative glycemic control in diabetic patients and reduced risk of postoperative infection, atrial fibrillation, and renal failure, as well as shortened ICU time and hospital stay close[18].Studies have shown that blood GV is a more accurate reflection of a patient's condition than hyperglycemia, and the greater the variability of blood glucose, the greater the adverse effects on the body[11],As a result, its clinical value is also higher. There are also many studies that have shown that intermittent hyperglycemia (IHG) is associated with more severe oxidative stress than persistently high blood glucose (CHG) levels[19].Thus, it may be more meaningful to continue glucose monitoring and derive intraoperative variability in blood glucose. Some of the most common metrics we've picked include: (Coefficient of Variation, CV),(Average Blood Glucose Value ,GluAve),(Blood Glucose Standard Deviation, GluSD) and (Mean Amplitude of Plasma Glucose -Excursions, MAGE)[17].

Finally, in this study, the blood glucose variability monitored by CGMS during cardiopulmonary bypass in 104 patients undergoing valve replacement was studied, and it was found that the blood glucose variability related indicators (CV, GluAve, GluSD and MAGE) were significantly higher than those in patients without POD, and there was a significant correlation between glycemic variability and the occurrence of POD, which indicated that increased glycemic variability may be one of the risk factors for postoperative delirium in diabetic patients, and this result also provided new clinical evidence for early prediction and early prevention of POD. After this study, we also found that the risk of postoperative POD increases with the extension of cardiopulmonary bypass time, so the duration of cardiopulmonary bypass may be an important risk factor for the occurrence of postoperative delirium.

5. Limitation

This study is a single-center study with a small sample size and population limitations, which further demonstrates that the results need to be replicated with multiple centers and large samples. In addition, due to the specificity of POD, we only performed the assessment for 3 days after surgery, and longer follow-up may be required to obtain more results. In addition, blood sugar levels undergo several changes during surgery, and surgical stress leads to an increase in the concentration of pro-inflammatory cytokines and hormones such as catecholamines, cortisol, growth hormone, glucagon, etc[20],Glucocorticoids, growth hormones, glucagon, thyroxine and other hormones are known to increase blood glucose concentrations and affect blood glucose measurements. Finally, the flow of blood through artificial material pipes in cardiopulmonary bypass inevitably produces a series of inflammatory factors. Many scholars believe that a variety of external inflammatory cytokines produced as a result of surgery are able to cross the blood-brain barrier, activate microglia, increase the secretion of inflammatory mediators, and ultimately induce POCD[21,22].In addition, anesthesia-related factors are also important risk factors for postoperative delirium, such as sevoflurane, one of the most commonly used inhalation anesthetics in clinical practice, and when inhaled at high concentrations or multiple inhalations, may induce mental retardation in children or lead to a higher incidence of POCD in older patients[23,24],Anesthesia and intestinal dysbiosis can synergistically promote the development of PND[25].However, this study only focused on the correlation between glycemic variability and the occurrence of POD, and did not include other factors that may lead to PND.

In summary, the variability of blood glucose monitored by CGMS during cardiopulmonary bypass in patients undergoing valve replacement with rheumatic heart disease is related to the occurrence of postoperative delirium, and the long duration of CPB and the increase of intraoperative blood glucose variability are independent risk factors for the occurrence of POD in patients with valve replacement with rheumatic heart disease.

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