Original Article

Increased glucose variability is associated with major adverse events in patients with infective endocarditis undergo surgical treatment

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Background: This study aimed to investigate the prognostic value of glucose variability (GV) in predicting postoperative major adverse events (MAEs) in patients with infective endocarditis (IE) who underwent surgical treatment.

Methods: This retrospective observational study included a total of 381 consecutive patients who underwent surgical treatment in our institution from October 2007 to August 2019. The MAEs included all-cause death, stroke, myocardial infarction, acute heart failure, IE recurrence, acute renal failure and sepsis. Postoperative GV in the first 24 hours was measured by the mean 24-hour glucose, standard deviation, coefficient of variation (CV) and mean amplitude of glycemic excursions. Univariate and multivariate logistic regression analyses were performed to identify the independent association of GV with MAEs.

Results: Of the 381 patients, 79 (20.7%) developed MAEs. The 30-day mortality of the overall study cohort was 5.23%. The multivariate logistic regression analysis indicated that 24-hour GV, measured as the CV [odds ratio (OR) =1.49, 95% CI, 1.23–3.57, P=0.012], was significantly associated with MAEs in IE patients. For every 10% increase in 24-hour CV, there was a 49% increase in the risk of MAEs. Furthermore, compared to patients in the low tertile of GV, patients in the top tertile of 24-hour GV had a higher 30-day mortality and an increased incidence of heart failure and hemodialysis as well as longer ventilation support.

Conclusions: The results of this retrospective investigation demonstrated that increased GV measured by CV is an independent predictor of postoperative MAEs in patients undergoing surgical treatment for IE.

Keywords: Infective endocarditis (IE); major adverse events (MAEs); glucose variability (GV)

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Introduction

The treatment of infective endocarditis (IE) remains challenging for cardiologists and cardiac surgeons in the new century despite recent advances in medicine over the past decades. According to recent reports, complications and mortality rates remain high in IE patients, even in the developed world (1). The major adverse events (MAEs) that occur in postoperative patients include all-cause death, stroke, myocardial infarction, acute heart failure, IE recurrence, acute renal failure and sepsis. These MAEs are closely associated with patient prognosis and mortality. Thus, the identification of a biomarker at the initial evaluation that could predict MAEs in patients after surgical intervention would be very valuable and helpful for clinical care.

The disease process of IE is usually accompanied by a systemic inflammatory response, which consequently causes aberrant fluctuations in serum glucose levels. Disturbances of glucose metabolism are frequently seen in critically ill patients with IE. Sustained hyperglycemia is an established risk factor for adverse ICU outcomes following cardiovascular surgery (2). Glucose variability (GV) is a relatively novel indicator which refers to swings in blood glucose levels (3), it has a broader meaning than glucose numerical value itself because it alludes to blood glucose oscillations that occur throughout the day, not only including hyperglycemia but also hypoglycemic periods and postprandial increases, as well as blood glucose fluctuations that occur at the same time period. It has been demonstrated that elevated GV is associated with MAEs after coronary artery bypass grafting (CABG) (4). Whether postoperative GV has important value in predicting the prognosis of IE patients remains unknown and needs further investigation. The aim of the present study was to retrospectively investigate the prognostic value of GV in predicting postoperative MAEs in IE patients. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-2692).

Methods

Patient cohort

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective observational study was approved by the institutional review board of the First Affiliated Hospital of Sun Yat-sen University (IRB-FAH-SYSU). The need

for informed consent was waived due to the retrospective nature of the study and the method of data extraction of medical records. The data for this retrospective study were extracted from electronic patient medical records using the hospital information system of the First Affiliated Hospital of Sun Yat-sen University (HIS/FAHSYSU) and the intensive care medical record system of the First Affiliated Hospital of Sun Yat-sen University (ICMRS/FAHSYSU).

Between October 2007 and August 2019, a total of 583 consecutive patients who received a diagnosis of definite IE in the First Affiliated Hospital of Sun Yat-sen University were screened for eligibility. Patients were excluded if they did not undergo surgical treatment, if they had incomplete postoperative glycemic records, or if they developed severe hypoglycemic events preoperatively. In total, 381 patients with IE who underwent surgical treatment at our institution were enrolled in the present study (*Figure 1*). IE was diagnosed according to the modified Duke criteria (5), and vegetation was classified by transthoracic or transesophageal echocardiography. Blood culture results were obtained from bacteriology laboratories, and antibiotics were administered according to results of antibiotic susceptibility testing.

Surgical techniques

Candidates for surgical treatment were determined in accordance with the ESC Guidelines for the management of IE (6). All surgeries were performed through median sternotomy, with cardiopulmonary bypass (CPB) in mild systemic hypothermia (32–34 ℃) and antegrade crystalloid cardioplegia. The surgical procedure was performed according to the predisposing heart disease (*Table 1*). Either valve replacement or valve repair procedures were performed if the native valves were affected (*Table 2*).

Protocol for postoperative glucose monitoring and control

After admission to the cardiothoracic intensive care unit of the First Affiliated Hospital of Sun Yat-sen University, patients received frequent glucose monitoring in accordance with the First Affiliated Hospital of Sun Yat-sen University Cardiovascular Surgical Intensive Care Unit Blood Glucose Monitoring and Control Protocol (https://cdn.amegroups.cn/static/public/JTD-20-2692-1.pdf). Continuous intravenous insulin infusion was administered if required, which aims for a target glucose range from 4–10 mmol/L (72–180 mg/dL). Of 381 patients, 199 (52.2%) required postoperative insulin infusion, and 320 patients (84.1%)
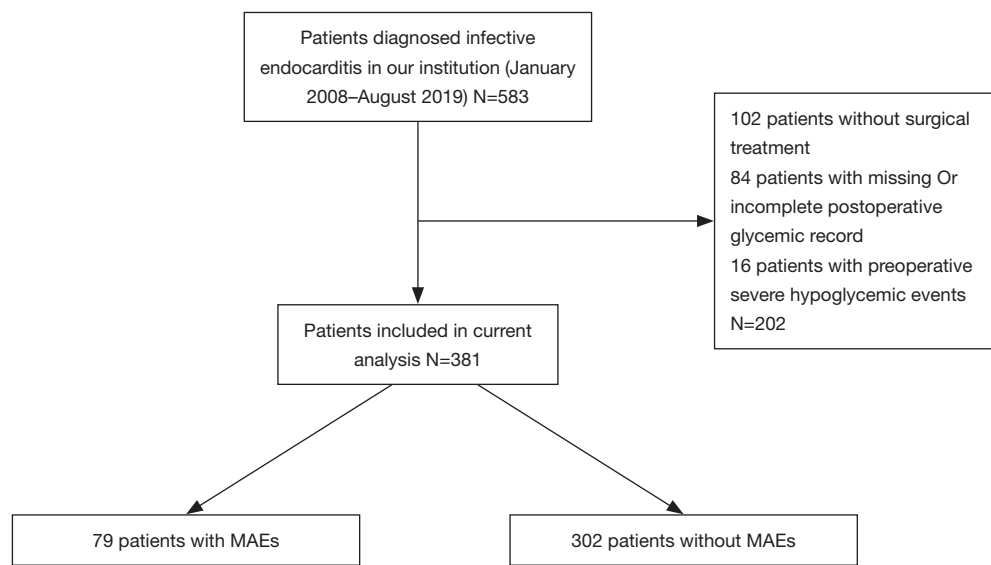
Figure 1 Flow diagram of the patient cohort. MAEs, major adverse events.

achieved the target postoperative glucose levels of 4–10 mmol/L. The glucose levels within the first 24 hours postoperatively were collected for further glycemic variability calculations. Episodes of hypoglycemic events (defined as a glucose level <70 mg/dL), severe hypoglycemic events (<50 mg/dL) and hyperglycemic events (>180 mg/dL) were recorded.

Glycemic variability parameters

Glycemic variability within the first 24 hours in the ICU was evaluated using the following parameters: (I) mean 24-hour glucose, defined as the mean of the glucose levels recorded within the first 24 hours. (II) standard deviation (SD), defined as the SD of all blood glucose readings in a patient within the first 24 hours postoperatively. (III) the coefficient of variability (CV), defined as the SD of blood glucose divided by the mean and expressed as a percentage. Although the SD can reflect the variation of glucose level swinging around the mean glucose, it is highly influenced by the mean glucose, i.e., patients with a higher mean glucose will have a higher SD. By dividing SD by mean glucose, CV is designed to adjust and normalize the variability among patients with different mean glucose levels and provide a more accurate and comparable metric of GV (3). (IV) the mean amplitude of glycemic excursions (MAGE) captures meal-time glucose fluctuations and is defined as the mean of blood glucose fluctuations larger than one SD of the glucose measurements (3).

Outcome assessment

The primary endpoint was the incidence of postprocedural MAEs occurring between the first day and the 30th day after open-heart surgery. This composite endpoint included 30-day death from all causes, postoperative neurological events, acute heart failure, IE recurrence, acute renal failure requiring dialysis, sepsis and prolonged ventilation.

Statistical analysis

All statistical analyses were performed using SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Data are presented as the mean ± SD or median (25th percentile–75th percentile). Student's t test was used to compare normally distributed data between the groups. The Mann-Whitney U test was used to compare the nonnormally distributed data. Categorical variables were compared with Fisher's exact test.

For the multivariable logistic regression, a previously reported purposeful selection model-building strategy was used to create a parsimonious model that included preoperative and operative factors (7). Preoperative and operative candidate covariates with a P value less than 0.10 in the univariate analysis or covariates reported in previous literature to be associated with adverse events in IE patients

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Table 1 Preoperative characteristics of patients with and without postoperative major adverse events

Variables	With MAEs (N=79)	Without MAEs (N=302)	P value
Male	56 (70.8)	183 (60.6)	0.117
Age (years)	45±17	41±16	0.058
BMI	21.7±3.5	22.4±2.9	0.33
NYHA class III or IV	36 (45.6)	116 (38.4)	0.249
Diabetes	8 (10.1)	24 (7.9)	0.650
Insulin-dependent diabetes	2 (2.5)	9 (3.0)	0.832
Hemoglobin A1c	6.1±1.4	6.4±1.2	0.277
Hyperlipidemia	7 (8.9)	21 (7.0)	0.628
Current smoker	14 (17.7)	26 (8.6)	0.023
Hypertension	18 (22.8)	51 (16.9)	0.184
Atrial fibrillation	9 (11.4)	39 (12.9)	0.849
Chronic lung disease	3 (3.8)	7 (2.3)	0.438
Steroid use	3 (2.5)	5 (1.6)	0.370
Neurological events*	11 (13.9)	26 (8.6)	0.198
Systemic emboli	7 (8.9)	11 (3.6)	0.036
CKD	7 (8.9)	12 (4.0)	0.144
Preoperative dialysis	2 (2.5)	4 (1.3)	0.608
Preoperative shock	4 (5.0)	6 (1.9)	0.226
Previous myocardial infarction	2 (2.5)	1 (0.3)	0.115
LVEF (%)	64±11	66±9	0.246
Microorganism			
Culture positive	41 (51.9)	138 (45.7)	0.375
Staphylococcus	10 (12.7)	19 (6.3)	0.090
Streptococcus	19 (24.1)	65 (21.5)	0.649
Other microbes	12 (15.2)	54 (17.9)	0.621
Uncontrolled infection#	8 (10.1)	12 (4.0)	0.043
Microorganism in uncontrolled infection			
Staphylococcus aureus	3	5	–
Coagulase-negative staphylococcus	2	2	–
Streptococcus	1	2	–
Enterococcus	1	1	–
Fungal	2	1	–
Other microbes	0	1	–

Table 1 (*continued*)

Table 1 (*continued*)

Variables	With MAEs (N=79)	Without MAEs (N=302)	P value
Predisposing heart disease			
Rheumatic heart disease	7 (8.9)	18 (6.0)	0.442
Degenerative	37 (46.8)	155 (51.3)	0.528
Congenital heart disease	8 (10.1)	25 (8.3)	0.653
Prosthetic valve endocarditis	3 (3.8)	2 (0.6)	0.0625
Lead involvement	0 (0)	2 (0.6)	1.000
Other diseases	25 (31.6)	99 (32.7)	0.893

Data are expressed as mean ± standard deviation and n (%). *Postoperative neurological events include the following events: stroke, embolic infarction, abscess and subarachnoid bleeding. #Uncontrolled infection: endocarditis refractory to sufficient antibiotics therapy for 2 weeks. MAEs, major adverse events; CKD, chronic kidney disease; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.

were included in the multivariable logistic regression. Variables not contributing to the model (P>0.05) were individually removed, and the model was refitted at each step to create the most parsimonious model. Model fit was assessed and determined by the Hosmer-Lemeshow test. A series of logistic regression models was created with nine preoperative and operative variables and 24-hour GV to determine the correlation between 24-hour GV and MAEs in the IE patient population. For all tests, P<0.05 was considered to indicate statistical significance.

Results

Baseline characteristics and intraoperative data

The preoperative characteristics and intraoperative parameters of the patients with and without MAEs are listed in *Tables 1* and *2*. Most preoperative parameters were identical between patients with or without MAEs, except for current smoking and the incidence of systemic emboli (P=0.023 and P=0.036, respectively). It is noteworthy that the incidence of diabetes, insulin-dependent diabetes and hemoglobin A1c were not significantly different between these two groups. The uncontrolled infection rate was significantly higher in patients with MAEs than in those without MAEs (P=0.043).

Episodes of MAEs in the study cohort

The total number of episodes of MAEs was 117 (*Table 2*). Of the entire study cohort, 20 patients died within 30 days postoperatively. The 30-day mortality of the entire study

cohort was 5.23%. Additionally, 31 patients developed heart failure in the postoperative phase, 21 patients needed hemodialysis in the ICU, 24 patients required prolonged ventilator support, 11 patients experienced neurological events, and sepsis and IE recurrence were found in 7 and 3 patients, respectively. Furthermore, the study population was divided into two groups of high and low postoperative glycemic fluctuation according to GV levels (*Table 3*). High GV is defined as the top tertile of 24-hour postoperative GV measured by CV, and low GV is the bottom tertile of 24-hour postoperative GV measured by CV. As demonstrated in *Table 3*, compared with patients with low GV, patients with high 24-hour GV had a higher 30-day mortality (P=0.019). Moreover, patients in the top tertile of 24-hour GV exhibited a higher incidence of heart failure, hemodialysis and prolonged ventilation support than patients in the low tertile of 24-hour GV (P=0.021, 0.006 and 0.003, respectively). The overall episodes of MAEs and the number of cases with MAEs were found to be significantly higher in patients with high 24-hour GV than in those with low 24-hour GV.

Glycemic variability

Measures of postoperative glycemic variability are listed in *Table 4*. Interestingly, there were no significant differences in the mean 24-hour glucose levels between the groups with and without MAEs (P=0.625). However, patients with MAEs had significantly higher SD, CV and MAGE glucose levels than patients without MAEs (P<0.001, P<0.001 and P=0.001, respectively), suggesting that the measures of glycemic fluctuation are more sensitive than the mean

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Table 2 Intraoperative and postoperative parameters of patients with and without postoperative major adverse events

Intraoperative variables	With MAEs (N=79)	Without MAEs (N=302)	P value
Emergency surgery	6 (7.6)	4 (1.3)	0.006
CPB time (min)	114±21	117±16	0.471
X-clamp time (min)	69±13	64±11	0.247
Valve involved			
Mitral	37 (46.8)	146 (48.3)	0.899
Aortic	14 (17.7)	49 (16.2)	0.735
Mitral and aortic	11 (13.9)	22 (7.3)	0.072
Tricuspid	2 (2.5)	3 (1.0)	0.277
Vegetation size ≥10 mm	36 (45.6)	90 (29.8)	0.011
Procedure			
Valve repair	2 (2.5)	3 (1.0)	0.277
Valve replacement	68 (86.1)	281 (93.0)	0.655
Tricuspid ring plasty	11 (13.9)	56 (18.5)	0.408
Bypass surgery	3 (3.8)	5 (1.7)	0.376
Aortic surgery	2 (2.5)	4 (1.3)	0.404
Other procedures	10 (12.7)	29 (9.6)	0.179
ICU stay (d)[#]	2 (2.75)[#]	1 (1)[#]	0.002
Hospital stay (d)	41±15	37±16	0.155
Postoperative MAEs			
30-day mortality	20	–	–
Heart failure	31	–	–
Recurrence of IE	3	–	–
Acute renal failure in need of dialysis	21	–	–
Sepsis	7	–	–
Prolonged ventilator	24	–	–
Postoperative neurological events*	11	–	–
Total onsets of MAEs (composite of above)	117	–	–

Data are expressed as mean ± standard deviation and n (%). [#]Data are expressed as median (25th–75th percentile); *Postoperative neurological events include the following events: stroke, embolic infarction, abscess and subarachnoid bleeding. MAEs, major adverse events; CPB, cardiopulmonary bypass; ICU, intensive care unit; X-clamp time, cross-clamp time.

glucose level. The number of patients who required postoperative insulin infusion were not different between the two groups (P=0.0579). Moreover, compared with those without MAEs, patients with MAEs had more recorded episodes of hypoglycemic events, severe hypoglycemic events and hyperglycemic events (P<0.001, P=0.009 and P<0.001, respectively).

Multivariable logistic regression to predict postoperative MAEs

Nine preoperative and intraoperative candidate covariates (*Table 5*) were included in the parsimonious model for multivariable logistic regression. After progressively adjusting for these covariates, 24-hour GV measured as CV (odds ratio 1.49, 95% confidence interval, 1.23–3.57,

Table 3 Postoperative major adverse events (MAEs) in patients with high and low postoperative glycemic fluctuation

Variables	High GV (N=127)	Intermediate GV (N=127)	Low GV (N=127)	P value
30-day mortality	11 (8.7)	7 (5.5)	2 (1.6)	0.019
Heart failure	16 (12.6)	10 (7.9)	5 (3.9)	0.021
Recurrence of IE	0 (0)	2 (1.5)	1 (0.8)	0.992
Acute renal failure in need of dialysis	15 (11.8)	3 (2.3)	3 (2.3)	0.006
Sepsis	2 (1.6)	5 (3.9)	0 (0)	0.498
Prolonged ventilator	14 (11.0)	6 (4.7)	2 (1.6)	0.003
Postoperative neurological events*	6 (4.7)	3 (2.3)	2 (1.6)	0.172
Total onset of MAEs (composite of above)	64 (50.4)	36 (28.3)	18 (14.2)	<0.001
Cases with MAEs	51 (40.2)	22 (17.3)	13 (10.2)	<0.001

High glucose variability is the top tertile of 24-hour postoperative glucose variability measured by coefficient of variation. Intermediate GV is the middle tertile of 24-hour postoperative glucose variability measured by coefficient of variation. Low glucose variability is the bottom tertile of 24-hour postoperative glucose variability measured by coefficient of variation. Data are expressed as mean ± standard deviation and n (%). *Postoperative neurological events included the following events occurred in central nervous system: stroke, embolic infarction, abscess and subarachnoid bleeding. GV, glucose variability; MAEs, major adverse events.

Table 4 Measures of postoperative glycemic fluctuation between patients with and without postoperative major adverse events

Variables	With MAEs (N=79)	Without MAEs (N=302)	P value
Mean 24-h glucose (mmol/dL)	10.05 (2.11)	10.18 (1.91)	0.625
Standard deviation of 24-h glucose	2.74 (2.29)	1.92 (1.26)	<0.001
Coefficient of variation of 24-h glucose	28 (16.0)	19 (10.0)	<0.001
Mean amplitude of glycemic excursions (MAGE) of 24-h glucose	4.2 (4.11)	3.08 (2.15)	0.001
Cases needed infusion of insulin	49 (62.0)	150 (49.7)	0.0579
Cases with hypoglycemic events (<70 mg/dL)	11 (13.92)	1 (0.3)	<0.001
Cases with severe hypoglycemic events (<50 mg/dL)	3 (3.80)	0 (0)	0.009
Cases with hyperglycemic events (>180 mg/dL)	72 (91.14)	300 (99.34)	<0.001

Variables of postoperative glycemic fluctuation are presented as medians (interquartile range), the enumeration data are presented as n (%). Mean 24-h glucose, Standard deviation of 24-h glucose, coefficient of variation of 24-h glucose and mean amplitude of glycemic excursions of 24-h glucose are presented as mmol/dL. MAEs, major adverse events.

P=0.012) was significantly associated with postoperative MAEs in IE patients. In the current study, the OR for 24-hour GV reflects a 10% change in GV measured as CV; thus, the current result exhibited in our patient cohort shows that, for every 10% increase in 24-hour CV, there was a 49% increase in the incidence of MAEs in IE patients.

Discussion

In the past decade, there have been quite a few advancements in diagnostic and therapeutic approaches for

IE; however, IE remains one of the most life-threatening cardiothoracic diseases and is associated with high mortality and morbidity (8-10). A better understanding of the association between clinical markers and the outcome is crucial to treatment decisions and prognostic evaluations. Although a small number of clinical markers were reported to not be responsible for the mortality and occurrence of MAEs in this population (5,11,12), the role of glucose levels and variability has not yet been investigated. Glucose levels are frequently monitored in the ICU, which makes GV a simple and cost-effective indicator for the prognostic

Table 5 Multivariable logistic regression of postoperative 24-h glucose variability and postoperative major adverse events

Variables	OR	95% CI	P value
24-h glucose variability and MAEs			
Age	1.08	0.98–1.21	0.262
Hemoglobin A1c	0.92	0.84–1.02	0.345
Systemic emboli	2.63	0.82–5.42	0.114
Staphylococcus infection	1.18	0.93–2.85	0.193
Uncontrolled infection	2.51	0.63–6.94	0.455
Prosthetic valve endocarditis	5.81	0.77–22.10	0.677
Emergency surgery	5.27	1.285–12.51	0.025
Vegetation size ≥10 mm	1.51	1.12–3.68	0.043
Mitral and aortic involvement	1.78	0.88–5.25	0.237
24-h glucose variability	1.49	1.23–3.57	0.012
Constant	0.02		0.010

MAEs, major adverse events.

evaluation of IE patients. A meta-analysis of twelve retrospective studies reported that GV had a statistically significant association with high mortality in patients who underwent general surgery in the ICU (13). However, to date, no study has reported the efficacy of glycemic variability for predicting outcomes of patients with IE. The main finding of our study is that increased GV measured by CV is associated with MAEs and is also an independent predictor of postoperative MAEs, and for every 10% increase in 24-hour CV, there is a 49% increase in the incidence of MAEs.

We retrospectively reviewed a study cohort of 381 IE patients who underwent surgical treatment in our institution in the past decade. Of these 381 patients, 79 patients (20.7%) developed MAEs postoperatively. The univariate analysis indicated that postoperative MAEs were associated with age, systemic emboli, staphylococcus infection, uncontrolled infection, prosthetic valve endocarditis, emergency surgery, vegetation size ≥10 mm and both mitral and aortic involvement. In the previous studies, these risk factors were reported to be associated in varying degrees with the outcomes of IE patients (12,14,15). On the other hand, although in the current study hemoglobin A1c did not show any significant difference between patients with and without MAEs, the study by Subramaniam *et al.* demonstrated that preoperative hemoglobin A1c identifies the risk for postoperative glycemic variability and had

somewhat of an effect on the incidence of MAEs following bypass surgery (16); thus, we also included hemoglobin A1c in our model to minimize its influence on postoperative glycemic variability. With these risk factors entered into the aforementioned parsimonious model and after adjusting for nine covariances in the multivariable logistic regression, the 24-hour glycemic variability measured as CV was identified as an independent predictor for postoperative MAEs. We also found that, compared to patients with low GV, patients with high 24-hour GV had a higher 30-day mortality and increased incidence of heart failure and hemodialysis as well as longer ventilation support.

The findings of the present study are clinically relevant because the study cohort was under tight glucose control with an insulin infusion following the aforementioned protocol in the ICU, which indicated that a more stable and lower GV would be measured. Nonetheless, the current results revealed that increased GV rather than hyperglycemia was more detrimental to IE patients. Several previous studies may provide some evidence to explain why GV is important in predicting clinical outcomes. Liu and colleagues demonstrated that oscillating high glucose could be more detrimental and toxic to human coronary artery endothelial cells than persistent high glucose, probably due to the enhancement of oxidative stress and cellular apoptosis induced by frequent glucose swings (17). Another study by Ying *et al.* reported that blood GV can worsen cardiac

Table 6 Measures of glycemic variability between patients underwent intensive glucose control[#] and conventional glucose control[*]

Variables	With intensive glucose control (N=32)	With conventional glucose control (N=349)	P value
Mean 24-h glucose (mmol/dL)	8.13 (3.62)	10.54 (2.24)	0.12
Standard deviation of 24-h glucose	3.19 (2.7)	2.36 (1.22)	0.33
Coefficient of variation of 24-h glucose	26 (19.0)	24 (14.0)	0.61
Mean amplitude of glycemic excursions (MAGE) of 24-h glucose	3.67 (3.1)	3.33 (2.55)	0.47
Cases needed infusion of insulin	22 (68.7)	177 (50.7)	0.025

Variables of postoperative glycemic fluctuation are presented as medians (interquartile range), the enumeration data are presented as n (%). Mean 24-h glucose, Standard deviation of 24-h glucose, Coefficient of variation of 24-h glucose and Mean amplitude of glycemic excursions of 24-h glucose are presented as mmol/dL. [#]Intensive glucose control: glucose levels are monitored and insulin infusion is used to achieve a rigorous glucose target (72 to 144 mg/ dL); [*]Conventional glucose control: glucose levels are monitored and insulin infusion is used to achieve a broad glucose target (72 to 180 mg/dL).

fibrosis, possibly through mechanisms involving oxidative stress, by inhibiting the AKT signaling pathway (18). Furthermore, in diabetic patients, compared to an aberrant mean glucose level, oscillating glucose levels were more deleterious to endothelial function and produced more oxidative stress (19). The above studies suggest that glycemic fluctuation results in endothelial impairment and metabolic disorders and causes further multiple organ dysfunction.

In 2009, Finfer *et al.* published a landmark glucose control study and demonstrated that intensive glucose control increased mortality among adults in the ICU comparing to conventional control (20). Afterwards the majority of guidelines concerning ICU glycose management recommended that insulin infusion should be used to achieve a broader glucose target (less than 180 mg/dL) other than previous rigorous target (less than 144 mg/dL). Therefore, the protocol of glucose management in our cardiovascular ICU was updated in August 2010 (https://cdn.amegroups.cn/static/public/JTD-20-2692-1.pdf). Apparently, the patients in the present study cohort who were hospitalized between 2007 to 2010 with initial glucose level between 144 to 180 mg/dL received more intensive glucose checks and earlier intervention of insulin than those who were admitted afterwards and managed following the updated protocol. To identify whether the changes in protocol of glucose management have influence on the findings of current study, we performed a statistical comparison between the patients who were admitted before update of protocol and afterwards. As showed in *Table 6*, Only a small proportion of patients (32 cases, 8.3%) were admitted to our institution

before protocol update whereas others (349 cases) were admitted afterwards. The metrics of GV did not show any statistically difference between patients treated with different strategies, which possibly was due to the small case number treated with intensive glucose control. Therefore, we believed the findings from current study is still clinically significant and applicable even though the criteria of glucose target and insulin infusion was changed during the study period.

There are several limitations in this study. First, in clinical practice, glucose monitoring in the ICU was not performed at the same interval, and critically ill patients and patients in need of intravenous insulin infusion were more likely to receive more frequent glucose measurements than other patients, which probably resulted in bias in the GV calculation. Because in accordance with the protocol of glucose management in current study, the patients whose blood glucose >144 mg/dL or in need of insulin infusion are able to receive a higher frequency of glucose measurements, patients with high frequency of measurements in the first 24 hours are likely to have a more stable and accurate standard deviation than those with less measurements. Given standard deviation as an important variable in calculating CV and MAGE, it's likely that there is a smaller bias of CV and MAGE calculation in patients with more measurements than those with less measurements. Second, the study population comprised patients with different underlying heart diseases who underwent different types of surgical procedures, e.g., valve surgeries and congenital heart surgeries. It is likely that the underlying disease and type of surgical treatment would have different influences on the outcome of the patients. Further investigation

focused on the response of individual populations to specific surgical treatments is warranted. Third, a small number of patients without complete perioperative glycemic records were excluded from this study, especially because hemoglobin A1c is not a mandatory preoperative test in our institution; however, we still believe that the evidence and data from the present cases are sufficient and convincing to support the current conclusion. Fourth, the available metrics of GV in present study, i.e., SD, CV and MAGE, cannot provide information that accounts for the time-duration of particular glucose value. We have noted continuous glucose monitoring (CGM), a novel continuous glucose monitoring technique, can offer better information of time-duration of glucose values and enable rapid and sensitive modification of insulin infusion. However, due to the consideration of cost performance and medical insurance policy, the CGM device is not yet in clinical use in our institution. Considering the findings of current study suggested the potential effectiveness of GV metrics in predicting MAEs in IE population, we believe introducing CGM has good prospects in this population and is deserving further investigation in the future.

Conclusions

In summary, the results of this retrospective investigation demonstrated that increased GV measured by CV is not only associated with MAEs but also an independent predictor of postoperative MAEs in patients undergoing surgical treatment for IE, and for every 10% increase in 24-hour CV, there is a 49% increase in the risk of MAEs.

Acknowledgments

Footnote

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