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ORIGINAL ARTICLE

Effects of Glucose Variability on Short-Term Outcomes in Non-Diabetic Patients After Coronary Artery Bypass Grafting: A Retrospective Observational Study

Xuting Li, MSN [a], Xuezhen Zhou, MSN [b,1], Juan Wei, MSN [c], Hongping Mo, MSN [d], Hongyu Lou, MSN [e], Ni Gong, PhD [e], Meifen Zhang, PhD [e*]**

[a]Clinical Nursing Teaching and Research Section, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China
[b]Department of Nursing, Sun Yat-sen Memorial Hospital, Guangzhou, Guangdong 510080, China
[c]Guangzhou Panyu Central Hospital, Guangzhou, Guangdong 510080, China
[d]Department of Intensive Care Unit, Sun Yat-sen Memorial Hospital, Guangzhou, Guangdong 510080, China
[e]School of Nursing, Sun Yat-sen University, Guangzhou, Guangdong 510080, China

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Background Postoperative hyperglycaemia has been shown to have adverse effects on patients after coronary artery bypass grafting surgery (CABG). However, whether glucose variability has an effect on patients' outcomes is still uncertain. The aim of this study is to explore the effects of glucose variability on short-term outcomes in non-diabetic patients undergoing coronary artery bypass grafting.

Methods This is a retrospective observational study utilising data collected after patients had left the hospital. This study was performed on 137 non-diabetic patients undergoing coronary artery bypass grafting from January 2011 to June 2013. Blood glucose at 72 hours post operation was obtained and glucose variability was measured by mean postoperative blood glucose and mean of daily difference (MODD). Short-term outcomes included duration of intensive care unit (ICU) stay, mechanical ventilation time, length of hospital stay, and occurrence of arrhythmia. Patients with mean postoperative blood glucose $\geq$7.00 mmol/L were defined as hyperglycaemic, and patients with MODD $\geq$1.40 mmol/L were considered to be abnormal. Outcome variables were compared between patients in euglycaemic and hyperglycaemic groups, and between patients in normal and abnormal groups.

Results In our study, patients with hyperglycaemia spent more time staying in ICU ($p < 0.01$), and patients with large glucose variability (abnormal MODD) had higher incidences of arrhythmia (23% vs 4.2%, $p < 0.05$). Regression analysis showed that MODD can affect occurrence of arrhythmia ($p = 0.004$) and that mean postoperative blood glucose levels can affect duration of ICU stay ($p < 0.001$).

*Corresponding author at: Department of Nursing, Sun Yat-sen University, No. 74 Zhongshan Road II, Guangzhou, Guangdong 510080, China. Tel.: +8613416225022/+8615013217344. Email: zhmfen@mail.sysu.edu.cn
**Corresponding author. Email: gongn@mail.sysu.edu.cn
[1] Co first author.

Conclusions Patients' postoperative glucose variability after CABG is an important predictor of the negative outcomes regarding duration of ICU stay and occurrence of arrhythmia. Large glucose variability can have negative effects on short-term outcomes in patients.

Keywords Glucose variability • Outcome • Coronary artery bypass grafting

Introduction

Ischaemic heart disease (IHD) has been one of the leading causes of death worldwide over the past decade [1,2]. Coronary artery bypass grafting (CABG) has been proven to be an important treatment to eliminate or relieve the symptoms of ischaemic heart disease [3]. CABG is mainly performed with the aid of cardiopulmonary bypass. During this procedure, blood is circulated through the body by an external mechanical pump, and the subsequent inflammatory response may cause metabolic disorders in patients after the surgery [4,5].

In patients undergoing CABG, hyperglycaemia is the most commonly reported metabolic disorder during and after surgery, and is a strong predictor of adverse outcomes such as higher frequency of arrhythmias, atelectasis and wound infections [6,7]. However, by applying a tight glycaemic control strategy in patients undergoing cardiac surgry, researchers have found that hypoglycaemia can also cause adverse outcomes [8]. This variation in blood glucose amplitude is defined as glucose variability. One observational cohort study indicated that glycaemic variability which increased postoperatively in patients with preoperative HbA1C ≥6.5% predicts major adverse events following CABG surgery [9]. In another prospective study focussing on patients after cardiovascular surgery, researchers found that high glycaemic variability during subcutaneous insulin injection was associated with increased risk for surgical site infections and atrial fibrillation [10]. However, one prospective observational study suggested that there was no association between postoperative glycaemic variability and major adverse events after isolated cardiac valvalar surgery in contrast to previous studies [11]. There was no adquate evidence clearly revealing relationships between glucose variability and outcomes in patients after cardiac surgery.

Our study focusses on non-diabetic patients, because postoperative hyperglycaemia is often considered to be a protective stress reaction and is often neglected. In previous studies, glucose variability was mainly discussed in diabetic patients undergoing CABG. Thus, the purpose of this current study is to explore the effects of glucose variability on short-term outcomes in non-diabetic patients undergoing CABG. Short-term outcomes included duration of ICU stay, mechanical ventilation time, length of hospital stay, and occurrence of arrhythmia. Studies show that mortality rates are higher in patients with prolonged mechanical ventilation time, prolonged ICU stay, and prolonged hospital stay [12–14]. Moreover, arrhythmias following CABG were considered as major postoperative morbidities [15].

Materials and Methods

Study Design

This is a retrospective observational study.

Patients and Sample Size

Patients undergoing CABG between January 2011 and June 2013 in a tertiary hospital in China participated in this study. Patients who had been diagnosed with diabetes, pancreatic cancer, glucagonoma, and pancreatitis, or had used corticosteroids within 3 days of the surgery were excluded, and patients who underwent open chest reoperation or did not survive 72 hours after surgery were also excluded. As this study is part of a project investigating glucose variability in patients undergoing coronary artery bypass grafting, sample size is calculated in the project. In multiple regression analysis, sample size is usually $5 \sim 10$ times the number of potential risk factors [16]. In the project, the number of potential risk factors is 21 and minimum sample size is 105. Two methods were used to group patients in this study. Patients with mean postoperative blood glucose ≥7.00 mmol/L were defined as hyperglycaemic, versus euglycaemic. And patients with MODD ≥1.40 mmol/L were considered as abnormal, versus normal. Short-term outcomes were compared between patients in euglycaemia and hyperglycaemia groups, and between patients in normal and abnormal groups.

The ethical application of this study including 150 patients undergoing CABG was approved by the Ethics Committee at the hospital.

Data Sources and Variables

All data was retrospectively obtained from the medical records. The presence of comorbidities was determined by directly taking the patients' histories. Coronary artery bypass grafting surgery was performed using standard cardiopulmonary bypass with bicaval and aortic cannulation. After the surgery, all patients returned to cardiac ICU. Baseline variables includes age, gender, body mass index (BMI), history of hypertension, history of smoking, preoperative blood glucose, ejection fraction (EF), and NYHA (New York Heart Association) class. Postoperative blood glucose data was collected by fasting blood sample for each patient every 6 hours and at 6 AM each day during the first 3 days after surgery. Glucose variability was measured by mean postoperative blood glucose and mean daily difference (MODD). Short-term outcomes included duration of ICU stay, mechanical ventilation time, length of hospital stay, and occurrence of arrhythmias during hospital stay. All data was objective and were collected and checked by two researchers.

Statistical Methods

Statistical analysis was performed using the SPSS 20.0 statistics software for Windows (SPSS Inc., Armonk, NY, USA). Categorical values have been presented as frequency (%), and continuous variables have been presented as mean ± standard deviation. The t-test was used for comparison of age, preoperative blood glucose and preoperative EF. Chi-square was used for comparison of gender, history of hypertension, history of smoking, NYHA class and occurrence of arrhythmia. A t-test for two independent samples was used to compare duration of ICU stay, mechanical ventilation time and length of hospital stay. Regression analysis was used to examine the predictors of each outcome, and predictors included baseline variables, mean postoperative blood glucose and MODD. In each statistical analysis, the test of significance was two-sided, and a p value of <0.05 was considered statistically significant.

Results

Of the 140 patients who met the inclusion criteria during the study period, 137 patients were recruited into this study and three patients were excluded because of incomplete data. Median age was 64.45 years and 67.9% of patients were male. There were 68 (49.6%) patients with a history of smoking. 36.5% of the patients had heart function of NYHA Class I.

Baseline variables are compared between patients in euglycaemia and hyperglycaemia group in Table 1. In Table 2 we compare baseline variables between patients in normal and abnormal MODD group. Higher rates of smoking history were shown in both the hyperglycaemia group and abnormal MODD group, and there were more patients with a cardiac function of NYHA III ~ IV in the abnormal MODD group. Other variables are comparable at baseline.

Short-term outcomes and comparisons between the two groups are shown in Tables 3 and 4. The average duration of ICU stay among 137 patients was 67.17 hours, and patients had an average mechanical ventilation time of 18.90 hours. Furthermore, patients stayed in the hospital for 18 days on average. There were 27 patients who developed arrhythmias after surgery. Patients with hyperglycaemia had a significantly longer duration of ICU stay ($p < 0.01$), and patients with abnormal MODD had a significantly higher rate of arrhythmia (23% vs 4.2%, $p < 0.05$). There were no significant differences in other aspects ($p > 0.05$).

Predictors of short-term outcomes are shown in Tables 5 and 6. Our results show that among all variables of short-term outcomes, mean postoperative blood glucose can affect ICU stay ($p < 0.001$) and MODD can affect incidence of arrhythmia ($p < 0.01$). With each 1.0 mmol/L increase in mean postoperative blood glucose, patients may stay in ICU for 7.44 days longer on average ($\beta_1 = 7.44$; $p < 0.001$). In addition, patients with abnormal MODD level had 1.5 times higher odds of having arrhythmia compared to those with normal MODD levels ($b_1 = 1.51$; $p = 0.004$).

Discussion

This study shows that postoperative glucose variability can impact outcomes in the following aspects. One is that mean postoperative blood glucose levels can affect duration of ICU

Table 1 Baseline variables of patients in euglycaemia and hyperglycaemia group (n = 137).

Variables	All (n = 137)	Euglycaemia (n = 11)	Hyperglycaemia (n = 126)	t/χ^2
Age(years), mean ± SD	64.45 ± 9.22	59.63 ± 10.94	64.88 ± 8.98	1.873
Gender				
Male, n(%)	93(67.9)	9(81.8)	84(66.7)	1.028
Females, n(%)	44(32.1)	2(18.2)	42(33.3)	
BMI, mean ± SD	23.60 ± 3.59	25.23 ± 3.51	23.46 ± 3.57	0.004
History of, n(%)				
Smoking	68(49.6)	9(81.8)	59(46.8)	4.96*
Hypertension	83(60.6)	2(18.2)	81(64.3)	2.99**
NYHA class, n(%)				3.25
I	50(36.5)	7(63.6)	43(34.1)	
II	62(45.3)	3(27.3)	59(46.8)	
III ~ IV	25(24.5)	1(9.1)	24(19.1)	
Preoperative blood glucose (mmol/L), mean ± SD	5.35 ± 1.05	4.86 ± 0.49	5.40 ± 1.07	2.109
Preoperative EF (%), mean ± SD	56.41 ± 10.98	62.18 ± 8.84	55.90 ± 11.04	1.407

Abbreviations: BMI, body mass index; NYHA class, New York Heart Association class; EF, ejection fraction.

*$p < 0.05$.

**$p < 0.01$.

Table 2 Baseline variables of patients in normal and abnormal MODD group (n = 137).

Variables	All (n = 137)	Normal MODD (n = 24)	Abnormal MODD (n = 113)	t/χ^2
Age(years), mean ± SD	64.45 ± 9.22	62.58 ± 11.65	64.86 ± 8.62	−0.91
Gender				3.19
Male, n(%)	93(67.9)	20(83.3)	73(64.6)	
Females, n(%)	44(32.1)	4(16.7)	40(35.4)	
BMI, mean ± SD	23.60 ± 3.59	24.25 ± 4.00	23.46 ± 3.50	0.183
History of, n(%)				
Smoking	68(49.6)	19(79.2)	49(43.4)	10.15**
Hypertension	83(60.6)	15(62.5)	68(60.2)	0.05
NYHA class, n(%)				1.19
I	50(36.5)	11(45.8)	39(34.5)	
II	62(45.3)	10(41.7)	52(46.0)	
III ~ IV	25(24.5)	3(12.5)	22(27.6)	
Preoperative blood glucose (mmol/L), mean ± SD	5.35 ± 1.05	5.24 ± 1.18	5.37 ± 1.02	−0.56
Preoperative EF (%), mean ± SD	56.41 ± 10.98	54.17 ± 11.20	56.88 ± 10.93	−1.10

Abbreviations: BMI, body mass index; NYHA class, New York Heart Association class; EF, ejection fraction.
** $p < 0.01$.

Table 3 Short-term outcomes of patients undergoing CABG in euglycaemia and hyperglycaemia group (n = 137).

Variables	All	Euglycaemia (n = 11)	Hyperglycaemia (n = 126)	Z/χ^2
Duration of ICU stay(min), mean ± SD	67.17 ± 38.22	41.45 ± 37.79	69.41 ± 37.57	−3.228**
The mechanical ventilation time(min), mean ± SD	22.54 ± 18.63	21.77 ± 19.81	22.61 ± 18.61	−0.757
Length of hospital stay(days), mean ± SD	19.89 ± 7.66	19.00 ± 12.26	19.96 ± 7.19	−1.353
Occurrence of arrhythmia, n(%)	27(19.7)	2(18.2)	25(19.8)	0.132

Abbreviations: ICU, intensive care unit; SD, standard deviation.
** $p < 0.01$.

Table 4 Short-term outcomes of patients undergoing CABG in normal and abnormal MODD group (n = 137).

Variables	All	Normal MODD	Abnormal MODD	Z/χ^2
Duration of ICU stay(min), mean ± SD	67.17 ± 38.22	62.37 ± 40.98	68.19 ± 37.72	−1.02
The mechanical ventilation time(min), mean ± SD	22.54 ± 18.63	23.15 ± 19.88	22.41 ± 18.45	−0.08
Length of hospital stay(days), mean ± SD	19.89 ± 7.66	22.13 ± 12.33	19.41 ± 6.22	−0.02
Occurrence of arrhythmia, n(%)	27(19.7)	1(4.2)	26(23)	2.10*

Abbreviations: ICU, intensive care unit; SD, standard deviation.
* $p < 0.05$.

stay and the other is that MODD can influence occurrence of arrhythmia.

The finding of the relationship between mean postoperative blood glucose levels and duration of ICU stay in this study is consistent with that of several previous findings on blood glucose control in cardiac surgery [17,18]. Although postoperative hyperglycaemia is often considered as a protective and stress reaction, studies show that blood glucose is

Table 5 Factors influencing duration of ICU stay (multiple regression analysis).

Selected variables	Unstandardised coefficients	Standardised coefficients	t	P value
Constant	85.89		3.83	<0.001
Mean of postoperative blood glucose	7.44	0.35	4.88	<0.001
Preoperative EF	−1.49	−0.43	−6.02	<0.001

$R^2 = 0.401$, $F = 44.77$, $p = 0.000$.
Abbreviation: EF, ejection fraction.

Table 6 Factors influencing the incidence of arrhythmia (binary logistic regression analysis).

Selected variables	Exp(B)	SE	95%CI	P value
Constant	0.76	0.49		<0.001
MODD	1.513	0.15	1.14 to 2.01	0.004

-2 Log likelihood = 127.32, $F = 8.68$, $p = 0.003$.
Abbreviations: Exp(B), regression coefficient; MODD, mean of daily difference; CI, confidence interval; SE, standard error.

an important factor influencing the mortality of patients in ICU [19]. Postoperative hyperglycaemia can enhance the glucose toxicity and oxidative stress reaction inside the body, which can increase tissue damage and insulin resistance. Meanwhile, it can induce arrhythmias by triggering the sympathetic nervous system, increasing the inotropy and chronotropy of cardiac muscle cells and shortening the refractory period [20]. Furthermore, regression analysis showed that preoperative EF is also a predictor of duration of ICU stay. Low ejection fraction signifies left ventricular dysfunction, and it is reported that patients with low EF are at a higher risk for postoperative complications and mortality [21]. The relationship between EF and the duration of ICU stay found in this study is the same as the relationships found in previous studies [22]. Moreover, we found that there were more patients having a history of smoking and hypertension in the hyperglycaemia group, but both variables failed to enter the regression equation identifying factors affecting the duration of ICU stay. Previous prospective studies reported that both smoking and hypertension were preoperative predictors of prolonged ICU stay in patients undergoing cardiac surgery [23,24], and that patients can benefit from smoking cessation prior to surgery [25]. But systematic review did not confirm the predicted effect of smoking and hypertension on prolonged ICU stay [26]. Thus, the effects of smoking and hypertension, which were different between patients with hyperglycaemia and euglycaemia, on duration of ICU stay in this study weren't strong enough and can be neglected based on literature and regression analysis.

Our study also reveals that non-diabetic patients with abnormal MODD have a greater chance of developing postoperative arrhythmia. Previous evidence shows that blood glucose variability plays an important role in the pathogenesis of arrhythmias [20]. The probable mechanism of the relationship between arrhythmia and glucose variability may be as follows [27,28]. Firstly, cells of different tissues can be antagonistic to the toxic effects of excessive glucose in the blood, but this antagonism function is weakened when the blood glucose variability is unstable. Large variabilities in blood glucose cause more damage to the nerve cells than constant hyperglycaemia, which affects electrophysiological signals in the heart. Secondly, large variability implies intermittent hyperglycaemia, which is known to accelerate apoptosis of endothelial cells, inhibiting cell proliferation and inducing production of oxygen free radicals [29,30]. These pathophysiological changes underlie arrhythmias. Lastly, intermittent hyperglycaemia can lead to the decreased release of the neurotransmitter nitric oxide (NO) along with the stiffening of endothelial cell membranes [31], which can exacerbate the vascular relaxation function disorder caused by hyperglycaemia, insulin resistance, and inflammatory response. Considering the effects on short-term outcomes of post-CABG patients, more attention should be paid to hyperglycaemic variability in the postoperative setting.

There were no statistically significant differences in mechanical ventilation time and length of hospital stay among different groups in this study. It has been reported that strict glucose control after surgery can shorten the mechanical ventilation time and length of hospital stay in patients undergoing cardiac surgery [32], which is different from this study. A possible reason for this difference may be that this study included only non-diabetic patients, and diabetic patients have a larger blood glucose variability than patients without diabetes. Thus, the effects of post-CABG strict blood glucose control on non-diabetic patients still require further investigation.

Our study mainly confirms that glucose variability can affect short-term outcomes in non-diabetic patients after CABG, which suggests that glycaemic control and monitoring should be practiced on not only diabetic patients but also non-diabetic patients as well. Stable glucose level is important in every individual after CABG.

This study has several limitations. Primarily, this study is limited by the sample size of participants, which is much smaller than that of most previous studies on glycaemic control, which have sample sizes of over one thousand. Additionally, because this study is a retrospective observational study, there may be bias. Also, in our study, baseline variables of participants in the two groups weren't completely comparable, as more patients in the hyperglycaemia and abnormal MODD group had a history of smoking and hypertension. Although these two variables didn't show up in the results of multiple regression analysis, we still can't completely rule out the effects of these two variables on outcomes, and further study may be needed.

Despite these limitations, our study may serve as a pilot study, showing that there are significant relationships between glucose variability and short-term outcomes in non-diabetic patients undergoing CABG, which suggests that doctors and nurses should pay more attention to glucose variability in patients after coronary artery bypass grafting. Further studies with a larger sample size may be necessary to confirm the results from our study. Further research may also focus on the specific pathophysiological mechanisms of the effects of glucose variability on the occurrence of arrhythmia, and on other factors that may explain the effects on prolonged ICU stay.

Conclusion

Glucose variability can influence the short-term outcomes in non-diabetic patients after coronary artery bypass grafting in several significant ways. Our study shows that glucose variability (measured by mean postoperative blood glucose and MODD) significantly affects duration of ICU stay and occurrence of arrhythmia, and large glucose variability is associated with longer duration of ICU stay and higher frequency of arrhythmias. Thus, more attention needs to be given to glucose variability in medical daily practice. Moreover, the mechanisms behind these effects and whether these effects can happen in patients after valve surgery need further investigation.

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