Association Between Blood Glucose Variability and the Characteristics of Vulnerable Plaque in Elderly Non-ST Segment Elevation Acute Coronary Syndrome Patients

Tao Zhang,¹ MD, Gong Su,¹ MD, Shu-hua Mi,¹ MD, Hong-xia Yang,¹ MD, Wei Xin,¹ MD, Wen-long Dai,¹ MD and Jing-hua Liu,¹ MD

Summary

Blood glucose variability is considered to be one of the risk factors for coronary heart disease, and there is growing evidence that blood glucose fluctuation is closely related to the characteristics of plaques. The aim of the study was to investigate the influence of blood glucose variability on the vulnerability of culprit plaques in elderly non-ST segment elevation acute coronary syndrome (NSTEMI-ACS) patients.

Coronary angiography and VH-IVUS were applied to evaluate the components of culprit plaque in NSTEMI-ACS patients. CGMS monitoring was performed for 72 hours and blood glucose variability was assessed by glycemic excursions (MAGE), absolute means of daily differences (MODD), postprandial glycemic excursions (PPGE), and the largest amplitude of glycemic excursions (LAGE). An oxidative stress indicator (urinary 8-iso-PGF_{2α}) was also tested.

Eighty two elderly NSTEMI-ACS patients were enrolled in this study. Higher glucose variability was associated with the increased culprit plaque instability. MODD was positively correlated with urinary 8-iso-PGF_{2α}. PPGE and urinary 8-iso-PGF_{2α} were independent risk factors for percent fibrous and necrotic volume in culprit plaques (PPGE: $\beta = -0.340$, $P = 0.024$; urinary 8-iso-PGF_{2α}: $\beta = -0.294$, $P = 0.013$).

Blood glucose variability is positively related to oxidative stress. With an increase in blood glucose variability, the instability of criminal plaques in elderly NSTEMI-ACS patients increased.

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Key words: Atherosclerosis, Glycometabolism, Oxidative stress, VH-IVUS

Acute coronary syndrome (ACS) and abnormal glucose metabolism are common diseases which threaten the life and health of elderly. Nowadays, the problem of aging is becoming more and more serious, therefore, we should pay attention and explore these health problems of the elderly. Patients with ACS are often associated with abnormal glucose metabolism which is closely related to the development of atherosclerotic plaque.¹⁾ It has been gradually recognized that abnormal glucose metabolism is not limited to the effects of chronic persistent hyperglycemia, but blood glucose fluctuations increase the severity of coronary plaques.²⁾ Our previous study found that blood glucose variability was related to the severity of coronary artery disease in patients with type 2 diabetes, moreover, it had an important effect on the adverse cardiovascular prognosis in patients with acute myocardial infarction.^{3,4)} Other studies have reported that the risk of death in ICU patients was not only related to average blood glucose levels, but also to the range of blood glucose fluctuations.⁵⁾ However, the mechanism of

blood glucose fluctuation on the occurrence and development of atherosclerosis is not completely clear. Blood glucose variability, as an important component of glucose metabolism, may affect plaque stability through direct or indirect effects. A previous study reported that oxidative stress was related to acute blood glucose fluctuation which could regulate the expression of matrix metalloproteinase (MMPs),⁶⁾ and then degrade the fibrous cap to reduce plaque stability and finally promote the formation of necrotic lipid core.⁷⁾ In addition, oxidative stress could increase the formation of oxidation LDL and foam cells, and promote apoptosis or necrosis of vascular smooth muscle cells, which further increased the plaque necrosis/lipid proportion of lipid core components, ultimately aggravating the plaque vulnerability.⁸⁾ However, previous small sample studies have suggested that blood glucose fluctuation might be associated with plaque instability in diabetic patients with coronary heart disease. However, there has been no relevant report on the relationship between blood glucose variability and plaque instability in

From the ¹Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China.

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Address for correspondence: Jing-hua Liu, MD, Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, No. 2 Anzhen Road, Chaoyang District, Beijing 100029, P.R. China. E-mail: liujinghua2017@126.com

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Figure 1. The patient was a 62 year old male diagnosed with unstable angina who had a history of dyslipidemia and hypertension. Coronary angiography showed localized severe stenosis in the proximal LAD with 84% plaque burden. VH-IVUS analysis showed the culprit lesion had higher percent lipid volume (18%) and necrotic core (26%). It should be considered as a vulnerable plaque.

elderly NSTEMI-ACS patients, and whether the relationship between blood glucose fluctuations and plaque instability is independent of oxidative stress still remains unknown.

Continuous glucose monitoring systems (CGMS), a kind of Holter minimally invasive blood glucose monitoring technology, can be used to continuously and accurately measure patient blood glucose excursion. Intravascular ultrasound combined with virtual histology (VH-IVUS) in the later stage can accurately and objectively evaluate the characteristics of coronary plaques. We will take advantage of these two measures to investigate whether glycemic fluctuations are independently related to plaque instability in elderly NSTEMI-ACS patients. The level of 24-hour urinary 8-iso-PGF_{2α} is a reliable oxidative stress indicator,⁹ and it will be measured to analyze whether the relationship between blood glucose fluctuations and plaque instability was independent of oxidative stress levels in the body.

Methods

This was a cross-sectional study which has been approved by the Institutional Ethics Committee of our university, and all subjects signed an informed consent form.

Patients: Patients in our institution were enrolled to take CGMS and VH-IVUS between January 1, 2016 to February 28, 2017. The inclusion and exclusion criteria were defined as follows:

Inclusion criteria: (1) over 60 years of age; (2) NSTEMI-ACS that consisted of non ST-segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UA)^{10,11}; (3) symptoms onset less than 48 hours; and (4) at least one vessel stenosis more than 30% according to coronary angiography.

Exclusion criteria: (1) diabetic ketoacidosis or diabetic hyperosmolar coma, severe hepatic or renal failure, cardiogenic shock (systolic pressure < 90 mmHg); (2) cancer, autoimmunity, hematological or infectious diseases; (3) lesions that cannot pass through the IVUS catheter, such as chronic total occlusion disease, severe calcification and severe angulation; and (4) a target vessel that has been treated with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

Laboratory examination: Venous blood samples were collected immediately after admission to test conventional glucose indicators (FPG, HbA1c) and lipid levels [total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG)]. Twenty-four hour urine samples were taken to test urinary 8-iso-PGF_{2α}.

IVUS procedure and VH-IVUS analysis: All patients underwent coronary angiography via a radial or femoral approach within 48 hours after admission. Heparin (100 units per kilogram) was administered intravenously before IVUS and PCI. Intracoronary nitroglycerine (200 µg) was administered to prevent coronary artery spasm. The culprit

Table I. Baseline Patient Characteristics

Variables	
Age (years)	66 ± 5
Sex (Male/Female)	53/29
BMI (kg/m ²)	26.3 ± 0.5
Smoking (%)	61%
DM (%)	41% (34/82)
Hypertension (%)	66% (54/82)
NSTEMI (%)	19.5% (16/82)
UA (%)	80.5% (66/82)
ALT (IU/L)	28.0 ± 16.7
Cr (mmol/L)	71.5 ± 20.8
TC (mmol/L)	3.95 ± 0.81
LDL-C (mmol/L)	2.40 ± 0.78
HDL-C (mmol/L)	1.06 ± 0.24
TG (mmol/L)	1.68 ± 1.01
Urinary 8-iso-PGF _{2α} (pg/mmol.creatinine)	600.8 ± 323.97
Blood indicators	
FPG (mmol/L)	6.9 ± 2.4
HbA1c (%)	6.6 ± 1.4
MAGE (mmol/L)	3.2 ± 1.4
MODD (mmol/L)	2.0 ± 1.0
PPGE (mmol/L)	3.6 ± 1.5
LAGE (mmol/L)	6.8 ± 2.3
Culprit vessel	
Left main	2
Left anterior descending artery	42
Left circumflex coronary artery	17
Right coronary artery	21
VH-IVUS parameters	
Plaque length (mm)	24.6 ± 7.1
Plaque volume (mm ³)	182.6 ± 100.9
Plaque burden (%)	83.6 ± 8.7
Percent fibrous volume (%)	62.1 ± 10.8
Percent lipid volume (%)	10.1 ± 3.1
Percent necrotic volume (%)	26.0 ± 9.0
Percent calcium volume (%)	1.8 ± 1.7

BMI indicates body mass index; DM, diabetes mellitus; NSTEMI, non-ST-elevation myocardial infarction; UA, Unstable angina pectoris; ALT, alanine aminotransferase; Cr, creatinine; TC, total cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; TG, triglycerides; FPG, fasting blood glucose; HbA1c, glycosylated hemoglobin; MAGE, mean amplitude of glycemic excursions; MODD, absolute means of daily differences; PPGE, postprandial glycemic excursions; and LAGE, largest amplitude of glycemic excursions.

lesion was determined based on electrocardiography, echocardiography, and coronary angiography by two cardiologists. More than two standard projection positions were taken to analyze the degree of coronary artery stenosis.

IVUS imaging was performed using a mechanical VH-IVUS system (Boston Scientific, USA) (Figure 1). After coronary angiography, a guide wire was inserted to the distal segment of the target vessel. Thrombus aspiration was performed prior to IVUS as necessary. An imaging catheter was advanced 10 mm to the culprit lesion along the guide wire before balloon dilation or stent implantation, and the automatic pullback speed was 0.5 mm/second. Images were archived for offline analysis.

VH-IVUS analysis was respectively performed by two experienced physicians who were blinded to baseline clinical information. Each culprit lesion was manually

traced at 1 mm intervals and the intercalary measurements of the remaining frames were automatically created. Ather plaques with more than 5 mm away from culprit lesion are considered to be another independent plaque which should be excluded. IVUS grayscale measurements included plaque length, plaque volume, and plaque burden. The mean value of two measurements was recorded. On the VH-IVUS images, fibrous areas were marked in green, lipid in yellow, necrotic core in red, and calcium in white. **CGMS analysis:** From the 2nd day post operation, all CGMS monitorings were performed for 72 hours without any additional anti-diabetic drugs compared with before admission to minimize the influence. An average value would be saved every 5 minutes, and 288 records were automatically recorded every day. The CGMS sensor probe was inserted into the abdominal subcutaneous fat tissue. It received an electrical signal every 10 seconds. Fingertip blood glucose was input to adjust the CGMS at least 4 times per day. The valid range of CGMS blood glucose monitoring was from 2.2 to 22.2 mmol/L. Blood glucose variability was evaluated by the mean amplitude of glycemic excursions (MAGE), absolute means of daily differences (MODD), postprandial glycemic excursions (PPGE), and largest amplitude of glycemic excursions (LAGE).

Statistical analysis: Continuous variables are expressed as the median (interquartile range). Categorical data are expressed as the number or frequency of occurrences. Comparison of continuous variables was performed using the nonparametric Mann-Whitney *U* test. The chi-square or Fisher exact test for sparse data was used for comparing the frequency of occurrence. Linear regression analysis was performed to investigate the correlation of laboratory data with the relative value of each plaque component evaluated by VH-IVUS. All clinical features along with the gray-scale and VH-IVUS results were evaluated in a univariate analysis. The factors were entered into multivariable models if their univariate *P* value was ≤ 0.1. Multivariate logistic regression analysis was used to determine the significant factors indicating the presence of vulnerable plaque.

Results

Baseline patient characteristics: Ninety consecutive patients with NSTEMI-ACS who met the inclusion criteria and had no exclusion criteria were enrolled in this study. Five patients with severe calcium and 3 patients with insufficient CGMS data were excluded. As a result, 82 patients underwent both VH-IVUS and CGMS examination.

Baseline patient characteristics are shown in Table I. The average age was 66 ± 5 years old, male patients accounted for 65%, and 41% of the patients had diabetes. The proportion of patients with NSTEMI was 19.5%, and 80.5% of the patients were diagnosed as UA. Baseline blood lipid levels were as follows: TC 3.95 ± 0.81 mmol/L, LDL-C 2.40 ± 0.78 mmol/L, HDL-C 1.06 ± 0.24 mmol/L, and TG 1.68 ± 1.01 mmol/L. Conventional glucose metabolism indicators: FBG 6.9 ± 2.4 mmol/L, HbA1c 6.6 ± 1.4%. Oxidative stress related indicator: urinary 8-iso-PGF_{2α} 600.8 ± 323.97 pg/mmol. creatinine.

Figure 2. Correlation between HbA1c and VH-IVUS indexes.

Figure 3. Correlation between MAGE and VH-IVUS indexes.

Figure 4. Correlation between PPGE and VH-IVUS indexes.

Table II. Correlation Between Blood Glucose and Oxidative Stress

	MAGE	MODD	LAGE	PPGE
Urinary 8-iso-PGF _{2α}				
<i>r</i>	0.214	0.266	-0.111	-0.182
<i>P</i> value	0.054	0.016	0.320	0.102

Abbreviations are shown in Table I.

After 72 hours consecutively CGMS monitoring, we obtained blood glucose variability parameters: MAGE 3.2 ± 1.4 mmol/L, MODD 2.0 ± 1.0 mmol/L, PPGE 3.6 ± 1.5 mmol/L and LAGE 6.8 ± 2.3 mmol/L.

Coronary angiography and VH-IVUS: According to the results of coronary angiography and IVUS examination combined with the clinical data, the culprit blood vessel was determined to include 2 cases of LM, 42 cases of LAD, 17 cases of LCX, and 21 cases of RCA. The VH-IVUS analysis results are as follows: culprit lesion volume 182.6 ± 100.9 mm³, plaque burden $83.6 \pm 8.7\%$, percent fibrous volume $62.1 \pm 10.8\%$, percent lipid volume $10.1 \pm 3.1\%$, percent necrotic volume $26.0 \pm 9.0\%$, and percent calcium volume $1.8 \pm 1.7\%$.

Correlation between glycemic index and VH-IVUS: We analyzed the relationship between VH-IVUS and blood glucose indicators including traditional indices and variability (as shown in the Figures 2-4). There was no significant correlation between FPG and plaque composition. HbA1c was negatively correlated with percent fibrous vol-

ume ($r = -0.233$, $P = 0.035$) but positively correlated with percent necrotic volume ($r = 0.294$, $P = 0.007$) and calcium volume ($r = 0.244$, $P = 0.027$). MAGE was negatively correlated with percent fibrous volume ($r = -0.238$, $P = 0.032$) but positively correlated with percent necrotic volume ($r = 0.352$, $P = 0.001$) and calcium volume ($r = 0.339$, $P = 0.000$). PPGE was negatively correlated with percent fiber volume ($r = -0.294$, $P = 0.007$) but positively correlated with percent necrotic volume ($r = 0.323$, $P = 0.003$).

Relationship between blood glucose and oxidative stress: In this study urinary 8-iso-PGF_{2α} was tested to evaluate the level of oxidative stress. We analyzed the correlation between oxidative stress indicators with blood glucose indicators (Table II). As a result, only urinary 8-iso-PGF_{2α} was significantly correlated with MODD ($r = 0.266$, $P = 0.016$).

Factors associated with percent fibrous and necrotic volume: Percent fibrous volume was significantly correlated with age, LDL-C, urinary 8-iso-PGF_{2α}, HbA1c, MAGE, and PPGE, but not significantly correlated with smoking, hypertension, statin or anti-diabetic drugs before admission, HDL-C, MODD, and LAGE. In the multiple regression analysis, all factors with P value < 0.1 on univariable analysis were included (Tables III and IV). Only PPGE and urinary 8-iso-PGF_{2α} were independent risk factors of percent fibrous volume (PPGE: $\beta = -0.340$, $P = 0.024$; urinary 8-iso-PGF_{2α}: $\beta = -0.294$, $P = 0.013$). PPGE and urinary 8-iso-PGF_{2α} were also independent risk factors of percent necrotic volume (PPGE: $\beta = 0.360$, $P =$

Table III. Factors Associated with Percent Fibrous Volume

Variables	Univariable		Multivariable	
	<i>r</i>	<i>P</i> value	β	<i>P</i> value
Age (years)	-0.103	0.040	-0.087	0.144
Smoking (%)	0.037	0.697		
Hypertension (%)	0.053	0.482		
Statin before admission	0.103	0.200		
Anti-diabetic drugs before admission	0.036	0.795		
LDL-C (mmol/L)	0.226	0.041	0.085	0.475
HDL-C (mmol/L)	-0.031	0.785		
Urinary 8-iso-PGF _{2α} (pg/mmol.creatinine)	-0.251	0.023	-0.294	0.013
FPG (mmol/L)	-0.017	0.876		
HbA1c (%)	-0.233	0.035	-0.245	0.118
MAGE (mmol/L)	-0.310	0.005	-0.026	0.876
MODD (mmol/L)	-0.117	0.294		
PPGE (mmol/L)	-0.238	0.032	-0.340	0.024
LAGE (mmol/L)	-0.184	0.099	0.154	0.336

Abbreviations are shown in Table I.

Table IV. Factors Associated with Percent Necrotic Volume

Variables	Univariable		Multivariable	
	<i>r</i>	<i>P</i> value	β	<i>P</i> value
Age (years)	0.184	0.022	0.106	0.176
Smoking (%)	0.041	0.764		
Hypertension (%)	0.027	0.568		
Statin before admission	0.019	0.631		
Anti-diabetic drugs before admission	0.108	0.875		
LDL-C (mmol/L)	-0.326	0.003	-0.144	0.206
HDL-C (mmol/L)	-0.073	0.514		
Urinary 8-iso-PGF _{2α} (pg/mmol.creatinine)	0.229	0.039	0.304	0.007
FPG (mmol/L)	0.099	0.378		
HbA1c (%)	0.294	0.007	0.286	0.058
MAGE (mmol/L)	0.352	0.001	-0.054	0.734
MODD (mmol/L)	0.152	0.172		
PPGE (mmol/L)	0.323	0.003	0.360	0.012
LAGE (mmol/L)	0.310	0.005	-0.045	0.764

Abbreviations are shown in Table I.

Table V. Factors Associated with Percent Necrotic Volume in Non DM Patients

Variables	Univariable		Multivariable	
	<i>r</i>	<i>P</i> value	β	<i>P</i> value
Age (years)	0.091	0.102		
Smoking (%)	0.037	0.798		
Hypertension (%)	0.035	0.478		
Statin before admission	0.021	0.705		
Anti-diabetic drugs before admission	0.205	0.305		
LDL-C (mmol/L)	-0.186	0.324		
HDL-C (mmol/L)	-0.062	0.628		
Urinary 8-iso-PGF _{2α} (pg/mmol.creatinine)	0.349	0.019	0.417	0.010
FPG (mmol/L)	0.133	0.476		
HbA1c (%)	0.205	0.117		
MAGE (mmol/L)	0.232	0.044	0.103	0.583
MODD (mmol/L)	0.217	0.033	0.908	0.437
PPGE (mmol/L)	0.296	0.007	0.312	0.027
LAGE (mmol/L)	0.256	0.019	0.019	0.790

Abbreviations are shown in Table I.

0.012; urinary 8-iso-PGF_{2α}: $\beta = 0.304$, $P = 0.007$). The non-diabetes mellitus subgroup analysis showed that PPGE and urinary 8-iso-PGF_{2α} were independent risk factors of percent necrotic volume (PPGE: $\beta = 0.312$, $P = 0.027$; urinary 8-iso-PGF_{2α}: $\beta = 0.417$, $P = 0.010$) (Table V).

Discussion

The main findings of this study can be summarized as follows: Blood glucose variability is related to vulnerability of plaque in elderly NSTEMI-ACS patients, and the correlation was independent of oxidative stress.

Vulnerable plaque evaluation with VH-IVUS: The thrombosis caused by rupture of coronary vulnerable plaque is the most common reason for ACS occurrence. The vulnerable plaque is characterized by a large lipid necrosis core and a thin fibrous cap formed by macrophage infiltration and it is closely related to cardiovascular events.^{12,13} Vulnerable plaques could be identified by non-invasive and invasive methods. As a kind of invasive examination with good penetrability, VH-IVUS could be used to distinguish and measure the content of fibrous, lipid, necrotic, and calcium constituents.¹⁴ However, due to its low resolution of only 100–200 μm , the measurement of plaque fiber cap thickness is not accurate enough. Compared with VH-IVUS, OCT technology has lower penetration but higher resolution, so it is more accurate to combine VH-IVUS and OCT to evaluate the plaque characteristics.^{15,16}

Relationship between blood glucose and vulnerable plaque: ACS patients often also have abnormal glucose metabolism which promotes the occurrence and development of coronary artery disease. Abnormal glucose metabolism not only increases the risk of hospitalization complications in ACS patients, but also is an independent predictor of patient survival rate. Studies have shown that traditional blood glucose indicators such as HbA1c, FPG and postprandial blood sugar could not adequately explain the impairment caused by abnormal glucose metabolism.¹⁷ It is reported that hypoglycemia and postprandial hyperglycemia may be important factors in the development of CAD residual risk other than dyslipidemia. Recent research also found that glycemic variability was significantly correlated with percent necrotic volume which presents the coronary plaque vulnerability.¹⁸ Kuroda reported that MAGE was positively related to the necrotic core, and it was one of the independent predictors of thin cap fiber plaques.¹⁹ Similar results were found in our study; MAGE, PPGE, and HbA1c were negatively correlated with the percent fibrous volume but positively correlated with the percent necrotic volume.

Compared with the conventional glucose index, the effects of blood glucose variability on oxidative stress were more pronounced than those of chronic hyperglycemia. It was found that fluctuating hyperglycemia had a higher oxidative stress level and was more damaging to endothelial function than sustained hyperglycemia in patients.²⁰ It has been shown that MODD as an index of inter day glycemic variability was correlated with a circulating marker of oxidative stress.^{21,22} Furthermore, oxidative

stress could regulate the expression of MMPs to increase plaque instability.

In our study, we observed that MAGE and MODD were positively correlated to the levels of urinary 8-iso-PGF_{2α}. But there was no correlation between traditional blood glucose indicators and oxidative stress. After we removed the influence of other factors including urinary 8-iso-PGF_{2α}, among the blood glucose indicators only PPGE was associated with percent fibrous and necrotic volume of plaques. This suggests that the blood glucose fluctuation index PPGE may be a predictor of plaque vulnerability. In addition, data CGMS (MAGE, MODD, PPGE and LAGE) was correlated with percent necrotic volume in NSTEMI-ACS patients without diabetes mellitus, but HbA1c was not. This suggests that data CGMS is a better predictor marker of plaque characteristics in this subgroup than HbA1c. Whether the fluctuation of blood glucose promotes the instability of plaques by way of enhancing the oxidative stress level needs to be confirmed in further studies.

Limitations: Our study has limitations which should be considered when interpreting the results. First, this is a single center, small sample observational study. Second, the study excluded STEMI patients, so the findings could not reflect the characteristics of all ACS patients. Third, all patients underwent CGMS examination on the second day after intervention therapy, and their blood glucose variability may be different from that before intervention. Fourth, the IVUS catheter may have an impact on extremely severe stenosis lesions which could affect the analysis of VH-IVUS. Fifth, the oxidative stress index tested in our study was urine 8-iso-PGF_{2α}, which may not fully reflect the oxidative stress level of NSTEMI-ACS patients. Sixth, we did not analyze non culprit lesions, and the result was lack of further insight into the potential vulnerable plaques. Finally, despite the removal of severe calcification cases, the rear acoustic image of mild partial calcification also had an effect on the analysis of plaque components.

Conclusion

This study found that blood glucose variability was positively related to oxidative stress. With an increase in blood glucose variability, the instability of coronary plaques in elderly NSTEMI-ACS patients increased, and this correlation was independent of oxidative stress. Therefore, blood glucose variability may be considered as one of the predictors of plaque vulnerability.

Disclosure

Conflicts of interest: None.

Ethical statements: No data, text, or theories by others are presented as if they were our own. The submission has been received explicitly from all co-authors. And authors whose names appear on the submission have contributed sufficiently to the scientific work and therefore share collective responsibility and accountability for the results.

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