Glycemic variability as predictor of contrast-induced nephropathy in diabetic patients with acute myocardial infarction undergoing percutaneous coronary intervention

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Background: Contrast-induced nephropathy (CIN) is a frequent complication in patients undergoing percutaneous coronary intervention (PCI). Diabetes mellitus (DM) and acute myocardial infarction (AMI) are associated with an increased risk of CIN. However, it remains unclear whether glycemic variability (GV) has the important prognostic significance of CIN in diabetic patients with AMI undergoing PCI. We conducted this study to investigate the independent prognostic value of the in-hospital GV in diabetic patients who presented with AMI and were treated with PCI.

Methods: The study group comprised 252 diabetic patients with AMI who underwent PCI and were assigned to CIN and non-CIN groups. A continuous glucose monitoring system (CGMS) was used to determine the mean amplitude of glycemic excursion (MAGE), a representative index of GV. Independent risk factors for CIN were determined by multivariate logistic regression analysis (MLRA), and receiver-operating characteristic (ROC) analysis was used to measure the prognostic potential of GV.

Results: A total of 55 patients had CIN and they showed markedly elevated MAGE compared with the non-CIN group. MLRA revealed that MAGE had potential to independently predict CIN. The area under the ROC curve, optimal cut-point value, sensitivity and specificity for MAGE were 0.739, 2.95, 70.91% and 61.42%, respectively.

Conclusions: In diabetic AMI patients undergoing PCI, high GV is associated with increased risk of CIN.

Keywords: Contrast-induced nephropathy (CIN); glycemic variability (GV); mean amplitude of glycemic excursion (MAGE); percutaneous coronary intervention (PCI)

Introduction

Contrast-induced nephropathy (CIN) refers to elevation of serum creatinine (SCr) following administration of contrast media. It is a frequent complication in patients undergoing percutaneous coronary intervention (PCI), and is linked to extended hospital stay and late adverse outcomes (1-3). In particular, AMI patients undergoing emergency PCI have a markedly accentuated risk of CIN compared with those undergoing elective PCI (4-6). However, apart from the recommendation to use intravenous hydration, there are no other precautions for preventing the occurrence of CIN (7). Therefore, effective and sensitive indicators are needed for timely detection and prevention of CIN, especially in individuals who are at high risk.

Diabetes mellitus (DM) is a major risk factor for coronary artery disease (CAD) (8), and dysglycemia is associated

with poor outcomes in CAD patients. Increasing evidence demonstrates that hyperglycemia enhances the CIN risk after PCI (9,10). It has been reported that the glycosylated hemoglobin (HbA_{1c}) level on admission is a useful marker of CIN in patients after coronary angiography or PCI (11,12), but glycemic variability (GV; i.e., fluctuation in glucose level) is a more comprehensive and important component of dysglycemia than conventional indices that entail single-point measurements. The mean amplitude of glycemic excursion (MAGE) calculated using a continuous glucose monitoring system (CGMS) is an index of GV. A recent study showed that GV has prognostic potential regarding complications, including deterioration of renal function in patients with type 2 DM (13). In addition, recent investigations have revealed that GV, but not the average glucose concentration, is a risk factor for acute kidney injury (14), and a major risk for nephropathy. Previous studies have shown that blood glucose variability is closely related to the severity of coronary heart disease. Blood glucose variability is an independent determinant of the degree of coronary artery stenosis. The larger fluctuation of blood glucose indicated the more severe the degree of coronary artery stenosis.

However, not much is known about the prognostic value of GV for CIN in diabetic AMI patients undergoing PCI, so we investigated this issue. We present the following article in accordance with the STARD reporting checklist (available at http://dx.doi.org/10.21037/atm-20-6968).

Methods

Patient population

In this prospective observational study, 252 diabetic patients who presented with AMI and received drug-eluting stents in the Cardiology Department of Zhongda Hospital Affiliated to Southeast University between July 2015 and October 2018 were the subjects. They were assigned to two groups: CIN and non-CIN. In this study, AMI referred to presence of chest pain and elevated troponin I, in the presence or absence of ST-segment elevation on ECG; DM was detected in line with the criteria of American Diabetes Association. In addition, patients on insulin therapy or glucose-lowering medication were deemed diabetic. CIN was defined as an elevation in baseline SCr level ≥25% or an absolute elevation ≥44.2 µmol/L within 48–72 h after PCI. Coronary angioplasty was performed in the conventional manner, and coronary stents were used

when required. Iodixanol (GE Healthcare, Cork, UK) was used as the contrast agent. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The procedures used in this investigation were approved by the Medical Ethics Committee of Zhongda Hospital Affiliated to Southeast University. Informed consent was given by the patients.

Exclusion criteria

Patients who had diabetic ketosis, cardiac arrest requiring cardiopulmonary resuscitation, or end-stage renal disease requiring dialysis were excluded from the study. In addition, patients who were in a non-ketotic hyperosmolar coma, and those who had cardiogenic shock were excluded.

Study protocol

The baseline SCr level was tested before angiography. Regular SCr test during 2–3 days after PCI was performed to diagnose CIN. Routine measurements of glucose, cardiac troponin I (cTnI), blood urea nitrogen (BUN), low-density lipoprotein cholesterol (LDL-C), uric acid, albumin and hemoglobin were also carried out. The estimated glomerular filtration rate (eGFR) for each patient was calculated using the Modification of Diet in Renal Disease (MDRD) equation, and left ventricular ejection fraction (LVEF) was measured using echocardiography. Each participant had continuous CGMS monitoring for 72 h post-PCI with the range of detectable glucose fixed at 2.2–22.2 mmol/L. Thus, any patient with data outside this range was excluded from the study. The data obtained using the CGMS were recorded and analyzed with CGMS software 3.0. The MAGE values were computed using a procedure described earlier (15).

Statistical analysis

Results are expressed as frequencies and percentages for categorical variables, and mean ± SD for continuous variables. Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, USA). Significant differences between groups were determined with Chi-square and unpaired *t*-tests. Risk factors for CIN were determined using multivariate logistic regression analysis (MLRA), and receiver-operating characteristic (ROC) analysis was used

Table 1 Baseline clinical data for the two groups of diabetic patients

Variable	CIN (n=55)	Non-CIN (n=197)	P
Male, n (%)	48 (87.27)	150 (76.14)	0.075
Age (years)	68.15±1.34	64.81±0.73	0.033
BMI (kg/m^2)	24.45±0.33	24.07±0.19	0.350
Hypertension, n (%)	43 (78.18)	116 (58.88)	0.011
Hyperlipidemia, n (%)	1 (1.82)	9 (4.57)	0.356
Smoking, n (%)	26 (47.27)	82 (41.62)	0.454
Family history of CAD, n (%)	10 (18.18)	27 (13.71)	0.407
Contrast dose (mL)	107.45±3.94	100.66±2.05	0.125
Number of stents (n)	1.38±0.07	1.28±0.03	0.144
Medications, n (%)			
Aspirin	53 (96.36)	190 (96.45)	0.977
Clopidogrel	50 (90.91)	170 (86.29)	0.364
β-blocker	40 (72.73)	160 (81.22)	0.169
Statin	49 (89.09)	184 (93.40)	0.284
ACEI/ARB	32 (58.18)	129 (65.48)	0.117
CCB	37 (67.27)	130 (65.99)	0.859
LMWH	49 (89.10)	178 (90.36)	0.782
Insulin	48 (87.27)	172 (87.31)	0.994

Data are presented as mean ± standard deviation, or as number (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker, BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; LMWH, low molecular weight heparin.

for determination of the predictive potential of MAGE. Statistical significance of differences was assumed at P<0.05.

Results

Baseline characteristics of the patients

The cumulative incidence of CIN was 21.83% (n=55/252) in the entire study population. The baseline patient characteristics and in-hospital medications are shown in *Table 1*. There were no significant differences between CIN and non-CIN groups regarding sex, body mass index, hyperlipidemia, smoking, family history of CAD, contrast dose, number of stents, and in-hospital medications (P>0.05). The CIN diabetic patients were markedly older (68.15±1.34 *vs.* 64.81±0.73 years, P=0.033) and were significantly more hypertensive (78.18% *vs.* 58.88%, P=0.011) than patients in non-CIN group.

Baseline laboratory test results

The baseline laboratory data of the patients are shown in *Table 2*. The CIN patients had significantly higher levels of MAGE (4.27±0.29 *vs.* 2.77±0.12 mmol/L, P<0.001), uric acid (398.36±9.15 *vs.* 373.95±5.42 mmol/L, P=0.032), BUN (8.94±0.35 *vs.* 7.92±0.22 mmol/L, P=0.025), and SCr (106.33±2.20 *vs.* 99.92±1.24 μmol/L, P=0.015) than those without CIN. Moreover, marked variations were observed in baseline eGFR (60.13±2.02 *vs.* 67.66± 1.22 mL/min/1.73 m^2, P=0.003), LVEF (49.89%±1.36% *vs.* 53.82%±0.72%, P=0.011), and albumin (33.20±0.65 *vs.* 34.61±0.33 g/L, P=0.048) between the two groups. However, levels of baseline glucose, cTnI, hemoglobin and LDL-C (P>0.05) were comparable between the two groups.

Logistic regression analysis

The association of MAGE with the incidence of CIN

Table 2 Baseline biochemical data for the two groups of diabetic patients

Variable	CIN (n=55)	Non-CIN (n=197)	P
MAGE (mmol/L)	4.27±0.29	2.77±0.12	<0.001
Glucose (mmol/L)	12.59±0.85	11.32±0.30	0.083
LVEF (%)	49.89±1.36	53.82±0.72	0.011
cTnI (μg/L)	14.80±3.31	10.35±1.47	0.177
Hemoglobin (g/L)	127.90±2.65	130.40±1.23	0.367
Albumin (g/L)	33.20±0.65	34.61±0.33	0.048
LDL-C (mmoles·L^{-1})	2.50±0.09	2.70±0.07	0.136
Uric acid (mmoles·L^{-1})	398.36±9.15	373.95±5.42	0.032
BUN (mmol/L)	8.94±0.35	7.92±0.22	0.025
Creatinine (μmol/L)	106.33±2.20	99.92±1.24	0.015
eGFR (mL/min/1.73 m^2)	60.13±2.02	67.66±1.22	0.003

Data are presented as mean ± standard deviation. BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; cTnI, cardiac troponin I; LDL-C, low-density lipoprotein cholesterol.

was studied using MRLA, with adjustments for age, hypertension, LVEF, albumin, uric acid, BUN, SCr and eGFR. Results of the analysis (*Table 3*) showed that MAGE [odds ratio (OR) =1.521, 95% confidence interval (CI) =1.282–1.805, P<0.001] was markedly correlated with the incidence of CIN. In addition, hypertension (OR =0.4, 95% CI =0.198–0.805, P=0.01); LVEF (OR =0.964; 95% CI =0.933–0.995, P=0.023); albumin (OR =0.926; 95% CI =0.86–0.997, P=0.042); uric acid (OR =1.004; 95% CI =1–1.008, P=0.034) and eGFR (OR =0.965, 95% CI =0.94–0.991, P=0.007) were independent determinants of CIN.

ROC curve for MAGE prediction of CIN

As shown in *Figure 1*, the area under the ROC curve for MAGE was 0.739 (95% CI =0.662–0.817, P<0.001). In addition, MAGE displayed significant predictive value for CIN in diabetic AMI patients undergoing PCI, and the optimum cut-point value of MAGE was 2.95, with sensitivity and specificity of 70.91% and 61.42%, respectively.

Discussion

MAGE is considered as the "gold standard" for GV (16) and our results showed that elevated MAGE was independently associated with a high risk of CIN after PCI in AMI diabetic patients. This is the first report showing

that GV is a powerful predictor of CIN in this group of cardiac patients.

CIN is an acute renal injury caused by contrast agents and is a frequent complication of PCI in patients with CAD. Moreover, DM is an important predisposing factor for CIN (17). Point-in-time blood glucose and HbA$_{1c}$ are classical markers for assessing immediate and long-term glycometabolic status, respectively. Both hyperglycemia and elevated HbA$_{1c}$ are associated with increased risk for CIN (9-12). However, compared with any of these traditional markers, GV is a more comprehensive and more sensitive maker of dysglycemia. Diabetic patients with comparable blood glucose or HbA1c profiles may have significant differences in GV (18), and the results of the present study were consistent with this finding. Severe glycemic excursion is more harmful than persistent hyperglycemia in the pathogenesis of cardiac adverse events (16,19). Severe glycemic excursion leads to sympathetic dysfunction, which is associated with ischemic injury of the renal medulla through promotion of the secretion of cortisol and catecholamine (20). Glycemic excursion activates the nuclear factor-κB and protein kinase C pathways, thereby aggravating inflammation (21-23). This is a critical step in the etiology of CIN (24). Glycemic excursion also induces oxidative stress, leading to kidney damage through overproduction of reactive oxygen species (ROS) (16,25,26). Because GV is linked to these multifactorial events that are involved in the development of CIN, it could have a

Table 3 Univariate and multivariate analyses for CIN predictors

Variable	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age	1.034	1.003–1.066	0.034	1.016	0.961–1.074	0.576
Hypertension	0.334	0.159–0.699	0.004	0.4	0.198–0.805	0.01
MAGE	1.485	1.248–1.767	<0.001	1.521	1.282–1.805	<0.001
LVEF	0.963	0.935–0.992	0.012	0.964	0.933–0.995	0.023
Albumin	0.928	0.865–0.996	0.037	0.926	0.86–0.997	0.042
Uric acid	1.006	1.001–1.01	0.009	1.004	1–1.008	0.034
BUN	1.109	0.994–1.238	0.064	–	–	–
Creatinine	1.022	1.004–1.04	0.016	1.029	0.994–1.065	0.103
eGFR	0.971	0.952–0.991	0.004	0.965	0.94–0.991	0.007

BUN, blood urea nitrogen; CIN, contrast-induced nephropathy; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MAGE, mean amplitude of glycemic excursion.
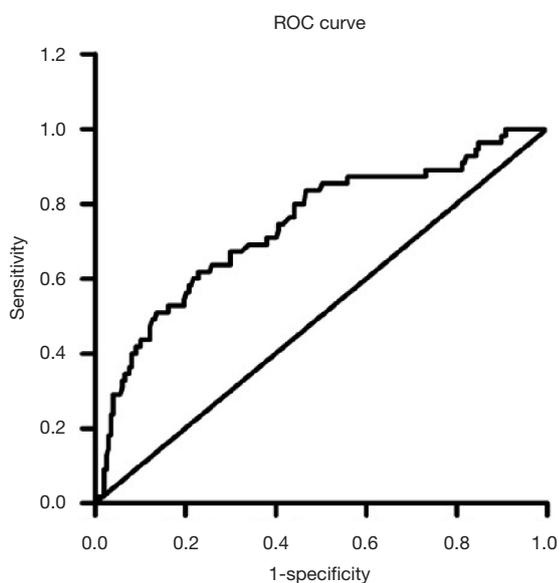

Figure 1 Area under the receiver-operating characteristic (ROC) curve analysis showing that mean amplitude of glycemic excursion has predictive potential for contrast-induced nephropathy.

powerful predictive effect for CIN, which was suggested by the results of this study. Further studies are needed to explore the specific mechanism by which GV is implicated in the etiology of CIN. Indeed, small sample size and single center are the limitations of this study. In the future, we need to use a multi-center study with a larger sample size to evaluate the correlation between blood glucose variability and contrast nephropathy, so as to further determine the predictive effect of blood glucose variability on contrast nephropathy.

Moreover, results from MLRA in the present investigation indicated that hypertension, LVEF, albumin, uric acid and eGFR are independent predisposing factors for CIN, which is are in agreement with those found by earlier studies (27-30).

Conclusions

We found that in diabetic AMI patients undergoing PCI, raised GV was linked to increased risk of CIN, which suggests that GV has important prognostic significance in this group of CAD patients.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-6968

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-6968). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The procedures used in this investigation were approved by the Medical Ethics Committee of Zhongda Hospital Affiliated to Southeast University. Informed consent was given by the patients.

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