Cardiovascular Intervention and Therapeutics (2019) 34:122–130
https://doi.org/10.1007/s12928-018-0531-z

ORIGINAL ARTICLE

Impact of glycemic variability on myocardial infarct size in patients with ST-segment elevation myocardial infarction: quantitative assessment of left ventricular wall motion severity

Keiichi Tsuchida[1] · Kota Nishida[1] · Satoshi Soda[2] · Takumi Akiyama[1] · Takahiro Hakamata[1] · Koji Sudo[1] · Komei Tanaka[1] · Yukio Hosaka[1] · Kazuyoshi Takahashi[1] · Hirotaka Oda[1]

Received: 29 January 2018 / Accepted: 24 May 2018 / Published online: 28 May 2018

Abstract

Glycemic variability (GV) is relevant to impaired myocardial salvage in acute ST-elevation myocardial infarction (STEMI). Severity of hypokinesis at the infarct site as assessed from contrast left ventriculography can reportedly predict infarct size in STEMI. We prospectively studied 58 consecutive patients (mean age, 63 ± 11 years) with anterior or inferior STEMI who underwent successful reperfusion therapy. Mean amplitude of glucose excursion (MAGE) was obtained from continuous glucose monitoring system. Patients were divided into the upper tertile of MAGE as Group H, and the other two-thirds as Group L. Serial regional wall motion severity at the infarct site was computed postprocedure and at follow-up using a quantitative left ventricular analysis system. Impaired myocardial salvage was defined as severity recovery ratio < 20%. Significantly shorter onset-to-balloon time (196.9 vs. 279.0 min, $p = 0.033$) and relatively lower postprocedural wall motion severity (2.4 vs. 2.9, $p = 0.096$) were observed in Group H, but absolute severity recovery was significantly smaller in Group H (0.5 vs. 1.3, $p = 0.017$). Multivariate analysis showed higher MAGE as predictive of impaired myocardial salvage (OR, 406.10; 95% CI, 4.41–37,366.60; $p = 0.009$). Recovery of reginal wall motion severity at the infarct site was compromised in STEMI patients with higher MAGE. Our results suggest that final infarct size is potentially larger than expected in STEMI patients with higher GV.

Keywords Glucose fluctuation · Myocardial infarction · Left ventricular wall motion

Introduction

Glycemic variability (GV), another component of glycemic disorder, has received growing interest as a novel aggravating factor for cardiovascular disease. GV has been noticed to represent a negative prognostic factor for patients with acute ST-elevation myocardial infarction (STEMI) [1]. Primary percutaneous coronary intervention (PCI) is the most commonly adopted treatment strategy for STEMI and has contributed to improving survival [2]. However, coronary blood restoration can raise the issue termed reperfusion injury, which leads to unfavorable myocardial salvage and is potentially associated with adverse clinical outcomes [3]. To date, the mechanisms underlying reperfusion injury are not fully understood. A preclinical study has demonstrated that GV aggravates susceptibility to ischemia/reperfusion injury [4]. Furthermore, acute-phase GV in STEMI patients is associated with impairment of myocardial salvage and subsequent infarct size after successful reperfusion therapy [5]. In a previous report, we showed the relationship between GV and electrocardiographic ST-segment resolution which is well known as a surrogate marker of reperfusion injury [6].

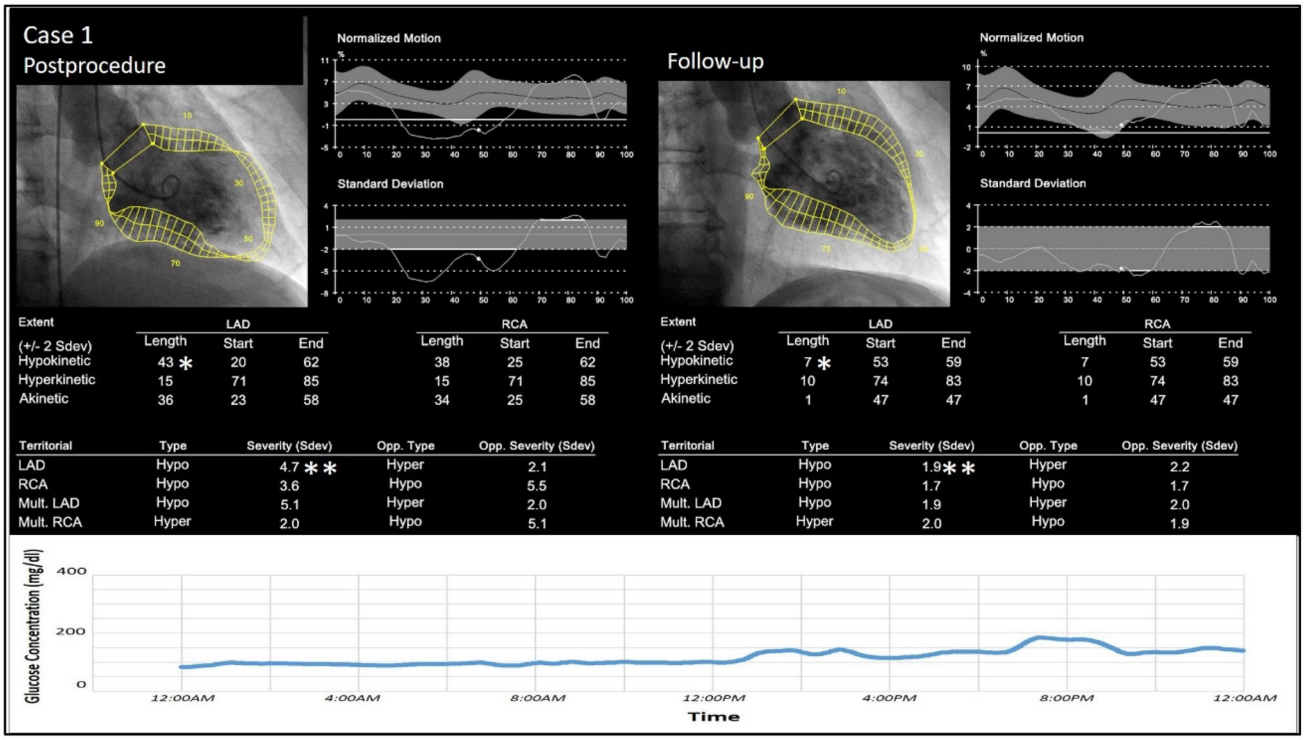
Several techniques have been employed to quantify the myocardium at risk or infarct size in STEMI, including radionuclear myocardial perfusion imaging [7] and magnetic resonance imaging [8]. Contrast left ventriculography (LVG) analysis for assessing regional wall motion abnormalities has been traditionally used to determine the myocardium at risk in daily practice. The wall motion severity at the site of infarction derived from LVG analysis correlates well with infarct size estimated from creatinine kinesis release [9] or myocardial perfusion imaging [10].

✉ Keiichi Tsuchida
keitsuchida97@gmail.com

[1] Department of Cardiology, Niigata City General Hospital, Shumoku 463-7, Chuo-ku, Niigata 950-1197, Japan

[2] Department of Endocrinology and Metabolism, Niigata City General Hospital, Niigata, Japan

A



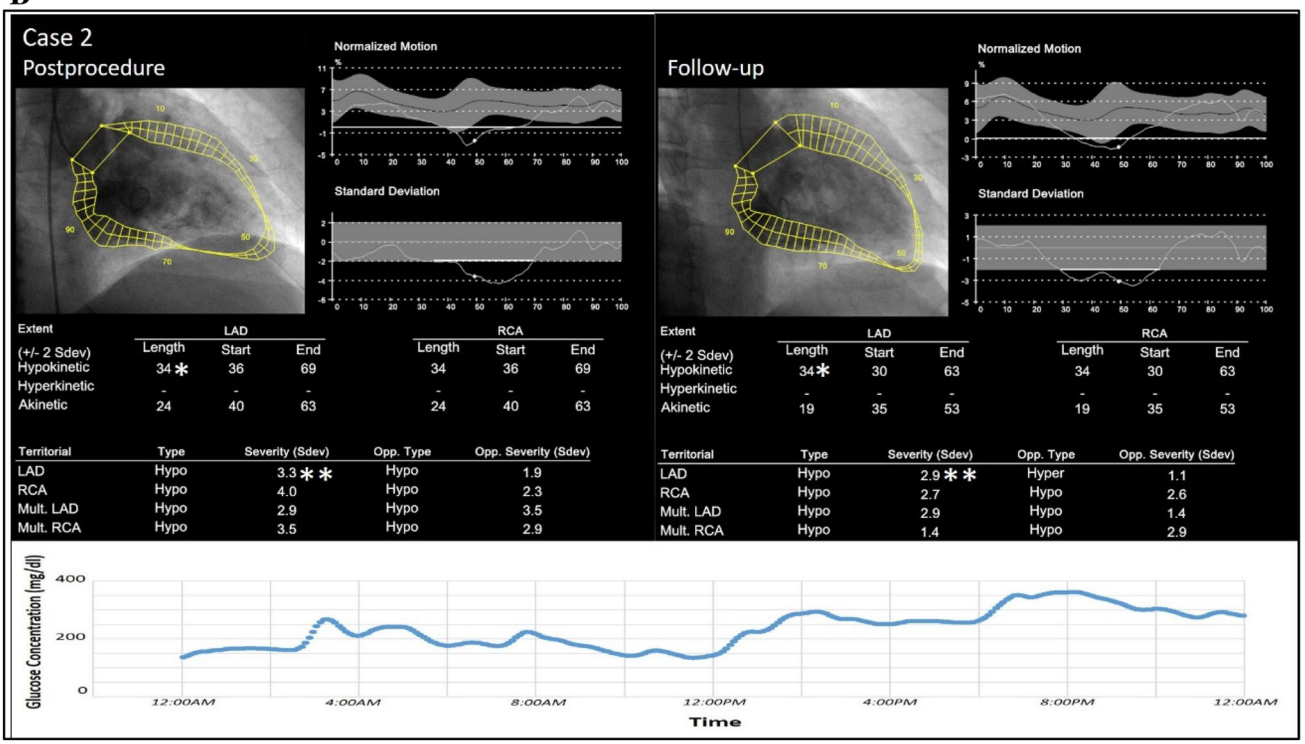
Extent	LAD			RCA		
(+/- 2 Sdev)	Length	Start	End	Length	Start	End
Hypokinetic	43 *	20	62	38	25	62
Hyperkinetic	15	71	85	15	71	85
Akinetic	36	23	58	34	25	58

Territorial	Type	Severity (Sdev)	Opp. Type	Opp. Severity (Sdev)
LAD	Hypo	4.7 **	Hyper	2.1
RCA	Hypo	3.6	Hypo	5.5
Mult. LAD	Hypo	5.1	Hyper	2.0
Mult. RCA	Hyper	2.0	Hypo	5.1

Extent	LAD			RCA		
(+/- 2 Sdev)	Length	Start	End	Length	Start	End
Hypokinetic	7 *	53	59	7	53	59
Hyperkinetic	10	74	83	10	74	83
Akinetic	1	47	47	1	47	47

Territorial	Type	Severity (Sdev)	Opp. Type	Opp. Severity (Sdev)
LAD	Hypo	1.9**	Hyper	2.2
RCA	Hypo	1.7	Hypo	1.7
Mult. LAD	Hypo	1.9	Hyper	2.0
Mult. RCA	Hyper	2.0	Hypo	1.9

B



Extent	LAD			RCA		
(+/- 2 Sdev)	Length	Start	End	Length	Start	End
Hypokinetic	34 *	36	69	34	36	69
Hyperkinetic	-	-	-	-	-	-
Akinetic	24	40	63	24	40	63

Territorial	Type	Severity (Sdev)	Opp. Type	Opp. Severity (Sdev)
LAD	Hypo	3.3 **	Hypo	1.9
RCA	Hypo	4.0	Hypo	2.3
Mult. LAD	Hypo	2.9	Hypo	3.5
Mult. RCA	Hypo	3.5	Hypo	2.9

Extent	LAD			RCA		
(+/- 2 Sdev)	Length	Start	End	Length	Start	End
Hypokinetic	34*	30	63	34	30	63
Hyperkinetic	-	-	-	-	-	-
Akinetic	19	35	53	19	35	53

Territorial	Type	Severity (Sdev)	Opp. Type	Opp. Severity (Sdev)
LAD	Hypo	2.9 **	Hyper	1.1
RCA	Hypo	2.7	Hypo	2.6
Mult. LAD	Hypo	2.9	Hypo	1.4
Mult. RCA	Hypo	1.4	Hypo	2.9

◂**Fig. 1** Output data of LVG analysis (CAAS II, Pie Medical Imaging, Maastricht, The Netherlands) and correspondent glycemic variability (GV) obtained from continuous glucose monitoring system (iPro2™, Medtronic, Northridge, CA, USA) in two representative cases. **a** Case 1: 67-year-old male with anterior STEMI. Hypo region length at postprocedure is 43 (*) and wall motion severity is 4.7 (**). At follow-up, Hyporegion length and severity recovered to 7 (*) and 1.7 (**), respectively. Wall motion severity recovery ratio is calculated as follows: (4.7–1.7) × 100/4.7 = 63.8%. Little GV is noted (mean amplitude of glycemic excursion; MAGE = 47 mg/dl). **b** Case 2: 57-year-old male with anterior STEMI. Hyporegion length at postprocedure is 34 (*) and wall motion severity is 3.3 (**). At follow-up, Hyporegion length and severity were 34 (*) and 2.9 (**), respectively. Wall motion severity recovery ratio is calculated as follows: (3.3–2.9) × 100/3.3 = 12.1%. Larger MAGE (126 mg/dl) is observed

The aim of the present work was to evaluate the relationship between the degree of GV and final infarct size estimated by serial contrast LVG analysis in STEMI.

Methods

Study design and population

This was a single-center, cross-sectional study. We prospectively included consecutive STEMI patients amenable to primary PCI between April 2014 and March 2015. STEMI patients was defined as those with persistent chest pain for longer than 30 min with an electrocardiographic ST-segment elevation of 1 mmor greater in 2 or more contiguous electrocardiogram leads [11]. Exclusion criteria were as follows: case of onset-to-door time ≥ 24 h, Killip 4, in-hospital onset, or prior myocardial infarction. Patients were diagnosed as diabetes if the fasting blood glucose level was ≥ 126 mg/dl, non-fasting blood glucose level was ≥ 200 mg/dl, or treatment had already been administered before primary PCI. When the diagnosis of diabetes was not made, an oral glucose tolerance test (OGTT) was performed and a 2-h postloaded glycemic level ≥ 200 mg/dl was also considered to have diabetes. Normal glucose tolerance (NGT) was defined as fasting blood glucose < 110 mg/dl plus a 2-h glucose level < 140 mg/dl with the OGTT. Impaired glucose tolerance (IGT) was defined as either fasting glucose level between 110 and 125 mg/dl or 2-h glucose levels of 140–199 mg/dl and those who had fasting blood glucose of 110–125 mg/dl and a 2-h glucose level < 140 mg/dl were diagnosed as having impaired fasting glucose [12]. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee. All the patients provided written informed consent after index PCI at CCU.

Continuous glucose monitoring

The sensor of continuous glucose monitoring system (CGMS) (iPro2™, Medtronic, Northridge, CA, USA) was placed on the patient's abdomen after index PCI at either coronary care unit (CCU) or ordinary ward, and subcutaneous interstitial glucose level was monitored over a period of 2 consecutive days including 3 regular meals with an appropriate caloric intake. The monitoring was started within approximately 24–48 h after admission. The following parameters were calculated: (1) mean blood glucose (MBG); and (2) the mean amplitude of glycemic excursions (MAGE). The 24-h MAGE was calculated by measuring the arithmetic mean of differences more than 1 standard deviation (SD) between consecutive peaks and nadirs; measurement in the peak-to-nadir or nadir-to-peak direction was determined according to the first qualifying excursion [13]. Patients were then divided into the upper tertile of MAGE as Group H, and the other two-thirds as Group L.

LVG analysis

The biplane LVG in the RAO and LAO projections was routinely performed after reperfusion therapy was completed unless cardiogenic shock, impaired renal function, elevated left ventricular end-diastolic pressure ≥ 25 mmHg, or prosthetic aortic valve were identified. Quantitative LVG analysis was conducted using the computer-based validated system (CAAS II, Pie Medical Imaging, Maastricht, the Netherlands). Two independent observers (K.N. and K.T.) blind to baseline data including MAGE performed the analysis. The wall motion assessment by centerline method has been described elsewhere [9, 14]. In brief, wall motion is measured along 100 chords constructed as perpendiculars to a line drawn midway between the end-diastolic and end-systolic left ventricular contours. The motion of each chord is compared with a normal range established from analysis of LVG from patients without heart disease. Next to the extent of wall motion abnormality also the severity of the abnormal motion in a region is calculated. To detect regional wall motion (RWM) abnormality, the left ventricular contour is divided into artery territories. Artery territories are regions which are supplied with blood by a specific coronary artery. Each artery territory has an opposite region. The numbers correspond with the chords as defined in the centerline wall motion algorithm. The severity of RWM abnormality is defined in relation to the local cord lengths for regions that are related to arteries. Of each territory, the severity is calculated according to the following formula:

$$\text{Severity} = \max\left(\left|_{i\in\text{sliding\_window}} \sum \text{abnormality}(i)\right|/N\right).$$

The sliding_window is a window within a territory with a window length of half the extent of that territory. N is the number of chords within the sliding window. A severity factor of more than 2 indicates a diseased coronary artery. When the regional normalized motion is below zero, a

region is labeled Hypo for hypokinetic. When the regional normalized motion is above zero, a region is labeled Hyper for hyperkinetic. LVG analysis output data of representative 2 cases are shown in Fig. 1. Serial regional wall motion severity at the infarct site was computed postprocedure and at follow-up. Follow-up study was performed at 3 months in patients treated with balloon angioplasty and at 12 months in patients undergoing stent implantation. Absolute severity change was severity at postprocedure—severity at follow-up. Severity recovery ratio was calculated as follows: absolute severity change × 100/severity at postprocedure. Impaired severity recovery was defined as severity recovery ratio < 20%, which was the first tertile value of severity recovery ratio in the study patients.

Interventional procedure

We performed primary PCI via the femoral artery unless otherwise contraindicated, using a 7-Fr guiding catheter. Five-thousand unit unfractionated heparin was intravenously given after insertion of the introducer sheath. Intervention strategy including either primary or provisional stenting was entirely left to the discretion of individual operators. Manual thrombus aspiration was almost mandatorily conducted before balloon dilatation for all cases. Angiographic analysis using quantitative angiographic analysis system has been described previously [6].

Statistical analysis

Continuous variables were expressed as mean ± SD or medians with interquartile ranges. Categorical variables were presented as frequency (%). Student's t test was used to compare the two groups with respect to normally distributed variables, and the Wilcoxon rank-sum test was used for other variables. The χ^2 test or the Fisher's exact test was used compare categorical variables. Multivariate logistic regression analysis was conducted to provide adjusted risk estimates for the association between GV and impaired severity recovery with 95% confidence intervals (CIs) after forcing eight variables including age, gender, preinfarction angina, admission glucose level, renal function, and peak CPK level. Explanatory variable selection for confounding adjustment was based on clinical relevancy and bibliographic consideration. Differences were assessed with 2-sided tests, with an alpha level of 0.05.

Results

The patient flow diagram is depicted in Fig. 2. Among the 116 patients with acute MI, 73 patients were equipped with CGMS and we excluded 15 cases for the following

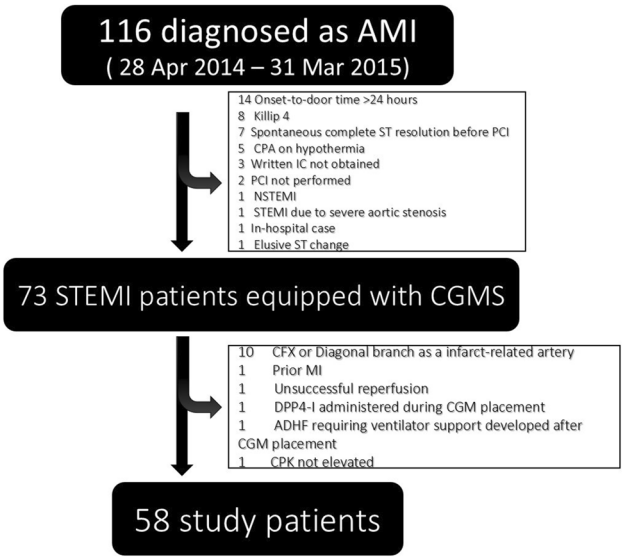


Fig. 2 Patient flowchart

reasons; circumflex or diagonal branch as an infarct-related artery ($n = 10$); unsuccessful reperfusion therapy ($n = 1$); administration of dipeptidyl peptidase-4 inhibitor ($n = 1$); acute decompensated heart failure requiring ventilator support that developed after CGMS placement ($n = 1$); no enzymatic elevation ($n = 1$). The final study population comprised 58 STEMI patients, consisting of 20 patients categorized to Group H, and 38 of Group L. There was no case developing target-lesion restenosis or de novo lesion in the target vessel with ≥ 75% diameter stenosis.

Baseline patient, glycemic, and lipid characteristics are shown in Tables 1 and 2. Patient baseline demographics and clinical characteristics were almost well balanced between Group H and Group L, although the patients in Group H tended to be older and took significantly shorter onset-to-door time than those in Group L (196.9 vs. 279.0 min, $p = 0.033$). The proportion of diabetes significantly differed between groups. Glycemic parameters were significantly higher in Group H than Group L except for the HOMR-IR. Lipid profiles were comparable between groups. Regarding the baseline lesion and procedural characteristics, there was no significant difference between groups (Table 3).

Quantitative LVG data including wall motion severity are summarized in Table 4. Figure 3 illustrates the good correlation between the wall motion severity and peak CK-MB level at baseline as well as at follow-up. Reflecting the difference of onset-to-door time between groups, higher left ventricular ejection fraction (LVEF) and lower wall motion severity of infarct area at postprocedure were observed in Group H, although statistically insignificant. However, absolute severity recovery was significantly smaller in Group H (0.5 vs.

Table 1 Baseline patients' characteristics

	Group L ($n=38$)	Group H ($n=20$)	p value
Age, y.o.	62.0 ± 11.7	67.7 ± 11.1	0.078
Male gender, %	34 (89.5)	15 (75.0)	0.251
Body mass index, kg/m^2	25.1 ± 3.7	23.1 ± 3.6	0.049
Hypertension, *n* (%)	25 (65.8)	11 (55.0)	0.570
Current smoker, *n* (%)	21 (55.3)	6 (30.0)	0.097
Medical history			
Previous PCI, *n* (%)	0	0	1.000
Cerebrovascular disease, *n* (%)	2 (5.3)	0	0.540
Preinfarction angina, *n* (%)	18 (47.4)	6 (20.0)	0.266
Medication at discharge			
ACEI/ARB, *n* (%)	31 (81.6)	14 (70.0)	0.339
Beta-blockers, *n* (%)	17 (44.7)	7 (35.0)	0.579
Aldosterone blockers, *n* (%)	3 (7.9)	0	0.544
Statins, *n* (%)	31 (81.6)	17 (85.0)	1.000
Metformin, *n* (%)	0	3 (15.0)	0.037
Pioglitazone, *n* (%)	8 (21.1)	5 (25.0)	0.750
DPP-4 inhibitors, *n* (%)	5 (13.2)	7 (35.0)	0.086
Alpha-GI, *n* (%)	3 (7.9)	3 (15.0)	0.405
Sulfonylureas/glinides, *n* (%)	2 (5.3)	3 (15.0)	0.328
Insulin provision, *n* (%)	0	3 (15.0)	0.037
LVEF, %	51.2 ± 9.3	56.1 ± 10.7	0.094
CrCl, ml/min	89.0 ± 33.7	67.8 ± 34.3	0.028
Killip class I, *n* (%)	35 (92.1)	20 (100)	0.544
Class II, *n* (%)	3 (7.9)	0	0.544
Onset-to-door time (min)	279.0 ± 140.3	196.9 ± 128.6	0.033
Door-to-balloon time (min)	76.3 ± 25.4	69.0 ± 19.7	0.269
CPK at peak, IU/l	3118 (1694, 4587)	1712 (649, 3659)	0.098
CK-MB at peak, IU/l	323 (148, 509)	206 (84, 359)	0.102
ST-segment resolution (%)	58.9 ± 23.1	57.4 ± 33.1	0.863

Continuous variables are expressed as mean ± SD or median (interquartile range)

ACEI angiotensin converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *CPK* creatine phosphokinase, *CrCl* creatinine clearance, *LVEF* left ventricular ejection fraction, *PCI* percutaneous coronary intervention, *STR* ST-segment resolution

1.3, $p=0.017$). A significant negative correlation was found between MAGE and absolute wall motion severity change ($r=-0.323$; $p=0.024$; Fig. 4). Consequently, impaired severity recovery was more prevalent in Group H than in Group L.

The logistic regression method was used to identify predicting factors of impaired wall motion severity recovery (Table 5). Univariate modeling showed only MAGE upper tertile (OR, 5.20; 95% CI, 1.26–21.49; $p=0.029$) was predictive of impaired severity recovery, whereas multivariate modeling demonstrated MAGE upper tertile (OR, 406.10; 95% CI, 4.41–37366.60; $p=0.009$) and onset-to-door time > 6 h (OR, 157.40; 95% CI, 1.34–18472.59; $p=0.037$) were associated with impaired severity recovery.

Discussion

The main finding of the present study is that higher GV is associated with impaired recovery of wall motion severity at the infarct area derived from LVG analysis, which is a surrogate marker of myocardial infarct size. Results of this study indicate that GV has negative impact on final infarct size after myocardial reperfusion therapy. Contrast LVG provides valuable information about global and segmental left ventricular function. While being invasive as compared with other alternative techniques including echo cardiogram, magnetic resonance imaging, and perfusion imaging test, LVG is safe and still a routine part

Table 2 Glycemic and lipid profiles

	Group L ($n=38$)	Group H ($n=20$)	p value
Diabetes mellitus, *n* (%)	12 (31.6)	15 (75.0)	0.002
Insulin provision, *n* (%*)	0	3 (15.0)	0.037
Impaired glucose tolerance, *n* (%)	19 (50.0)	4 (20.0)	0.047
Impaired fasting glucose, *n* (%)	1 (2.6)	0	1.000
Normal glucose tolerance, *n* (%)	6 (15.7)	1 (5.0)	0.403
Fasting blood glucose, mg/dl	104.7 ± 17.8	130.2 ± 35.8	0.005
Blood glucose at admission, mg/dl	159.8 ± 45.6	227.8 ± 80.4	0.002
HbA1c, %	6.0 ± 0.7	7.5 ± 1.9	<0.0001
HOMA-R	2.5 ± 1.4	3.2 ± 2.1	0.176
HOMA-ß	90.0 ± 49.8	60.8 ± 45.4	0.036
CGMS data			
Mean blood glucose, mg/dl	124.9 ± 22.6	177.7 ± 42.2	<0.0001
MAGE, mg/dl	42.5 ± 13.8	113.9 ± 28.4	<0.0001
LDL-C, mg/dl	108.9 ± 29.5	96.1 ± 24.7	0.103
HDL-C, mg/dl	41.3 ± 7.5	42.8 ± 13.3	0.655
LDL/HDL ratio	2.75 ± 0.93	2.40 ± 0.90	0.176
Triglyceride, mg/dl	101 (64, 143)	97 (49, 181)	0.941

Continuous variables are expressed as mean ± SD or median (interquartile range). * The value is calculated using the number of diabetes mellitus as a denominator

GMS continuous glucose monitoring system, *MAGE* mean amplitude of glycemic excursions, *STR* ST-segment resolution

Table 3 Lesion and procedural characteristics

	Group L (n = 38)	Group H (n = 20)	p value
Baseline			
Infarct-related artery			
LAD, *n* (%)	24 (63.2)	13 (65.0)	1.000
RCA, *n* (%)	14 (36.8)	7 (35.0)	1.000
Multivessel disease, *n* (%)	6 (15.8)	5 (25.0)	0.487
TIMI flow grade 0/1, *n* (%)	32 (84.2)	16 (80.0)	0.724
Thrombus containing, *n* (%)	29 (76.3)	14 (70.0)	0.754
Reference vessel diameter, mm	3.01 ± 0.71	2.75 ± 0.82	0.239
Lesion length, mm	13.69 ± 5.24	14.24 ± 6.51	0.748
Postprocedure			
TIMI flow grade 3, *n* (%)	32 (84.2)	17 (85.0)	1.000
Corrected TIMI frame count	26.6 ± 12.3	25.7 ± 10.3	0.786
Slow flow, *n* (%)	10 (26.3)	2 (10.0)	0.187
Reperfusion arrhythmias, *n* (%)	5 (13.1)	4 (20.0)	0.704
Stent usage, *n* (%)	25 (65.8)	15 (75.0)	0.559

LAD left anterior descending artery, *RCA* right coronary artery

of diagnostic cardiac catheterization in patients being evaluated for coronary artery disease. Various methods of analyzing quantitative regional wall motion abnormality of LVG have been developed to measure the myocardium at risk after reperfusion therapy. The centerline method has been most commonly employed for measurement of myocardium at risk of infarction.

Successful reperfusion with thrombolytic therapy or primary PCI leads to greater myocardial salvage and improved clinical outcome [2, 15, 16]. However, reperfusion injury has been known as a detrimental aspect of prompt recanalization for infarct-related artery and may explain in part why the mortality rate after acute MI still approaches 10% despite successful reperfusion [3]. Oxidative stress can mediate myocardial injury during

Table 4 Quantitative left ventriculography data

	Group L ($n=38$)	Group H ($n=20$)	p value
Post procedure			
LVEDVI, ml/m^2	67.3 ± 16.2	62.4 ± 11.6	0.274
LVESVI, ml/m^2	29.8 ± 16.8	23.4 ± 10.5	0.158
SVI, ml/m^2	35.6 ± 10.7	39.0 ± 8.7	0.262
LVEF, %	56.4 ± 13.3	63.3 ± 11.9	0.075
Wall motion severity	2.92 ± 1.03	2.39 ± 1.20	0.096
Follow-up			
LVEDVI, ml/m^2	67.5 ± 21.1	59.8 ± 13.1	0.245
LVESVI, ml/m^2	26.5 ± 12.7	21.2 ± 9.5	0.196
SVI, ml/m^2	41.1 ± 12.5	38.7 ± 7.0	0.532
LVEF, %	61.9 ± 10.1	65.5 ± 8.7	0.267
Wall motion severity	1.61 ± 1.21	1.88 ± 1.01	0.463
Absolute severity change	1.32 ± 1.09	0.49 ± 1.02	0.017
Severity recovery ratio, %	46.5 ± 39.2	30.1 ± 32.3	0.178
Impaired severity recovery, n (%)	5 (13.2)	7 (35.0)	0.029

LVEDVI left ventricular end-diastolic volume index, *LVEF* left ventricular ejection fraction, *LVESVI* left ventricular end-systolic volume index, *SVI* stroke volume index

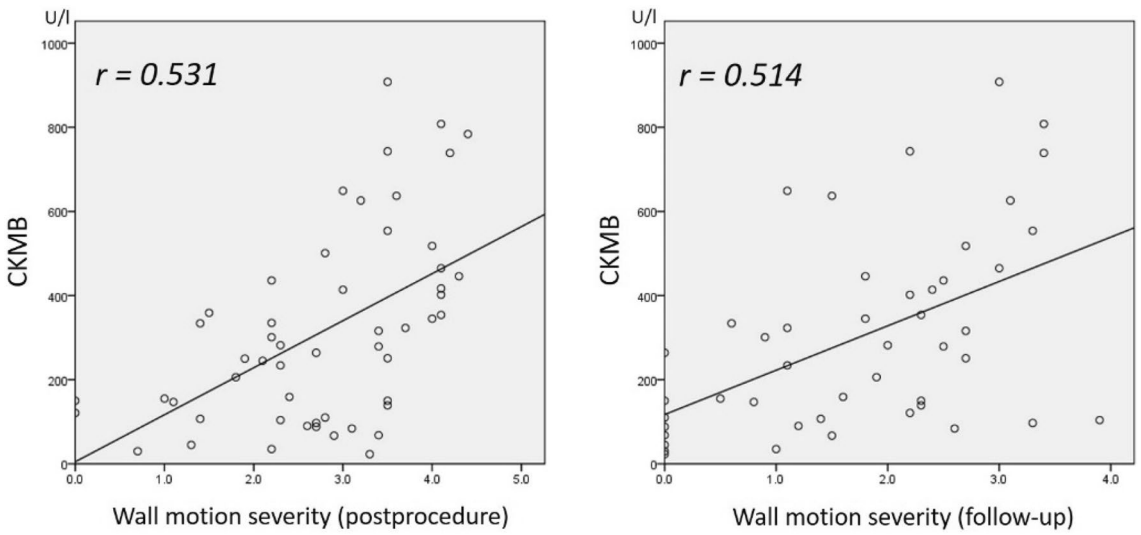


Fig. 3 Linear regression scatter plots showing the relationship between peak CK-MB value (U/L) and wall motion severity at postprocedure and at follow-up of each study patient

reperfusion of ischemic myocardium [3]. Although several potential mediators of reperfusion injury have been proposed [3], the mechanism remains to be fully elucidated. Glycemic disorder is a major predictor of poorer clinical outcome in STEMI [17, 18] and is not just limited to constant hyperglycemia. Interest in GV as a potential deleterious factor in cardiovascular disease has recently been growing. Su and colleagues reported that STEMI patients with higher MAGE (≥ 3.9 mmol/l) showed poorer 12-month clinical outcomes than those with lower MAGE [1]. Teraguchi et al. described a correlation between GV and final infarct size computed from magnetic resonance imaging in STEMI patients [5]. Earlier, we showed the relationship between GV and electrocardiographic ST-segment resolution, well known as a surrogate marker of reperfusion injury [6]. An animal experiment showed GV increased the generation of reactive oxygen species (ROS) and enhanced ischemia/reperfusion injury in diabetic hearts [19]. A clinical study also demonstrated that GV exhibits a more specific triggering effect on oxidative stress than chronic sustained hyperglycemia [20]. In a different perspective from oxidative stress, this impaired

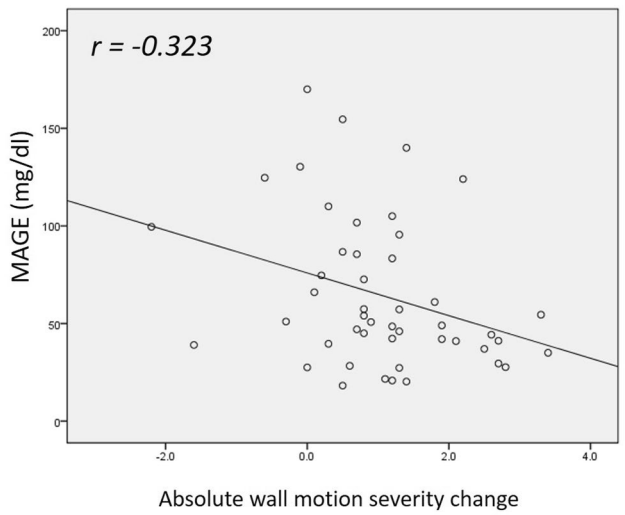


Fig. 4 Linear regression scatter plots showing the relationship between MAGE value (mg/dl) and absolute wall motion severity change of each study patient

myocardial salvage may be accounted for by the duration of hyperglycemia. Our data showed there was no significant difference in HOMA-R value between Group H and L, despite the significantly higher, fasting and admission blood glucose, or HbA1c in Group H. This result suggests that Group H potentially includes more patients with longer period of hyperglycemia and subsequent poorer insulin secretion. Long-term or chronic hyperglycemia poses coronary microvascular dysfunction [21], which may be involved large part of myocardial damage secondary to STEMI. Furthermore, reduced insulin secretion leads to blood glucose elevation, or more specifically higher GV. Although the role of GV in the pathogenesis of increased myocardial damage in STEMI has not been established, several studies have indicated that impaired glucose metabolism, and GV in particular, can exacerbate myocardial injury [1, 5, 19]. In this study, patients in higher GV group took significantly shorter onset-to-door time by chance. The shorter onset-to-door time might relate to the relatively lower peak creatine kinase level and wall motion severity at risk in Group H. Despite the advantage in earlier reperfusion therapy, the absolute wall motion severity change in Group H was significantly smaller. This finding may provide a coherent perspective with Teraguchi's report describing the quantitative assessment of infarct area using magnetic resonance imaging. Our clinical findings, in accord with those reported by Saito et al. *[*19], suggest that GV may represent a potential therapeutic target to reduce myocardial reperfusion injury in STEMI. So far, a few therapeutic options of glycemic management have been demonstrated to alleviate this paradoxical phenomenon following myocardial reperfusion therapy and yield subsequent beneficial clinical outcomes. Further studies are needed to determine whether reducing glucose fluctuations can provide positive results for STEMI patients undergoing reperfusion therapy.

The present study has several limitations. First, this was a single-center study. Second, the study population was small. The possibility of a type II error might be considered. Third, the optimal timing and duration of continuous glucose monitoring have not been settled. We inserted the CGMS sensor within approximately 24–48 h, while Teraguchi et al. started monitoring 24 h after the onset of acute MI [5]. Because we believe that the ideal monitoring should be available when patients take substantial meals, a relatively later timing was adopted. Finally, significantly shorter onset-to-door time by chance in patients with higher GV group may influence the present results.

In conclusions, GV was potentially associated with an impaired myocardial salvage in STEMI patients undergoing reperfusion therapy. Our results suggest that final infarct size is potentially larger than expected in STEMI patients with higher GV.

Table 5 Logistic regression analysis showing the risk of wall motion severity recovery < 20%

Variables	Univariate			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age ≥ 75 y.o.	0.51	0.05–4.87	1.000	6.57	0.21–205.69	0.283
Male gender	0.41	0.04–3.81	0.655	0.02	0.00–1.07	0.054
Preinfarction angina	1.90	0.50–7.25	0.501	3.37	0.32–34.53	0.306
Admission glucose ≥ 180 mg/dl	1.14	0.28–4.76	1.000	0.09	0.01–1.90	0.124
MAGE upper tertile	5.20	1.26–21.49	0.029	406.10	4.41–37366.60	0.009
Slow flow	1.04	0.23–4.81	1.000	7.31	0.34–155.94	0.202
CrCl < 60 ml/min	1.07	0.71–1.61	0.728	0.25	0.01–3.44	0.306
Peak CPK at peak ≥ 3000 IU/l	1.42	0.32–1.25	0.321	2.11	0.22–20.10	0.514
Onset-to-door time ≥ 6 h	5.17	0.75–35.85	0.109	157.40	1.34–18472.59	0.037

CPK creatine phosphokinase, *CrCl* creatinine clearance, *MAGE* mean amplitude of glycemic excursions

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

References

1. Su G, Mi SH, Tao H, Li Z, Yang HX, Zheng H, Zhou Y, Tian L. Impact of admission glycemic variability, glucose, and glycosylated hemoglobin on major adverse cardiac events after acute myocardial infarction. Diabetes Care. 2013;36:1026–32.
2. Fox KA, Steg PG, Eagle KA, Goodman SG, Anderson FA Jr, Granger CB, Flather MD, Budaj A, Quill A, Gore JM, Investigators G. Decline in rates of death and heart failure in acute coronary syndromes, 1999–2006. JAMA. 2007;297:1892–900.
3. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. N Engl J Med. 2007;357:1121–35.
4. Saito S, Thuc LC, Teshima Y, Nakada C, Nishio S, Kondo H, Fukui A, Abe I, Ebata Y, Saikawa T, Moriyama M, Takahashi N. Glucose fluctuations aggravate cardiac susceptibility to ischemia/reperfusion injury by modulating MicroRNAs expression. Circ J. 2016;80:186–95.
5. Teraguchi I, Imanishi T, Ozaki Y, Tanimoto T, Ueyama M, Orii M, Shiono Y, Shimamura K, Ishibashi K, Yamano T, Ino Y, Yamaguchi T, Hirata K, Kubo T, Sanke T, Akasaka T. Acute-phase glucose fluctuation is negatively correlated with myocardial salvage after acute myocardial infarction. Circ J. 2014;78:170–9.
6. Tsuchida K, Nakamura N, Soda S, Sakai R, Nishida K, Hiroki J, Kashiwa A, Fujihara Y, Kimura S, Hosaka Y, Takahashi K, Oda H. Relationship between glucose fluctuations and ST-segment resolution in patients with ST-elevation acute myocardial infarction. Int Heart J. 2017;58:328–34.
7. Mahmarian JJ, Mahmarian AC, Marks GF, Pratt CM, Verani MS. Role of adenosine thallium-201 tomography for defining long-term risk in patients after acute myocardial infarction. J Am Coll Cardiol. 1995;25:1333–40.
8. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, Bundy J, Finn JP, Klocke FJ, Judd RM. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation. 1999;100:1992–2002.
9. Sheehan FH, Bolson EL, Dodge HT, Mathey DG, Schofer J, Woo HW. Advantages and applications of the centerline method for characterizing regional ventricular function. Circulation. 1986;74:293–305.
10. Lapeyre AC 3rd, St Gibson W, Bashore TM, Gibbons RJ. Quantitative regional wall motion analysis with early contrast ventriculography for the assessment of myocardium at risk in acute myocardial infarction. Am Heart J. 2003;145:1051–7.
11. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P and Group ESCSD. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39:119–177.
12. Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes M, Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, Araki E, Ito C, Inagaki N, Iwamoto Y, Kasuga M, Hanafusa T, Haneda M, Ueki K. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Investig. 2010;1:212–28.
13. Service FJ, O'Brien PC and Rizza RA. Measurements of glucose control. Diabetes care. 1987;10:225–37.
14. Sheehan FH, Schofer J, Mathey DG, Kellett MA, Smith H, Bolson EL, Dodge HT. Measurement of regional wall motion from biplane contrast ventriculograms: a comparison of the 30 degree right anterior oblique and 60 degree left anterior oblique projections in patients with acute myocardial infarction. Circulation. 1986;74:796–804.
15. Schomig A, Mehilli J, Antoniucci D, Ndrepepa G, Markwardt C, Di Pede F, Nekolla SG, Schlotterbeck K, Schuhlen H, Pache J, Seyfarth M, Martinoff S, Benzer W, Schmitt C, Dirschinger J, Schwaiger M, Beyond 12 hours Reperfusion AlternatiVe Evaluation Trial I. Mechanical reperfusion in patients with acute myocardial infarction presenting more than 12 hours from symptom onset: a randomized controlled trial. JAMA. 2005;293:2865–72.
16. McManus DD, Gore J, Yarzebski J, Spencer F, Lessard D, Goldberg RJ. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. Am J Med. 2011;124:40–7.
17. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet. 2000;355:773–8.
18. Ishihara M, Kojima S, Sakamoto T, Asada Y, Tei C, Kimura K, Miyazaki S, Sonoda M, Tsuchihashi K, Yamagishi M, Ikeda Y, Shirai M, Hiraoka H, Inoue T, Saito F, Ogawa H and Japanese Acute Coronary Syndrome Study I. Acute hyperglycemia is associated with adverse outcome after acute myocardial infarction in the coronary intervention era. Am Heart J. 2005;150:814–20.
19. Saito S, Thuc LC, Teshima Y, Nakada C, Nishio S, Kondo H, Fukui A, Abe I, Ebata Y, Saikawa T, Moriyama M and Takahashi N. Glucose fluctuations aggravate cardiac susceptibility to ischemia/reperfusion injury by modulating MicroRNAs expression. Circ J. 2015.
20. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA. 2006;295:1681–7.
21. Di Carli MF, Janisse J, Grunberger G, Ager J. Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. J Am Coll Cardiol. 2003;41:1387–93.