Advance Publication by-J-STAGE

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

Non-Contrast T1-Weighted Magnetic Resonance Imaging at 3.0 Tesla in a Patient Undergoing Elective Percutaneous Coronary Intervention

– Clinical and Pathological Significance of High-Intensity Plaque –

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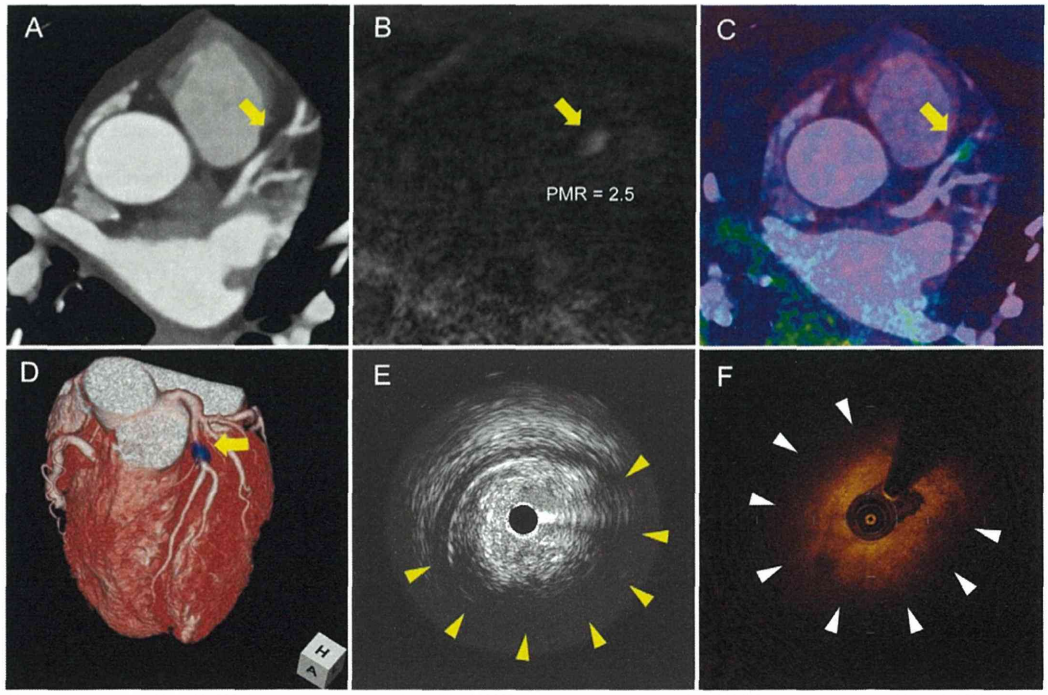

Figure 1. Computed tomography angiography (CTA) and magnetic resonance imaging of the coronary artery prior to percutaneous coronary intervention. (**A**) Coronary CTA showing a lesion of the left anterior descending artery (LAD) with significant stenosis and positive vessel remodeling (yellow arrow). (**B**) Non-contrast T1-weighted magnetic resonance imaging (T1WI) at 3.0 T showing a high-intensity plaque with a plaque-to-myocardium signal intensity ratio (PMR) of 2.5 in a LAD lesion, which corresponds to a coronary plaque detected on CTA (yellow arrow). (**C**) Two-dimensional fusion image between coronary CTA and non-contrast T1WI at 3.0 T (Ziostation 2; Ziosoft, Tokyo, Japan). (**D**) Three-dimensional fusion image between coronary CTA (volume-rendered image) and non-contrast T1WI at 3.0 T. (**E**) Intravascular ultrasound (View It, Terumo, Tokyo, Japan) showing the heterogeneous appearance of a large intimal plaque and low-echogenicity region in the deeper intima with remarkable attenuation (yellow arrowheads). (**F**) Optical coherence tomography (ILUMIEN OPTIS, St. Jude Medical Japan, Tokyo, Japan) showing an extensive signal-poor region with low backscattering and a lipid arc of 286° (white arrowheads).

Received August 12, 2014; revised manuscript received September 11, 2014; accepted September 23, 2014; released online October 24, 2014 Time for primary review: 12 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-14-0897

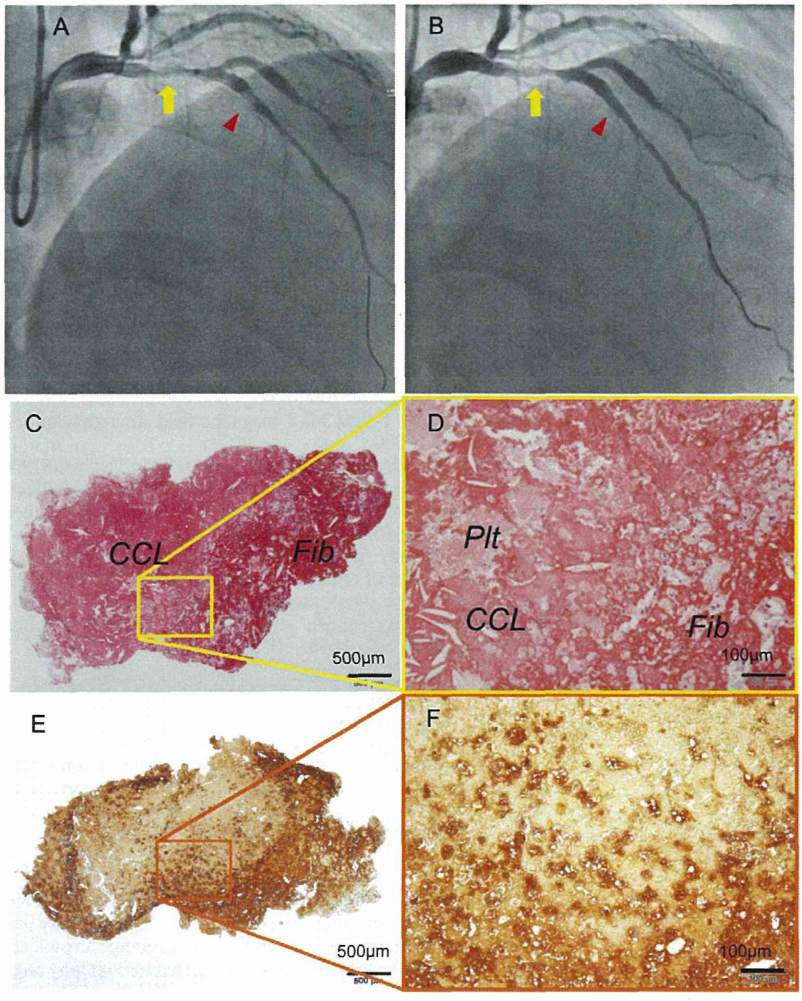

Figure 2. Coronary angiography during percutaneous coronary intervention and microscopy of the specimen aspirated from the target vessel. (**A**) Coronary angiography immediately after pre-dilatation at the target lesion (yellow arrow) showing a filling defect in the distal segment of the left anterior descending artery (red arrowhead). (**B**) The filling defect disappeared after intra-coronary aspiration (red arrowhead). (**C**) Low- and (**D**) high-magnification microscopy of the aspirated specimen showing an acute thrombus containing a large amount of the necrotic core with numerous cholesterol clefts (CCL), fibrin (Fib), and platelets (Plt) (H&E). (**E**) Low- and (**F**) high-magnification immunohistochemistry indicating extensive infiltration of $CD68^+$ macrophages within the necrotic core and thrombus.

Vulnerable or high-risk atherosclerotic plaque is prone to rupture and to thus cause acute coronary syndrome, but detecting this plaque on coronary plaque imaging has been challenging.[1] In previous studies we described the characteristics of coronary high-intensity plaque (HIP) on non-contrast T1-weighted magnetic resonance imaging (T1WI),[2,3] and showed that this plaque was associated with the slow- or no-reflow phenomenon and with periprocedural myocardial injuries during elective percutaneous coronary intervention (PCI), as well as with future coronary events.[2,4,5] High-spatial-resolution 3.0-T magnetic resonance imaging (MRI) of carotid plaques had substantial improvement in imaging quality and signal-to-noise and contrast-to-noise ratios compared with 1.5-T MRI.[6] Few studies, however, have involved coronary plaque imaging using non-contrast T1WI with 3.0-T clinical MRI.

In a 46-year-old man with stable effort angina pectoris, coronary computed tomography angiography showed significant stenosis with a low-density coronary plaque and positive vessel remodeling in the proximal portion of the left anterior descending artery (LAD; **Figure 1A**; **Movie S1**). Non-contrast T1WI was done on 3.0-T MRI with a 32-channel cardiac coil (MAGNETOM Verio; Siemens AG Healthcare Sector, Erlangen, Germany). Coronary plaque imaging was performed using an inversion recovery-prepared 3-D T1W turbo fast low-angle shot sequence with an electrocardiographic trigger, navigator-gated free-breathing, and fat suppression, with transaxial sections covering the whole heart (inversion time, 650 ms; field of view, 280×228 mm; acquisition matrix, 256×187; reconstruction matrix, 512×374; acquisition slice thickness, 1.0 mm; reconstruction spatial resolution, 0.6×0.5×0.6 mm; repetition time/echo, 4.7 ms/2.13 ms; flip angle, 12°; GRAPP factor, 2; navigator gating window, ±1.5–2.5 mm; and data acquisition window, 84–120 ms). The trigger delay and acquisition window were set based on the period of minimal right coronary artery motion as determined on cine-MRI.[5] Acquisition time and navigation efficiency in this case were 15 min and 35%, respectively. The plaque-to-myocardium signal intensity ratio, defined as the signal intensity of the coronary plaque divided by that of the nearby left ventricular myocardium, was calculated to be 2.5 (**Figure 1B**; **Movie S2**). Intravascular ultrasound showed a large intimal plaque and a region of low echogenicity that had remarkable attenuation (**Figure 1E**). Optical CT showed an extensive signal-poor region with low backscattering and a lipid arc of 286° (**Figure 1F**). The patient underwent elective PCI for proximal LAD lesion. Following the first balloon dilatation, a filling defect was observed in the distal segment of the LAD and the slow-flow phenomenon developed (**Figure 2A**); this defect disappeared following intra-coronary aspiration

(**Figure 2B**). Microscopy of the aspirated specimen showed a large amount of the necrotic core with overlying platelet- and fibrin-rich thrombus (**Figures 2C,D**). Immunohistology confirmed numerous $CD68^+$ macrophages within the aspirated specimen (**Figures 2E,F**), suggesting that the coronary embolus may have involved the large necrotic core with extensive inflammation.

In the present case, we successfully imaged coronary plaque defined as HIP on non-contrast T1WI using 3.0-T MRI. MRI was originally developed for carotid artery examinations but has emerged as a novel modality for atherosclerotic plaque characterization.[7] In particular, high-intensity signals observed in carotid plaque using inversion recovery-based 3-D T1WI have been found to be associated with recent ischemic cerebrovascular events and are related to the American Heart Association classification type VI complex plaque, which is characterized by luminal surface defects, intraplaque hemorrhage, thrombus, or calcified nodules.[7,8] Plaque imaging at 3.0 T is expected to provide improved imaging quality and better signal-to-noise and contrast-to-noise ratios compared with 1.5-T MRI. There have been few reports, however, of coronary artery imaging using 3.0-T MRI. Future studies comparing 1.5-T and 3.0-T MRI are warranted to assess coronary plaque.

Importantly, in this particular case, the coronary plaque defined as HIP on non-contrast T1WI at 3.0 T was associated with coronary embolus and slow flow following PCI. Specimens collected from the coronary artery contained atheroma with lipid-rich necrotic cores (**Figure 2**), consistent with MRI findings of hyperintense carotid plaque. Further studies are also needed to identify the plaque components of coronary HIP visualized on T1WI, and thus elucidate the mechanisms underlying acute coronary syndrome and the development of atherosclerosis.

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Supplementary Files

Supplementary File 1

Movie S1. Serial imaging of the heart with enhanced computed tomography angiography showing coronary plaque with severe stenosis, positive vessel remodeling, and low plaque density at the proximal portion of the left anterior descending artery (orange arrow).

Supplementary File 2

Movie S2. Serial imaging of the heart on non-contrast T1-weighted magnetic resonance imaging at 3.0 T showing a high-intensity plaque at the proximal left anterior descending artery (orange arrow), corresponding with the lesion detected on computed tomography angiography.

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-14-0897

Impact of Acute and Chronic Hyperglycemia on In-Hospital Outcomes of Patients With Acute Myocardial Infarction

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This study was undertaken to assess the impact of acute hyperglycemia (acute-HG) and chronic hyperglycemia (chronic-HG) on short-term outcomes in patients with acute myocardial infarction (AMI). This study consisted of 696 patients with AMI. Acute-HG was defined as admission plasma glucose ≥200 mg/dl and chronic-HG as hemoglobin A1c ≥6.5%. Acute-HG was associated with higher peak serum creatine kinase (4,094 ± 4,594 vs 2,526 ± 2,227 IU/L, p <0.001) and in-hospital mortality (9.8% vs 1.6%, p <0.001). On the contrary, there was no significant difference in peak creatine kinase (2,803 ± 2,661 vs 2,940 ± 3,181 IU/L, p = 0.59) and mortality (3.3 vs 3.7%, p = 0.79) between patients with chronic-HG and those without. Multivariate analysis showed that admission plasma glucose was an independent predictor of in-hospital mortality (odds ratio 1.15, 95% confidence interval 1.05 to 1.27, p <0.001), but hemoglobin A1c was not. When only patients with acute-HG were analyzed, chronic-HG was associated with a significantly smaller infarct size (3,221 ± 3,001 vs 5,904 ± 6,473 IU/L, p <0.001) and lower in-hospital mortality (5.5 vs 18.9%, p = 0.01). In conclusion, these results suggested that acute-HG, but not chronic-HG, was associated with adverse short-term outcomes after AMI. Paradoxically, in patients with acute-HG, chronic-HG might abate the adverse effects of acute-HG. **(Am J Cardiol 2014;114:1789–1793)**

It has been reported that hyperglycemia (HG) causes oxidative stress, enhances inflammation, induces apoptosis, and activates coagulation, which deteriorate myocardial damage in the setting of ischemia.[1–3] In the clinical practice, admission plasma glucose is used as a measure of acute-HG and hemoglobin A1c (HbA1c) for chronic-HG. However, it remains unclear how acute-HG and chronic-HG affect short-term outcomes in patients with acute myocardial infarction (AMI). The purpose of the present study was to investigate impact of acute-HG and chronic-HG on short-term outcomes after AMI.

Methods

From January 2007 to June 2012, 760 consecutive patients who were admitted to National Cerebral and Cardiovascular Center of Japan within 48 hours after the onset of AMI were prospectively enrolled to the observational single-center registry and were retrospectively analyzed. In this registry, AMI was defined by a combination of 2 of the following 3: chest pain longer than 30 minutes, electrocardiographic signs, and elevation of serum creatine kinase more than twice the upper normal limit. Patients for whom laboratory data were lacking (n = 64) were excluded from the present study. Finally, this study consisted of the remaining 696 patients who constituted the study population with short-term clinical follow-up. The allocation of emergency coronary angiography and coronary intervention was determined by the physician's decision. The study protocol was approved by the Institutional Review Board of National Cerebral and Cardiovascular Center and was conducted in accordance with regulations governing epidemiological studies issued by the Ministry of Health, Labor, and Welfare of Japan.

On admission, age, gender, body mass index, and comorbidities such as hypertension, diabetes, dyslipidemia, smoker, and previous myocardial infarction were recorded. Plasma glucose was obtained at the time of admission, and HbA1c, during hospitalization. Serum creatine kinase was measured every 3 hours until it reached the peak value. Acute-HG was defined as admission plasma glucose ≥200 mg/dl.[4] Chronic-HG was defined as HbA1c ≥6.5%.[5] Chronic kidney disease is defined as estimated glomerular filtration rate ≤30 ml/min/1.73 m^2 in this study.

Continuous data were shown as mean ± SD. Continuous variables were compared by use of the *t* test and categorical

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The present study was supported by the Intramural Research Fund, grant number 26-4-3, for Cardiovascular Diseases of the National Cerebral and Cardiovascular Center.

See page 1792 for disclosure information.

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http://dx.doi.org/10.1016/j.amjcard.2014.09.015

Table 1
Baseline characteristics of patients with and without acute hyperglycemia

Variables	Acute Hyperglycemia		p Value
	Yes (n=163)	No (n=533)	
Age (yrs)	68.7 ± 11.9	67.4 ± 12.8	0.268
Men	72%	72%	0.921
Body mass index (kg/m^2)	24.4 ± 3.8	23.3 ± 3.7	0.002
Diabetes Mellitus	69%	24%	<0.001
Hypertension	72%	66%	0.214
Dyslipidemia	61%	54%	0.105
Smoker	32%	33%	0.964
Chronic kidney disease	48%	29%	<0.001
Previous myocardial infarction	9%	10%	0.881
ST elevation myocardial infarction	80%	84%	0.342
Anterior location	39%	39%	1.000
Killip class 2 to 4	35%	14%	<0.001
Elapsed time (hour)	7.1 ± 10.2	7.5 ± 9.7	0.701
Primary percutaneous coronary intervention	90%	86%	0.349
Medication before infarction			
Antiplatelet agent	21%	18%	0.494
Angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers	31%	22%	0.021
Calcium-channel blocker	27%	26%	0.919
Beta-blocker	12%	10%	0.562
Statin	23%	17%	0.066
Oral hypoglycemic agent	29%	8%	<0.001
Insulin	9%	2%	<0.001

Table 2
Baseline characteristics of patients with and without chronic hyperglycemia

Variables	Chronic Hyperglycemia		p Value
	Yes (n=212)	No (n=484)	
Age (yrs)	68.6 ± 12.4	67.3 ± 12.7	0.192
Men	74%	71%	0.583
Body mass index (kg/m^2)	24.4 ± 3.9	23.2 ± 3.7	<0.001
Diabetes Mellitus	83%	13%	<0.001
Hypertension	73%	65%	0.065
Dyslipidemia	62%	53%	0.031
Smoker	34%	32%	0.736
Chronic kidney disease	36%	32%	0.296
Previous myocardial infarction	8%	10%	0.491
ST elevation myocardial infarction	80%	84%	0.229
Anterior location	36%	41%	0.238
Killip class 2 to 4	20%	19%	0.754
Elapsed time (hour)	8.1 ± 10.3	7.1 ± 9.6	0.206
Primary percutaneous coronary intervention	88%	87%	0.711
Medication before infarction			
Antiplatelet agent	20%	18%	0.600
Angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers	31%	21%	0.007
Calcium-channel blocker	27%	26%	0.926
Beta-blocker	10%	11%	1.000
Statin	22%	18%	0.090
Oral hypoglycemic agent	35%	4%	<0.001
Insulin	9%	1%	<0.001

variables with chi-square statistics or Fisher's exact test. Logistic regression analysis was used to obtain odds ratio (OR) and 95% confidence interval (CI) for in-hospital mortality. In multivariate analysis, the association between acute-HG and chronic-HG were adjusted for baseline variables, including age, gender, smoker, previous myocardial infarction, elapsed time, ST-elevation myocardial infarction, Killip classification ≥2, and primary coronary intervention. Multivariate analysis was also performed when plasma glucose and HbA1c were analyzed as a continuous variable. Values of $p < 0.05$ were considered statistically significant. All statistical analyses were performed using JMP (version 11.0, SAS Inc., Tokyo, Japan).

Results

This study consisted of 696 patients. A total of 652 patients (94%) underwent emergency coronary angiography. Primary coronary intervention was performed in 606 patients (87%), mostly with stents (92%). Final Thrombolysis In Myocardial Infarction grade 3 flow was obtained in 553 patients (91%).

Acute-HG was found in 163 patients (23%). Table 1 lists the baseline characteristics of patients with and without acute-HG. Patients with acute-HG had significantly higher plasma glucose on admission (276 ± 75 vs 139 ± 28 mg/dl, $p < 0.001$) and HbA1c (7.2 ± 1.9 vs 5.6 ± 0.8%, $p < 0.001$) than those without acute-HG. Acute-HG was associated with more diabetes, more chronic kidney disease, more Killip classification ≥2, and higher body mass index.

There were 212 (30%) patients with chronic-HG. The baseline characteristics of patients with chronic-HG and without chronic-HG were listed in Table 2. Both admission plasma glucose and HbA1c were higher in patients with chronic-HG than without chronic-HG (223 ± 86 vs 148 ± 52 mg/dl, $p < 0.001$ and 7.5 ± 1.5 vs 5.4 ± 0.3%, $p < 0.001$, respectively). Chronic-HG was associated with more diabetes and more dyslipidemia.

Peak creatine kinase was obtained in 691 patients (99%). Patients with acute-HG had a significantly higher peak creatine kinase than those without ($p < 0.001$; Figure 1). There was no significant difference in peak creatine kinase between patients with chronic-HG and those without ($p = 0.59$; Figure 1). In-hospital mortality rate was significantly higher in patients with acute-HG than in those without ($p < 0.001$; Figure 1), but chronic-HG was not associated with in-hospital mortality ($p = 0.79$; Figure 1).

In univariate analysis, acute-HG was associated with a sixfold increase in in-hospital mortality risk (OR 6.34, 95% CI 2.8 to 15.3, $p < 0.001$). When plasma glucose was analyzed as a continuous variable, an increase of 1 mmol/L (18 mg/dl) in plasma glucose was associated with an increase in mortality risk of 18% (OR 1.18, 95% CI 1.10

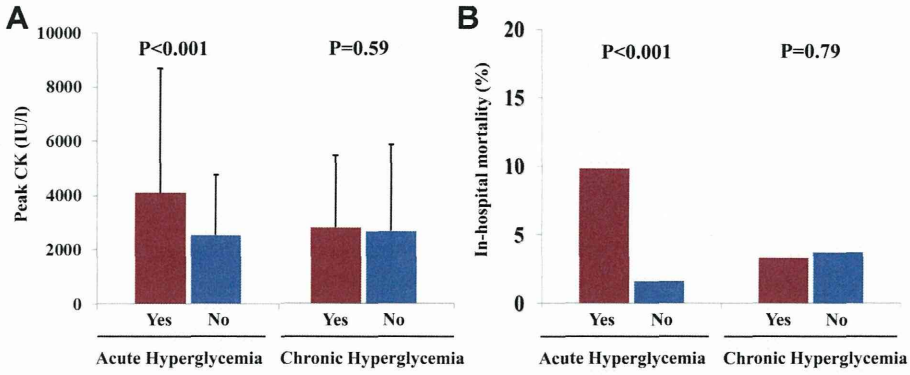

Figure 1. Effects of acute-HG and chronic-HG on peak creatine kinase and in-hospital mortality. *(A)* Patients with acute-HG had a significantly higher peak creatine kinase than those without (4,094 ± 4,594 vs 2,526 ± 2,227 IU/L, p <0.001). There was no significant difference in peak creatine kinase between patients with and without chronic-HG (2,803 ± 2,661 vs 2,940 ± 3,181 IU/L, p = 0.59). *(B)* In-hospital mortality rate was significantly higher in patients with acute-HG than in patients without (9.8% vs 1.6%, p <0.001). There was no significant difference in mortality between patients with and without chronic-HG (3.3 vs 3.7%, p = 0.79). CK = creatine kinase; HG = hyperglycemia.

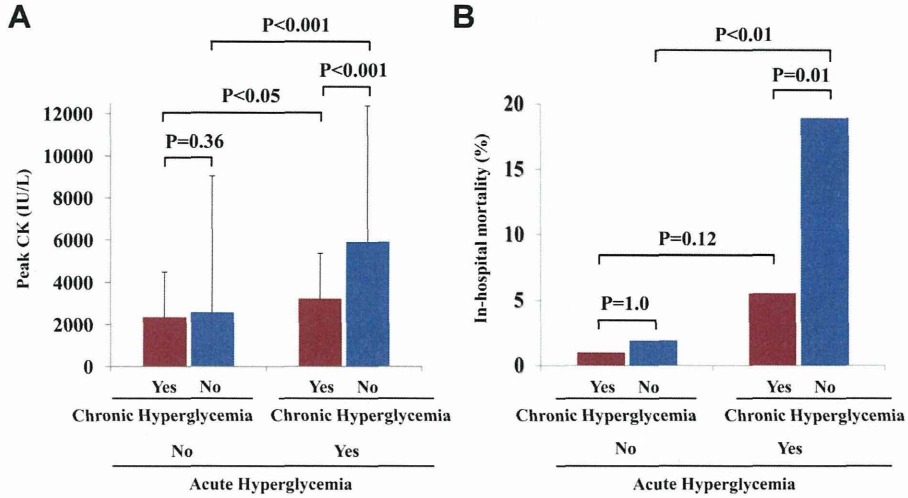

Figure 2. Effects of chronic-HG on peak creatine kinase and in-hospital mortality in patients with acute-HG and in those without acute-HG. (A) When only patients without acute-HG were analyzed, there was no significant difference in peak creatine kinase (2,348 ± 2,156 vs 2,572 ± 2,244 IU/L, p = 0.36) and in-hospital mortality (1.0 vs 1.9%, p = 1.00) between patients with and those without chronic-HG. (B) On the contrary, in patients with acute-HG, chronic-HG was associated with smaller peak creatine kinase (3,221 ± 3,001 vs 5,904 ± 6,473 IU/L, p <0.001) and lower mortality (5.5 vs 18.9%, p = 0.01). CK = creatine kinase; HG = hyperglycemia.

to 1.26, p <0.001). On the contrary, chronic-HG (OR 0.88, 95% CI 0.34 to 2.06, p = 0.79) and HbA1c (OR 1.14, 95% CI 0.85 to 1.43, p = 0.31) were not predictive factors of in-hospital mortality.

In multivariate analysis, acute-HG was independently associated with in-hospital mortality (OR 6.35, 95% CI 2.29 to 18.9, p <0.001), but chronic-HG was not (OR 0.47, 95% CI 0.15 to 1.37, p = 0.16). Analyzed as a continuous variable, plasma glucose was an independent predictor for in-hospital mortality (OR 1.21, 95% CI 1.09 to 1.35, p <0.001), but HbA1c was not (OR 0.85, 95% CI 0.57 to 1.20, p = 0.36).

Peak creatine kinase and in-hospital mortality are shown in Figure 2, stratified according to acute-HG and chronic-HG. Acute-HG was associated with large infarct size and high in-hospital mortality in both patients with and without chronic-HG. In 528 patients without acute-HG, there was no significant difference in peak creatine kinase and in-hospital mortality between patients with and without chronic-HG. On the contrary, in 163 patients with acute-HG, chronic-HG was associated with smaller peak creatine kinase and lower in-hospital mortality.

Discussion

The major findings of this study were (1) acute-HG was associated with large infarct size and high in-hospital mortality in patients with AMI, but chronic-HG was not and (2) in patients with acute-HG, chronic-HG was paradoxically associated with small infarct size and low mortality after AMI.

As previous studies have reported,[6–10] the present study showed that acute-HG is associated with larger infarct size and higher in-hospital mortality in patients with AMI. Although there had a been debate as to whether acute-HG is causally related to poor outcome after AMI or is simply an

epiphenomenon of the severe disease conditions, most recent studies have demonstrated that acute-HG is causally associated with further deterioration of myocardial damage and poor outcomes after reperfusion.

Acute-HG is observed not only in diabetic but also in nondiabetic patients with AMI. Although earlier studies classified nondiabetic patients with acute-HG as preexisting undiagnosed diabetes, recent studies have shown that acute-HG in nondiabetic patients does not represent preexisting undiagnosed diabetes.[11] In the thrombolysis era, it has been reported that diabetes and chronic glucose dysregulation, as assessed by HbA1c levels, are prognostic factors for in-hospital mortality in patients with AMI.[12] However, recent studies have shown that diabetes is not associated with short-term outcomes after AMI in patients who underwent primary coronary intervention.[9,13,14] In the present study, we also showed that chronic-HG assessed by HbA1c did not predict infarct size and in-hospital mortality in patients with AMI who were mostly treated with primary coronary intervention.

Several clinical and experimental studies have shown that acute increase of plasma glucose causes several unfavorable effects, including oxidative stress, inflammation, apoptosis, endothelial dysfunction, and hypercoagulation, that may contribute to the poor outcomes in patients with AMI. Esposito et al[1] reported that the plasma cytokine levels increased as the plasma glucose level increased during consecutive pulses of intravenous glucose but immediately returned to normal as plasma glucose returned to normal levels. Of note, when the first elevation in the blood glucose level was maintained by subsequent continuous intravenous glucose infusion, plasma cytokine concentrations gradually returned to normal levels, despite sustained high plasma glucose level. Apoptosis is also enhanced by intermittent, rather than constant, high glucose concentration.[2]

In patients with AMI who underwent primary coronary intervention, Iwakura et al[15] have shown that no-reflow phenomenon assessed by contrast echocardiography was predicted by acute-HG but not by a history of diabetes or by HbA1c. Recently, Teraguchi et al[16] reported, using continuous glucose measurement and cardiac magnetic resonance imaging, that there was a significant negative relation between glucose fluctuation and myocardial salvage index. In addition, we have previously reported that acute-HG abolishes ischemic preconditioning that has potent endogenous cardioprotective effect against myocardial ischemia.[17] These findings suggest that acute elevation of plasma glucose (acute-HG), but not constant high glucose concentration, deteriorates myocardial damage and outcomes after AMI.

In this study, we showed that acute-HG was associated with large infarct size and high in-hospital mortality in both patients with chronic-HG and those without. In patients without acute-HG, peak creatine kinase was small and mortality was low, regardless of the presence or absence of chronic-HG. Interestingly, chronic-HG was associated with small peak creatine kinase and low mortality in patients with acute-HG. There are several possible mechanisms that may explain this paradoxical finding. The magnitude of acute glucose elevation may become small in patients with chronic-HG because baseline glucose level should be high in these patients. Experimental studies have suggested that diabetic heart is paradoxically more resistant to ischemic insults. Decreased activity of sodium proton exchanger in diabetic myocardium may prevent reperfusion injury.[18] Also, decreased glucose utilization observed in diabetic cells may be beneficial in a circumstance of high plasma glucose.

Results of previous studies that have investigated whether continuous insulin infusion to normalize the glucose level will improve the outcome of patients with AMI are inconsistent.[19,20] Most of these studies consisted of patients with diabetes and/or acute-HG. Because impact of acute-HG is more pronounced in patients without chronic-HG, glucose control to correct acute-HG may be more beneficial for patients without chronic-HG or diabetes. Further studies should be warranted into the appropriate management in patients with AMI and acute-HG in the contemporary intervention era.

This study has the limitations of all retrospective investigations. However, this study consisted of consecutive patients with AMI who received contemporary management, including primary coronary intervention in 87% of patients. A small sample size is another limitation of this study. Because of the nature of observational study, the cause-effect relation between plasma glucose and outcomes and impact of acute management of plasma glucose on outcomes were not investigated.

Acknowledgment: We appreciate the assistance of our secretaries, Hiromi Maeda and Chieko Nagasawa.

Disclosures

The authors have no conflicts of interest to disclose.

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