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Association of Admission Glycaemia With High Grade Atrioventricular Block in ST-Segment Elevation Myocardial Infarction Undergoing Reperfusion Therapy

An Observational Study

Bi Huang, MD, Xinjie Wang, MD, Yanmin Yang, MD, PhD, Jun Zhu, MD, Yan Liang, MD, PhD, Huiqiong Tan, MD, Litian Yu, MD, PhD, Xin Gao, MD, PhD, Han Zhang, MD, and Juan Wang, MD

Abstract: Several studies have demonstrated the association between elevated admission glycaemia (AG) and the occurrence of some arrhythmias such as atrial fibrillation, ventricular tachycardia, and ventricular fibrillation after myocardial infarction. However, the impact of elevated AG on the high grade atrioventricular block (AVB) occurrence after ST-segment elevation myocardial infarction (STEMI) remains unclear.

Included were 3359 consecutive patients with STEMI who received reperfusion therapy. The primary endpoint was the development of high grade AVB during hospital course. Patients were divided into non-diabetes mellitus (DM), newly diagnosed DM, and previously known DM according to the hemoglobin A1c level. The optimal AG value was determined by receiver operating characteristic curves analysis with AG predicting the high grade AVB occurrence.

The best cut-off value of AG for predicting the high grade AVB occurrence was 10.05 mmol/L by ROC curve analysis. The prevalence of AG $\geq$ 10.05 mmol/L in non-DM, newly diagnosed DM, and previously known DM was 15.7%, 34.1%, and 68.5%, respectively. The incidence of high grade AVB was significantly higher in patients with AG $\geq$ 10.05 mmol/L than $<$10.05 mmol/L in non-DM (5.7% vs. 2.1%, $P < 0.001$) and in newly diagnosed DM (10.2% vs.1.4%, $P < 0.001$), but was comparable in previously known DM (3.6% vs. 0.0%, $P = 0.062$). After multivariate adjustment, AG $\geq$ 10.05 mmol/L was independently associated with increased risk of high grade AVB occurrence in non-DM (HR = 1.826, 95% CI 1.073–3.107, $P = 0.027$) and in newly diagnosed DM (HR = 5.252, 95% CI 1.890–14.597, $P = 0.001$). Moreover, both AG $\geq$ 10.05 mmol/L and high grade AVB were independent risk factors of 30-day all cause-mortality (HR = 1.362, 95% CI 1.006–1.844, $P = 0.046$ and HR = 2.122, 95% CI 1.154–3.903, $P = 0.015$, respectively).

Our study suggested that elevated AG level ($\geq$10.05 mmol/L) might be an indicator of increased risk of high grade AVB occurrence in patients with STEMI.

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Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, AG = admission glycaemia, ARB = angiotensin-receptor blockade, AVB = atrioventricular block, CCB = calcium channel blockers, CK-MB = creatine kinase-MB, DM = diabetes mellitus, FFA = free fat acid, HbA1c = hemoglobin A1c, MI = myocardial infarction, PCI = percutaneous coronary intervention, ROC = operating characteristic, SBP = systolic blood pressure, STEMI = ST-segment elevation myocardial infarction, TnI = troponin I.

INTRODUCTION

High grade atrioventricular block (AVB) is a common complication in patients with ST-segment elevation myocardial infarction (STEMI)[1] and the incidence is reported to be 2.0–6.9%,[2–6] and in the setting of inferior myocardial infarction (MI), as high as 19–22.5%.[7–9] Although reperfusion therapy reduced the incidence of high grade AVB in recent decades,[2,3] high grade AVB remains an important risk factor of poor short-term outcomes.[2–4,10–12] Therefore, identification of patients at high risk for high grade AVB is of great importance for risk stratification and appropriated treatment.

Elevated admission glycaemia (AG), also known as stress hyperglycaemia, is a common phenomenon after MI, which independently predicts poor outcome in patients with MI.[13–17] In recent years, several studies have shown that elevated AG after MI was associated with increased risk of occurrence of some arrhythmias, such as atrial fibrillation (AF),[18] ventricular tachycardia (VT), and ventricular fibrillation (VF).[19–23] However, the association between AG levels and the occurrence of high grade AVB after STEMI has not been well understood. Moreover, some studies also suggested that the AG levels may have different impact on the occurrence of these arrhythmias between diabetic and nondiabetic patients.[19,22] Therefore, the present study aims to evaluate the association of AG levels with the occurrence of high grade AVB in STEMI patients with and without diabetes mellitus (DM) undergoing reperfusion therapy.

MEHTODS

Study Population

This is a retrospective study of consecutive patients presented with acute STEMI within 12 hours from symptoms onset undergoing reperfusion therapy from 2001 to 2004 in 247

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From the State Key Laboratory of Cardiovascular Disease, Emergency and Critical Care Center, National Center for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China (BH, XW, YY, JZ, YL, HT, LY, XG, HZ, JW).
Correspondence: Yanmin Yang, Emergency and Critical Care Center, Fuwai Hospital No. 167, Beilishi Road, Xicheng District, Beijing 100037, People's Republic of China (e-mail: yangymfuwai@163.com).
B.H. and X.W. contributed equally to this work.
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hospitals in China. Although it is a retrospective study, data were collected prospectively and recorded. STEMI was defined according to the Definition of Myocardial Infarction[24] as chest pain or equivalent symptoms in combination with electrocardiographic changes consistent with STEMI (new or presumed new ST segment elevation at the J point in 2 or more contiguous leads with the cut-off points $\geq$0.2 mV in leads V1, V2, or V3 and $\geq$0.1 mV in other leads), and increased serum biochemical markers of cardiac necrosis, including creatine kinase-MB (CK-MB) and troponin I (TnI).

Study Protocol

Study protocols were approved by the ethical committees of Fuwai hospital and complied with the declaration of Helsinki. All subjects were provided with written informed consent.

On admission, baseline data such as sex, age, weight, and histories of cardiovascular including MI, stroke, hypertension, DM, and heart failure were obtained. Admission vital signs, location of MI, and Killip class were also recorded. Venous blood was drawn from patients to measure the AG, potassium, hemoglobin, and other biochemical markers. For measurement of hemoglobin A1c (HbA1c), admission whole-blood samples were frozen at the original hospital and transported to the single-site laboratory (Fuwai Hospital, Beijing, China), where HbA1c level was assayed by an automated, high-performance liquid chromatography analyzer (Bio-Rad Variant Analyzer; GMI Inc, Ramsey, MN).

After admission to hospital, patients were given electrocardiographic monitoring continuously and received medication treatment including antiplatelet, anticoagulation, statins, beta blocker, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-receptor blockade (ARB), nitrates, and calcium channel blockers (CCB) as far as possible to follow the guidelines recommended for the management of STEMI. Those who were appropriate for reperfusion therapy were treated with thrombolysis or percutaneous coronary intervention (PCI) according to the clinical circumstances.

Study Endpoints and Definitions

The main outcome measure was occurrence of high grade AVB including advanced II°AVB and complete AVB. Advanced II°AVB was defined as incomplete AVB with a 2:1 or greater degree of block. Complete AVB was defined as periods of complete atrioventricular dissociation with atrial rates faster than ventricular rate. Identification of high grade AVB was performed by means of electrocardiogram (ECG), Holter document, and electrocardiographic monitoring that was recorded in the medical records.

The secondary outcomes included 30-day all-cause mortality, reinfarction, cardiogenic shock, stroke, heart failure, bleeding, and recurrent myocardial ischemia. The definitions of these events were as follows: all-cause mortality was defined as death from any cause within 30 days after admission. Reinfarction was defined as the recurrence of ischemic chest pain with new ischemic electrocardiographic alterations (ST reelevation or depression, or new Q waves) and an abnormal reelevation in enzyme levels (to twice the upper limit of normal range if it had returned to baseline or if already elevated, with a further elevation by 50%). Cardiogenic shock was defined as systolic blood pressure of persistently less than 90 mm Hg that did not respond to fluid titration and required an intra-aortic balloon pump (IABP) or intravenous inotropic therapy. Stroke was defined as focal neurologic signs thought to be of vascular origin that persisted for more than 24 hours, confirmed by computed tomographic scans or magnetic resonance imaging. Heart failure was defined as left ventricular ejection fraction (LVEF) $\leq$40% and NYHA class II, III, or IV evaluated by echocardiography and cardiologist, respectively. Bleeding included major bleeding and minor bleeding. Major bleeding was defined as the occurrence of any of the following: intracranial bleeding, bleeding leading to surgical intervention, or overt bleeding associated with a fall in hemoglobin level $\geq$2 g/dL or leading to a transfusion $\geq$2 units of blood, fatal bleeding. Minor bleeding was defined as clinically overt bleeding that was not major. Recurrent myocardial ischemia was defined as ischemic chest pain with new electrocardiographic changes, but the enzymic change did not reach the criterion of reinfarction.

Definition of DM and Hyperglycemia

DM was defined as follows: prior history of DM obtained from hospital records, or receiving oral hypoglycemic drugs or insulin therapy or HbA1c$\geq$6.5% according to the American Diabetes Association (ADA) criteria.[25] Patients were divided into 3 groups according to the diabetes status. Non-DM was defined as without history of DM and HbA1c $<$ 6.5%; newly diagnosed DM was defined as without known DM but HbA1c$\geq$6.5%; previously diagnosed DM was defined as with a history of DM. Because the hyperglycemia cut-off values are poorly defined, the proposed AG threshold in our study was based on optimizing the sum of sensitivity and specificity by receiver operating characteristic (ROC) curves analysis, which predicted the occurrence of high grade AVB.

Statistical Analysis

Continuous variables were presented with mean $\pm$ standstandard deviation or median with interquartile range according to the distribution characteristics and compared by Student *t* test if the data were normal distribution; otherwise, Wilcoxon signed rank test was used. Categorical variables were presented as percentage and were compared by Pearson χ^2 test. The optimal AG value threshold was determined by ROC curve. Cumulative incidence curves were performed by the Kaplan–Meier method. Log rank tests were used to compare the curves of groups. Multivariate Cox proportional hazard regression models were performed to identify the association of AG and high grade AVB with the 30-day all-cause mortality and the models were adjusted for age, sex, weight, medical histories, onset-to-admission interval, admission vital signs, location of MI, and clinical management. Multivariate Cox proportional hazard regression models were also used to analyze the association of AG with the occurrence of high grade AVB. The adjusted hazard ratios (HRs) with their respective 95% confidence intervals (CIs) for each group were calculated. All statistical tests were 2-tailed, and *P* values were statistically significant at $<$0.05. All statistical analyses were carried out using the SPSS statistical software, version 19.0 (SPSS Inc, Chicago, IL).

RESULTS

A total of 3359 consecutive patients with STEMI undergoing reperfusion treatment were analyzed, of which 2445 patients were nondiabetic, 549 patients were newly diagnosed DM, and 365 patients were previously known DM according to the ADA criteria. The best cut-off value of AG for predicting the high grade AVB occurrence was 10.05 mmol/L by ROC curve

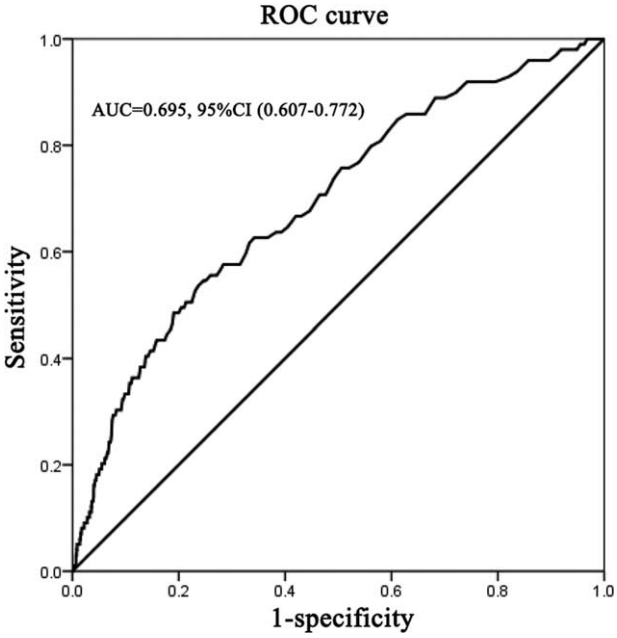

FIGURE 1. The receiver operation characteristic curve with admission glycaemia predicting high grade AVB occurrence. AG = admission glycaemia; AUC = area under curve; ROC = receiver operating characteristic.

analysis, and the sensitivity and specificity were 50.5% and 76.4%, respectively (area under curve [AUC] = 0.695; 95% CI 0.607–0.772, Figure 1).

Baseline Characteristics

Table 1 shows the clinical characteristics in patients with AG≥10.05 mmol/L and <10.05 mmol/L according to the diabetes status. In nondiabetic patients, 15.7% (383/2445) presented with AG≥10.05 mmol/L and they tended to be older, female, and presented with lower admission blood pressure, and worse Killip class (all $P < 0.001$). In newly diagnosed DM, 34.1% (187/549) of patients had AG≥10.05 mmol/L and they were more likely to be female and had higher percentage of worse Killip class, but had less history of MI compared with those with AG < 10.05 mmol/L (all $P < 0.05$). In contrast, more patients with previously known DM (68.5%) presented with AG≥10.05 mmol/L; however, demographic characteristics, medical histories, and admission variables were comparable between patients with AG≥10.05 mmol/L and < 10.05 mmol/L (all $P > 0.05$).

After admission to hospital, reperfusion strategies, antiplatelet therapy, and statins use were comparable between nondiabetic patients with AG≥10.05 mmol/L and <10.05 mmol/L, whereas patients with AG≥10.05 mmol/L were more likely to use diuretics and insulin, but use less beta blocker and nitrates (all $P < 0.05$). In contrast, newly diagnosed diabetic patients with AG≥10.05 mmol/L were more likely to receive PCI and tended to use clopidogrel, statins, diuretics, and insulin compared with those with AG < 10.05 mmol/L (all $P < 0.05$). In previously diagnosed diabetic patients, except for a higher percentage of insulin use and less nitrates use in patients with AG≥10.05 mmol/L, most management was similar between patients with AG≥10.05 mmol/L and <10.5 mmol/L.

Occurrence of High Grade AVB and AG Level

During hospital course, 99 patients (2.9%) experienced high grade AVB, of which 82 (82.8%) occurred within 48 hours after admission to hospital and 14 patients received temporary pacemaker treatment. Figure 2 displays the incidence of high grade AVB according to the AG levels and diabetes status. It was shown in nondiabetic patients, incidence of high grade AVB in patients with AG≥10.05 mmol/L was significantly higher than <10.05 mmol/L (5.7% vs. 2.1%, $P < 0.001$). Similar trend was found in newly diagnosed diabetic patients (10.2% in AG≥10.05 mmol/L and 1.4% in <10.05 mmol/L, $P < 0.001$). Noteworthily, in previously known diabetic patients, all high grade AVB occurred in patients with AG≥10.05 mmol/L although it did not reach statistically difference between in AG≥10.05 mmol/L and <10.05 mmol/L ($P = 0.062$).

Main Cardiovascular Events and Occurrence of High Grade AVB

Table 2 shows the 30-day main cardiovascular events in patients with and without high grade AVB stratified by diabetes status. In nondiabetic patients, those who experienced high grade AVB had significantly higher 30-day all-cause mortality (18.2% vs. 8.1%, $P = 0.010$) and cardiogenic shock (30.0% vs. 5.0%, $P < 0.001$) than those without high grade AVB. Similar findings were found in newly diagnosed diabetic patients. Moreover, the incidence of stroke in patients experienced high grade AVB was higher than in patients without high grade AVB (12.5% vs. 0.4%, $P = 0.001$). In contrast, in previously known diabetic patients, 30-day all-cause mortality was comparable between patients with and without high grade AVB (11.1% vs. 10.4%, $P = 1.000$); however, the incidence of cardiogenic shock in patients with high grade AVB was significantly higher than in those without high grade AVB (44.4% vs. 3.9%, $P < 0.001$).

Association of AG Level with the Occurrence of High Grade AVB

Figure 3 shows the cumulative incidence of high grade AVB according to the AG level and diabetes status. Compared with those with AG < 10.05 mmol/L, patients with AG≥10.05 mmol/L had significantly higher cumulative incidence of high grade AVB, regardless of the diabetes status (Log rank $P < 0.001$ for non-DM and newly diagnosed DM, and Log rank $P = 0.046$ for previously known DM).

Table 3 shows the independent risk factors associated with the occurrence of high grade AVB in nondiabetic and newly diagnosed diabetic patients. In nondiabetic patients, after multivariate adjustment, AG≥10.05 mmol/L was associated with 1.8-fold increased risk of development of high grade AVB compared with those with AG < 10.05 mmol/L (HR = 1.826, 95% CI 1.073–3.107, $P = 0.027$). Other independent risk factors associated with the occurrence of high grade AVB included inferior MI and diuretics use, while higher admission SBP and heart rate were protectors. In newly diagnosed diabetic patients, AG≥10.05 mmol/L was associated with 5.2-fold increased risk of development of high grade AVB compared with those with AG < 10.05 mmol/L (HR = 5.252, 95% CI 1.890–14.597, $P = 0.001$). Diuretics use and higher admission heart rate were independent risk factors and protector, respectively. In previously known diabetic patients, due to all high grade AVB occurred in those with AG≥10.05 mmol/L, the analysis of relative risk of high grade AVB between AG≥10.05 mmol/L and <10.05 mmol/L was unavailable. The independent factors

TABLE 1. Baseline Characteristics and Treatment in Patients According to Admission Glycaemia Level (mmol/L) and Diabetes Status

	Non-DM (n = 2445)			Newly Diagnosed DM (n = 549)			Previously known DM (n = 365)		
	AG≥10.05 (n = 383)	AG < 10.05 (n = 2062)	*P* Value	AG≥10.05 (n = 187)	AG < 10.05 (n = 362)	*P* Value	AG≥10.05 (n = 250)	AG < 10.05 (n = 115)	*P* value
Age, yrs	62.8 ± 11.4	60.0 ± 11.5	<0.001	61.1 ± 11.8	60.3 ± 11.3	0.453	63.0 ± 10.1	63.6 ± 9.8	0.577
Male (n, %)	263 (68.7)	1612 (78.2)	<0.001	122 (65.2)	276 (76.2)	0.009	148 (59.2)	74 (64.3)	0.359
Weight, kg	66.3 ± 12.5	67.9 ± 11.4	0.018	69.2 ± 12.8	68.6 ± 11.2	0.604	68.3 ± 11.0	67.7 ± 11.0	0.619
History of MI (n, %)	26 (6.8)	128 (6.2)	0.648	5 (2.7)	28 (7.7)	0.022	22 (8.8)	15 (13.0)	0.262
History of hypertension (n, %)	138 (36.0)	771 (37.4)	0.645	77 (41.2)	125 (34.5)	0.136	119 (47.6)	59 (51.3)	0.573
History of heart failure (n, %)	9 (2.3)	23 (1.1)	0.080	3 (1.6)	4 (1.1)	0.695	10 (4.0)	2 (1.7)	0.353
History of stroke (n, %)	39 (10.2)	152 (7.4)	0.062	16 (8.6)	26 (7.2)	0.612	28 (11.2)	14 (12.2)	0.860
Onset-to-admission interval, hr	4.2 (3.0–6.3)	4.5 (3.0–7.1)	0.043	4.7 (2.8–6.9)	4.4 (3.0–7.0)	0.789	5.2 (3.0–8.0)	4.5 (3.0–7.3)	0.122
SBP, mm Hg	118.7 ± 32.6	124.9 ± 24.2	<0.001	123.6 ± 29.7	126.3 ± 23.3	0.242	125.7 ± 24.8	129.6 ± 25.0	0.161
DBP, mm Hg	74.5 ± 22.1	78.8 ± 15.7	<0.001	77.8 ± 19.3	78.4 ± 14.1	0.721	78.1 ± 14.8	80.1 ± 15.1	0.224
Heart rate, bpm	75.0 (60.0–86.0)	74.0 (64.0–84.0)	0.165	76.0 (62.0–90.0)	75.0 (62.0–84.0)	0.291	80.0 (68.0–92.0)	75.0 (65.0–88.0)	0.055
Killip class (n, %)			<0.001			0.002			0.219
I	285 (74.4)	1801 (87.3)		148 (79.1)	321 (88.7)		196 (78.4)	99 (86.1)	
II	59 (15.4)	208 (10.1)		30 (16.0)	34 (9.4)		37 (14.8)	13 (11.3)	
III	12 (3.1)	19 (0.9)		0 (0.0)	3 (0.8)		11 (4.4)	1 (0.9)	
IV	27 (7.0)	34 (1.6)		9 (4.8)	4 (1.1)		6 (2.4)	2 (1.7)	
Location of MI [n (%)]			0.418			0.076			0.147
Anterior MI	190 (49.6)	1071 (51.9)		82 (43.9)	188 (51.9)		133 (53.2)	62 (53.9)	
Inferior MI	187 (48.8)	944 (45.8)		103 (55.1)	165 (45.6)		114 (45.6)	48 (41.7)	
Serum potassium, mmol/L	3.9 ± 0.7	3.9 ± 0.6	0.568	4.0 ± 0.7	4.0 ± 0.6	0.331	4.1 ± 0.6	4.1 ± 0.6	0.770
AG, mmol/L	13.7 ± 4.7	6.8 ± 1.5	<0.001	15.8 ± 4.9	6.9 ± 1.5	<0.001	15.8 ± 4.7	8.0 ± 1.4	<0.001
Hemoglobin, g/L	135.3 ± 20.2	138.0 ± 18.3	0.009	139.6 ± 18.0	138.5 ± 17.9	0.520	132.7 ± 17.2	132.4 ± 17.0	0.886
Treatment [n (%)]									
Thrombolysis	314 (82.0)	1663 (80.6)	0.572	135 (72.2)	305 (84.3)	0.001	172 (68.8)	80 (69.6)	0.904
PCI	69 (18.0)	399 (19.4)	0.572	52 (27.8)	57 (15.7)	0.001	80 (32.0)	35 (30.4)	0.809
Heparin	339 (88.5)	1741 (84.4)	0.252	156 (83.4)	305 (84.3)	0.326	203 (81.2)	86 (74.8)	0.174
Aspirin	374 (97.7)	2009 (97.4)	1.000	183 (97.9)	349 (96.4)	0.442	246 (98.4)	111 (96.5)	0.267
Clopidogrel	133 (34.7)	742 (36.0)	0.685	78 (41.7)	114 (31.5)	0.018	117 (46.8)	52 (45.2)	0.822
Beta blocker	228 (59.5)	1362 (66.1)	0.017	118 (63.1)	209 (57.7)	0.234	165 (66.0)	77 (67.0)	0.905
ACEI (or ARB)	270 (70.5)	1500 (72.7)	0.384	144 (77.0)	267 (73.8)	0.468	191 (76.4)	88 (76.5)	1.000
Statins	284 (74.2)	1587 (77.0)	0.238	158 (84.5)	270 (74.6)	0.009	202 (80.8)	98 (85.2)	0.377
Nitrates	333 (86.9)	1899 (92.1)	0.002	173 (92.5)	342 (94.5)	0.358	216 (86.4)	108 (93.9)	0.048
CCB	33 (8.6)	189 (9.2)	0.772	16 (8.6)	44 (12.2)	0.248	37 (14.8)	22 (19.1)	0.358
Diuretics	98 (25.6)	394 (19.1)	0.004	56 (29.9)	79 (21.8)	0.047	78 (31.2)	32 (27.8)	0.541
Insulin	65 (17.0)	185 (9.0)	<0.001	58 (31.0)	35 (9.7)	<0.001	121 (48.4)	33 (28.7)	<0.001

ACEI = angiotensin-converting enzyme inhibitors; AG = admission glycaemia; ARB = angiotensin receptors blockers; CCB = calcium channel blocker; DBP = diastolic blood pressure; DM = diabetes mellitus; MI = myocardial infarction; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.

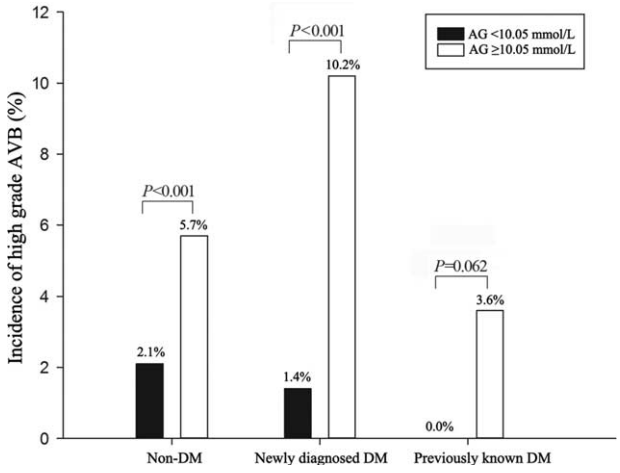

FIGURE 2. Incidence of high grade atrioventricular block in patients according to admission glycaemia level and diabetes status. AG = admission glycaemia; AVB = atrioventricular block; DM = diabetes mellitus.

associated with the high grade AVB occurrence included admission heart rate and higher admission Killip class.

AG Level, High Grade AVB, and 30-Day All-Cause Mortality

Table 4 shows the independent factors associated with 30-day all-cause mortality by multivariate Cox analysis. After multivariate adjustment, patients who experienced high grade AVB during hospital course have 2.1-fold increased risk of 30-day all-cause mortality compared with those without high grade AVB (HR = 2.122, 95% CI 1.154–3.903, $P = 0.015$). Meanwhile, AG≥10.05 mmol/L was also an independent risk factor and was associated with 1.3-fold increased risk of 30-day all-cause mortality compared with that of AG < 10.05 mmol/L (HR = 1.362, 95% CI 1.006–1.844, $P = 0.046$). Other independent factors related to 30-day all-cause mortality are displayed in Table 4.

DISCUSSION

The main findings of the present study are as follows. First, about one quarter of STEMI patients presented with hyperglycemia with AG≥10.05 mmol/L and hyperglycemia existed in nearly half of diabetic patients and in one-sixth of nondiabetic patients. Second, patients with AG≥10.05 mmol/L had higher incidence of high grade AVB than in patients with AG < 10.05 mmol/L, regardless of the diabetes status. After adjusting for confounders, AG≥10.05 mmol/L was still an independent risk factor for development of high grade AVB in nondiabetic and newly diagnosed diabetic patients. Third, both AG≥10.05 mmol/L and occurrence of high grade AVB were independent risk factors associated with 30-day all-cause mortality after multivariate adjustment. To the best of our knowledge, this was the first article that highlighted the importance of AG level for high grade AVB occurrence in diabetic and nondiabetic patients with STEMI undergoing reperfusion therapy.

Elevated AG is a common phenomenon during the early phase after MI, even in the absence of a history of DM. As a pathologic stress, a series of neurohumor reactions are aroused after MI, of which sympathetic nerve is overactivated. On the one hand, increased sympatho-adrenergic activation and

TABLE 2. The 30-Day Cardiovascular Events in Patients With and Without High Grade Atrioventricular Block

	Non-DM (n = 2445)			Newly Diagnosed DM (n = 549)			Previously Known DM (n = 365)		
Events (n, %)	High Grade AVB (n = 66)	No High Grade AVB (n = 2,379)	*P* Value	High Grade AVB (n = 24)	No High Grade AVB (n = 525)	*P* Value	High Grade AVB (n = 9)	No High Grade AVB (n = 356)	*P* value
All-cause mortality	12 (18.2)	193 (8.1)	0.010	7 (29.2)	31 (5.9)	0.001	1 (11.1)	37 (10.4)	1.000
Reinfarction	3 (4.5)	40 (1.7)	0.108	0 (0.0)	14 (2.7)	1.000	1 (11.1)	5 (1.4)	0.140
Cardiogenic shock	20 (30.0)	120 (5.0)	<0.001	7 (29.2)	27 (5.1)	<0.001	4 (44.4)	14 (3.9)	<0.001
Stroke	1 (1.5)	22 (0.9)	0.469	3 (12.5)	2 (0.4)	0.001	0 (0.0)	4 (1.1)	1.000
Recurrent ischemia	7 (10.6)	183 (7.7)	0.351	5 (20.8)	47 (9.0)	0.066	1 (11.1)	39 (11.0)	1.000
Bleeding	6 (9.1)	123 (5.2)	0.158	2 (8.3)	24 (4.6)	0.316	0 (0.0)	13 (3.7)	1.000
Revascularization	4 (6.1)	125 (5.3)	0.777	0 (0.0)	25 (4.8)	0.618	0 (0.0)	27 (7.6)	1.000

AVB = atrioventricular block; DM = diabetes mellitus.

TABLE 3. Independent Predictors of High Grade Atrioventricular Block in Nondiabetic and Diabetic Patients by Multivariate Cox Analysis

	HRs	95% CI	*P* Value
Non-DM			
AG≥10.05 mmol/L	1.826	1.073–3.107	0.027
Inferior MI (vs. anterior MI)	11.844	3.663–38.293	<0.001
Admission SBP	0.985	0.977–0.993	<0.001
Admission heart rate	0.945	0.926–0.964	<0.001
Diuretics	2.471	1.482–4.121	0.001
Newly diagnosed DM			
AG≥10.05 mmol/L	5.252	1.890–14.597	0.001
Admission heart rate	0.934	0.909–0.960	<0.001
Diuretics	4.556	1.856–11.186	0.001
Previously known DM			
Admission heart rate	0.901	0.855–0.949	<0.001
Killip class (>I)	5.777	1.252–26.668	0.025

AG = admission glycaemia; AVB = atrioventricular block; CI = confidence interval; DM = diabetes mellitus; HRs = hazard ratios; MI = myocardial infarction; SBP = systolic blood pressure.

dysregulation of the adrenergic receptors, such as beta-adrenergic receptors modulated by G protein-coupled receptor kinases (GRKs),[26] may contribute to the development of some complications such as heart failure and arrhythmias;[27,28] on the other hand, the sympatho-adrenergic system is an important regulator of glucose homeostasis and insulin release through the beat-adrenergic receptors. The dysregulated expression of beat-adrenergic receptors and the abnormal activation of GRKs after MI may cause impaired glucose tolerance.[29,30] Meanwhile, stress-induced activation of cortisol and noradrenalin, growth hormone, and glucagon release may affect glucose homeostasis and insulin secretion, resulting in insulin insufficiency and acute hyperglycaemia.[31] The proportion of patients presented with elevated AG ranged from 3% to 71% in nondiabetic patients and from 46% to 84% in diabetic patients depending on the threshold AG levels used to define elevated AG (ranging from 6.7 to 11.0 mmol/L).[13,20,32] Due to the lack of consensus on the appropriate definition of acute hyperglycemia for patients with MI, in our study, the optimal cut-off value of AG determined by ROC curve was 10.05 mmol/L, which is similar to the cut-off value adopted by some studies (10 mmol/L)[33–35] and also approaches the value that current guidelines recommend (<10 mmol/L) in patients with STEMI.[1] In our study, nearly half of diabetic and one-sixth of nondiabetic patients presented with elevated AG, consistent with previous reports. Although some studies found that the elevated AG levels and diabetic status, independent of chronic glycaemic control, were not associated with increased risk of some cardiovascular events such as periprocedural MI undergoing PCI,[36] numerous studies have demonstrated that elevated AG was associated with significant increase in the short- and long-term mortality after MI.[13–17] In accordance with these results, our study also confirmed that elevated AG was an independent risk factor of 30-day mortality.

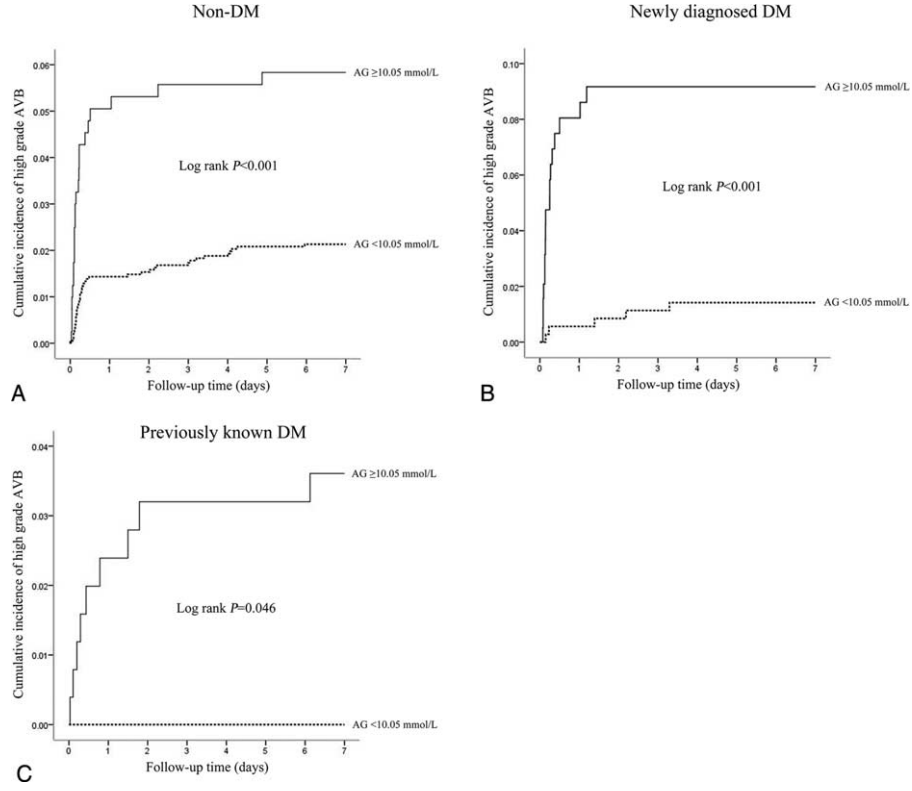

FIGURE 3. Cumulative incidence curves of high grade atrioventricular block according to AG level and diabetes status. A, Cumulative incidence curves of high grade AVB in non-DM; B, Cumulative incidence curves of high grade AVB in newly diagnosed DM; C, Cumulative incidence curves of high grade AVB in previously known DM. AG = admission glycaemia; AVB = atrioventricular block; DM = diabetes mellitus.

TABLE 4. Predictors of 30-Day All Cause Mortality by Multivariate Cox Analysis

Variables	HRs	95% CI	*P* Value
Age	1.035	1.020–1.051	<0.001
Female (vs. male)	1.912	1.413–2.588	<0.001
History of MI	1.907	1.200–3.030	0.006
Anterior MI (vs. inferior MI)	2.049	1.472–2.852	<0.001
Admission heart rate	1.015	1.009–1.022	<0.001
Killip class IV (vs. class I)	2.598	1.658–4.070	<0.001
Clopidogrel	0.561	0.385–0.818	0.003
Beta blocker	0.530	0.383–0.733	<0.001
ACEI (or ARB)	0.347	0.253–0.478	<0.001
Stains	0.532	0.388–0.730	<0.001
Diuretics	1.722	1.255–2.363	0.001
Occurrence of high grade AVB	2.122	1.154–3.903	0.015
AG≥10.05 mmol/L	1.362	1.006–1.844	0.046

ACEI = angiotensin-converting enzyme inhibitors; AG = admission glycaemia; ARB = angiotensin receptors blockers; AVB = atrioventricular block; CI = confidence interval; HRs = hazard ratios; MI = myocardial infarction.

In recent years, several studies focused on the relationship between elevated AG and arrhythmia occurrence in patients with MI and found admission hyperglycemia was associated with increased risk of AF[18], VT, and VF.[19–23] Some previous studies have mentioned the high grade AVB occurrence in patients with elevated AG levels after MI, such as in Gardner et al's [37] and Blasco et al's [38] studies; however, due to a limited sample size or not specifically designed to analyze the association between AG levels and high grade AVB occurrence, they did not reach a reliable conclusion regarding the impact of AG levels on the development of high grade AVB after MI. Our study demonstrated that elevated AG was independently associated with increased risk of high grade AVB occurrence after STEMI in both nondiabetic and newly diagnosed diabetic patients. Although the incidence of high grade AVB was not statistically different between patients with and without elevated AG in previously known diabetic patients ($P = 0.062$), all high grade AVB events occurred in patients with AG≥10.05 mmol/L. A limited sample size of DM and a relatively low incidence of high grade AVB in our study may affect the statistical power and more studies are needed to clarify the effect of elevated AG on the high grade AVB occurrence after MI in previously known DM.

Previous studies have reported some risk factors with high grade AVB occurrence after MI, such as older age, female sex, inferior MI, prior MI, hypertension, worse Killip class, and diabetes.[2–4] Our study found some factors that were different from previous findings associated with the development of high grade AVB after STEMI and some of these factors were identical between non-DM and newly diagnosed DM, such as elevated AG≥10.05 mmol/L, admission heart rate, and diuretics use. Higher admission heart rate may reflect relatively normal conduction of electrical activity and is therefore unlikely to develop AVB. Diuretics use may cause severe electrolyte disturbances which increase the risk of high grade AVB occurrence. Interestingly, inferior MI was not an independent risk factor for high grade AVB in both newly diagnosed DM and previously known DM. We inferred that autonomic neuropathy resulting from chronic hyperglycemia may affect cardiac conduction, which may alter the correlation between location of MI and cardiac conduction abnormalities. Moreover, studies have shown presence of DM was independently associated with increased risk of AVB in the setting of MI and non-MI.[2,4,39] Combining these results, more attention should be paid to diabetes and nondiabetes with AG≥10.05 mmol/L after STEMI because they are at high risk of high grade AVB occurrence.

The mechanism by which elevated AG is associated with increased risk of high grade AVB occurrence in patients with MI is not fully clear. Previous studies have demonstrated that, at the electrophysiological level, acute hyperglycemia produces significant increments of Q-Tc and Q-Tc dispersion,[40] which is an important risk factor of electrical instability, leading to malignant arrhythmias such as VT and VF. Furthermore, in the setting of MI, excessive accumulation of FFA may increase the severity of ischaemic damage and possibly be arrhythmogenic.[41] Moreover, a series of metabolic change associated with acute hyperglycaemia, such as insulin resistance, inflammation, cellular stress,[42] and extracellular osmotic pressure alteration may affect the cardiac excitability and conduction, resulting in conduction block. Given the complicated mechanism involved in the development of high grade AVB, more studies are needed to investigate the effect of hyperglycemia on the cardiac conduction system especially in the setting of MI.

The clinical implication of the findings from our study should also be mentioned. Given the most of high grade AVB events occurred within 48 hours after admission to hospital, admission AG level might be a convenient bedside marker for assessing the risk of high grade AVB occurrence in STEMI patients, especially in nondiabetic and newly diagnosed diabetic patients. However, whether control glucose by insulin therapy can reduce the incidence of high grade AVB and the optimal glucose level for minimizing the event deserve further study.

There are some limitations in our study. First, the AG level was affected by multifactors such as the interval between the last meal and admission to hospital, and therefore, continuous monitoring of glucose level may be more valuable than single glucose measurement. Second, the cut-off value for hyperglycemia determined by the ROC curve in our study was based on AG values of the whole patients but not analyzed separately according to diabetes status. The cut-off value for hyperglycemia may not be the same for patients with and without DM because these patients are very different in terms of glycoregulation and recent comments pointed out that a single cut-off value for hyperglycemia may decrease the predictive accuracy of admission hyperglycemia.[43] Third, the portion of patients who were given temporary pacemaker treatment was relatively low, which may adversely influence the outcome. Fourth, the data reflecting the MI size and cardiac function such as the CK-MB and TnI levels as well as LVEF that are of prognostic significance are unavailable. In addition, the duration of DM and detailed treatment in previously known diabetes before study enrolment and in those with elevated AG after hospitalization was inadequate. Finally, the sample size of diabetes was relatively small and the incidence of high grade AVB was relatively low, which may limit the statistical power. Therefore, more studies with big sample size are needed to confirm our results.

In conclusion, our study suggested elevated AG level (≥10.05 mmol/L) might be an indicator of increased risk of high grade AVB occurrence in patients with STEMI.

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