Glycaemic variability is associated with adverse cardiovascular outcomes in patients hospitalised with an acute myocardial infarction

Thora Y. Chai[a,b,*], Mark McLean[a,c,d], Vincent W. Wong[e], N. Wah Cheung[a,b]

[a] Department of Diabetes and Endocrinology, Westmead Hospital, Westmead, NSW, Australia
[b] Sydney Medical School, The University of Sydney, Sydney, NSW, Australia
[c] Department of Diabetes and Endocrinology, Blacktown Hospital, Blacktown, NSW, Australia
[d] School of Medicine, University of Western Sydney, Campbelltown, NSW, Australia
[e] Department of Diabetes and Endocrinology, Liverpool Hospital, Liverpool, NSW, Australia

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ABSTRACT

Unlike admission hyperglycaemia, there is significant controversy surrounding whether acute glycaemic variability is associated with major adverse cardiovascular events (MACE) in patients immediately after an acute myocardial infarction (AMI). We conducted a retrospective post-hoc analysis in an AMI population and determined fluctuating glycaemia is associated with a higher risk of 3–month MACE.

Introduction

Glycaemic variability, defined as fluctuations in the measurement of blood glucose levels (BGLs) over a given interval of time, has been associated with increased mortality, length of stay and infections in hospitalised patients with or without diabetes [1–3]. Whether glycaemic variability is an important predictor of adverse cardiovascular outcomes following acute myocardial infarction (AMI) remains controversial, with previous studies demonstrating conflicting results [4–9]. Glycaemic variability can deleteriously affect endothelial function and oxidative stress than constant hyperglycaemia, possibly impacting on the prognosis of patients during and after an AMI [10–12].

We hypothesise that in an AMI population, an increased risk of major adverse cardiovascular events (MACE) is associated with glycaemic variability, measured as mean amplitude of glucose excursion (MAGE) and standard deviation of glucose (SD). MAGE is the arithmetic average of all BGLs exceeding 1 standard deviation above the mean BGLs within an observed period [1].

Methods

We conducted a post–hoc analysis of data from the Hyperglycaemia: Intensive Insulin Infusion In Infarction (HI–5) Study, a prospective multicentre randomised controlled trial of insulin – dextrose infusion for glycaemic control amongst hyperglycaemic or diabetic patients admitted with an AMI between 2001 and 2005 [13]. The details of the protocol and the results of the study have previously been described [13]. In brief, patients with known diabetes or without diabetes with an admission BGL > 7.8 mmol/L who presented with an AMI at six hospitals in the state of New South Wales, Australia were randomised to intensive insulin therapy (received insulin – dextrose infusion therapy for at least 24 h to maintain their fingerprick BGLs between 4 and 10 mmol/L) or conventional therapy (received their usual diabetes therapy (excluding metformin) with supplemental subcutaneous short-acting insulin if fingerprick BGLs exceeded 16 mmol/L). The HI–5 study conformed with good clinical practice guidelines and the recommendations of the Declaration of Helsinki. Approval was obtained from all local ethics committees [13].

A post–hoc analysis was conducted on 121 patients from the intensive treatment arm of the HI–5 study. The systematic collection and recording of hourly capillary fingerprick BGLs in the intensive insulin therapy group provided us with the opportunity to calculate glycaemic variability and determine if any association existed with MACE.

MAGE and SD were calculated using the EasyGV calculator from the University of Oxford [14] in patients with > 3 BGLs whilst on insulin – dextrose infusion. MAGE and SD values were dichotomised into HIGH (MAGE value > 2.8 mmol/L and SD value > 1.6 mmol/L) and LOW (MAGE value ≤ 2.8 mmol/L and SD value ≤ 1.6 mmol/L) groups. The values for dichotomising MAGE and SD were obtained from a prior study [2].

* Corresponding author at: Department of Diabetes and Endocrinology, Westmead Hospital, Westmead, NSW 2145, Australia.
E-mail addresses: thora.chai@sydney.edu.au (T.Y. Chai), mark.mclean@health.nsw.gov.au (M. McLean), vincent.wong1@health.nsw.gov.au (V.W. Wong), wah.cheung@sydney.edu.au (N.W. Cheung).

Table 1
Baseline characteristics of the AMI population categorised into high and low MAGE/SD (total n = 121).

Variables	HIGH (n = 61)	LOW (n = 60)	*p*–value
Age (years)	62 (53–68)	64 (55–73)	0.26
Males	48 (78.7%)	48 (80.0%)	0.86
Admission BGL (mmol/L)	11.5 (9.2–16.0)	8.9 (7.4–9.8)	< 0.01*
Hypoglycaemic event(s)†	9 (14.8%)	3 (5.0%)	0.07
Length of hospital stay (days)	7 (5–14)	8 (5–10)	0.97
Risk Factors			
Diabetes	53 (86.9%)	21 (35.0%)	< 0.01*
HbA1c‡			
%	7.4 (6.6–9.0)	5.9 (5.5–6.5)	< 0.01*
mmol/mol	57 (49–75)	41 (37–48)	< 0.01*
Prior AMI	18 (29.5%)	11 (18.3%)	0.15
Hyperlipidaemia	35 (57.4%)	32 (53.3%)	0.66
Hypertension	35 (57.4%)	29 (48.3%)	0.32
Current smoker	14 (23.0%)	20 (33.3%)	0.16

Data presented as median (IQR) and number (% of n).

*p–value significant at < 0.05.

†Hypoglycaemia defined as a fingerprick BGL < 3.5 mmol/L, irrespective of the occurrence of symptoms.

‡n = 101.

AMI, acute myocardial infarction; MAGE, mean amplitude of glucose excursion; SD, standard deviation of glucose; HIGH, high MAGE/SD value; LOW, low MAGE/SD value; BGL, blood glucose level; HbA1c, glycated haemoglobin.

Patients were defined as having diabetes if they had a prior diagnosis or if their glycated haemoglobin level (HbA1c) was ≥ 6.5%. MACE was defined as the composite endpoint within 3–months of admission, comprising of cardiogenic shock, mortality, re-infarction, cardiac arrest, atrial/ventricular arrhythmia, non–fatal stroke or congestive cardiac failure. The precise time to MACE was not available during our post–hoc analysis.

Statistical analysis was conducted using IBM SPSS version 25.0 software program (*Armonk, NY, USA*). Mann–Whitney *U* test compared continuous variables and Pearson's Chi–squared test compared categorical variables between HIGH and LOW groups. Logistic regression models were adjusted for clinically significant parameters to determine whether MACE was associated with glycaemic variability. Statistical significance was taken as *p*–value < 0.05.

Results

Baseline characteristics of the 121 subjects categorised into HIGH (n = 61) and LOW (n = 60) groups are outlined in Table 1. Sixty–one percent of the study subjects had diabetes and the mean number of fingerprick BGLs were 15 ± 4 per patient. A significantly higher proportion of subjects in the HIGH group had diabetes, an increased admission blood glucose level (BGL) and HbA1c level compared with the LOW group (Table 1). There was a trend towards an increased incidence of hypoglycaemia in the HIGH group compared with the LOW group (7.4% vs 2.5%, p = 0.07).

MACE within 3–months of hospital admission occurred in 41 patients (34%): 7 patients (5.8%) died, 14 patients (11.6%) had a cardiac arrest, 9 patients (7.4%) developed congestive cardiac failure, 6 patients (5.0%) had cardiogenic shock, 1 patient suffered a re–infarction (0.8%), 31 patients (25.6%) developed atrial/ventricular arrhythmia and 2 patients (1.7%) had a non–fatal stroke. On unadjusted analyses, no association was identified between MACE and high MAGE (p = 0.23) or MACE and high SD (p = 0.14).

Subgroup analyses via stratification by diabetes status identified no difference in MACE outcomes (Diabetes 28.4% vs No diabetes 42.6%, p = 0.11). After separation into HIGH and LOW groups, a trend towards increased MACE occurred in subjects in the LOW group without diabetes compared to those with diabetes (38.5% vs 15.0%, p = 0.05). This was not statistically significant in the HIGH group between subjects

Table 2
The effect of sequential adjustment for diabetes and AdBGL on MAGE and SD.

Glucose Variability Metric	Adjusted for Diabetes Alone		Adjusted for Diabetes & AdBGL	
	OR (95% CI)	*p*–value	OR (95% CI)	*p*–value
MAGE	1.37 (1.09–1.73)	0.01*	1.27 (0.98–1.63)	0.07
SD	2.07 (1.34–3.18)	< 0.01*	1.89 (1.11–3.25)	0.02*

n = 121.

*p–value significant at < 0.05.

AdBGL, admission blood glucose levels; MAGE, mean amplitude of glucose excursion; SD, standard deviation of glucose; OR, odds ratio; CI, confidence interval.

without and those with diabetes (62.5% vs. 34.0%, p = 0.12).

When adjusted for diabetes in our regression model, an increased risk of MACE occurred with high MAGE (OR 1.37, 95% CI 1.09–1.73; p = 0.01) and SD (OR 2.07, 95% CI 1.34–3.18; p < 0.01). After adjusting for both diabetes and admission BGL in our regression model, an increased risk of MACE remained with SD (OR 1.89, 95% CI 1.11–3.25; p = 0.02). However, only a trend towards higher MACE with MAGE occurred when adjusted for diabetes and admission BGL (OR 1.27, 95% CI 0.98–1.63; p = 0.07) (Table 2).

Subgroup analyses between MACE and other risk factors for cardiovascular disease (hypertension, prior AMI, hypercholesterolaemia, smoking status) were also performed. There were no differences demonstrated in MACE among subjects with hypertension (39.1% vs 28.1%, p = 0.20), hypercholesterolaemia (31.3% vs 37.0%, p = 0.51), smoking status (36.7% vs 28.6%, p = 0.37) or a prior history of AMI (44.8% vs 30.4%, p = 0.15) and thus were not included in our adjusted regression model.

Discussion

Our study suggests that acute glycaemic variability in patients admitted immediately post AMI is associated with a higher risk of MACE. This is clinically important, as measuring and correcting inpatient glycaemic variability could help improve clinical outcomes in patients with an AMI.

It has been postulated in recent years that glycaemic variability is a determinant of vascular complications [10–12]. Fluctuating BGLs can increase oxidative stress more than sustained hyperglycaemia, particularly accelerating superoxide production in the mitochondria and vascular inflammation [12]. Vascular inflammation can occur through activation of the nuclear factor–κβ and protein kinase C pathway, resulting in increased expression of adhesion molecules and excess formation of advanced glycation end products [15]. As such, reducing glycaemic variability may be a potential target to help safely reduce not only mean BGLs, but also its direct effects on vascular complications, which is particularly detrimental to patients immediately post AMI.

Both Lipska and colleagues [7] and Mellbin and colleagues [8] were unable to determine whether glycaemic variability had any association with MACE in patients admitted with an AMI. Unlike Lipska and colleagues [7], we did not adjust for hypoglycaemia in our multivariable logistic regression models, given the minimal frequency of hypoglycaemia occurring in our population. Mellbin and colleagues [8] used three differing glucose variability metrics (root mean square error, range of all BGLs within a 48 h period and best fitted regression line of BGLs over 24 h) which are not as reasonable a measure of glycaemic variability in patients with coronary artery disease, with MAGE and SD reported as independent risk factors for coronary stenosis [17,18]. Whilst Su and colleagues [5] identified elevated admission glycaemic variability was more significant than admission hyperglycaemia in predicting 1–year MACE in patients with AMI, our study has raised the

Table 3
Summary of studies on the association of glycaemic variability with MACE outcomes in AMI patients.

Study	Type of Study	Population	Diabetes	GV metric	MACE outcomes
Kosiborod et al. (2008) [5]	Retrospective	n = 16 871	29.0%	Mean BGL, Hyperglycaemic index, Time-averaged BGL	*Unadjusted model:* S for ↑ mean BGL (mean BGL > 7.0†); *Adjusted model:* S for ↑ mean BGL (mean BGL > 7.0†)
Borg et al. (2011) [6]	Prospective	n = 427	100.0% (T2DM 37.2%)	MAGE, CONGA, SD	NS with GV metric; S with ↑ average BGL and HbA1c
Lipska et al. (2012) [7]	Retrospective	n = 18 563	38.0%	Range, SD, MAGE, MAG, Average daily risk range	*Unadjusted model:* S for range and average daily risk range; *Adjusted model:* NS
Mellbin et al. (2013) [8]	Retrospective	n = 578	100.0% (All T2DM)	Root mean square error, range, best fitted regression line over 24 h	*Unadjusted model:* NS; *Adjusted model:* NS
Su et al. (2013) [9]	Prospective	n = 222	53.6%	MAGE	*Unadjusted model:* S with ↑ MAGE (MAGE ≥ 3.9†); *Adjusted model:* S with ↑ MAGE (MAGE ≥ 3.9†)
Okada et al. (2015) [16]	Prospective	n = 57	49.1%	MAGE	*Unadjusted model:* S with ↑ MAGE (MAGE ≥ 3.3†); *Adjusted model:* S with ↑ MAGE (MAGE ≥ 3.3†)
Akasaka et al. (2017) [17]	Prospective	n = 65	0.0% (no diabetes)	MAGE, RHI	*Unadjusted model:* S with ↑ MAGE and ↓ RHI (MAGE ≥ 3.5†); *Adjusted model:* S with ↑ MAGE and ↓ RHI (MAGE ≥ 3.5†)
Gerbaud et al. (2019) [18]	Prospective	n = 327	100.0% (T2DM 93.9%)	MAGE, SD	*Unadjusted model:* S with ↑ SD (SD > 2.7†); *Adjusted model:* S with ↑ SD (SD > 2.7†)
Chai et al. (2019)	Post-hoc analysis	n = 121	61.0%	MAGE, SD	*Unadjusted model:* NS; *Adjusted model:* S for ↑ SD (SD > 1.6†)

†BGL, MAGE and SD measured in mmol/L.

AMI, acute myocardial infarction; GV, glycaemic variability; MACE; major adverse cardiovascular events; BGL, blood glucose level; S, significant; NS, non–significant; T2DM, type 2 diabetes; MAGE, mean amplitude of glucose excursion; CONGA, continuous overlapping net glycaemic action; MAG, mean absolute glucose change; HbA1c, glycated haemoglobin; RHI, reactive hyperaemia index.

possibility that acute inpatient glycaemic variability immediately post AMI is as detrimental (i.e. is associated with 3–month MACE). Table 3 summaries our study's findings, along with those findings from prior studies focusing on glycaemic variability and association with MACE in patients admitted with an AMI.

Despite a higher proportion of subjects with high MAGE/SD values having diabetes, there was no difference in MACE outcomes after stratification by diabetes status. This was a similar finding to the primary results of the HI–5 study, where no difference in mortality at any stage was demonstrated between subjects with diabetes and those without [13]. Interestingly, Kosiborod and colleagues [19] identified that subjects without diabetes had a higher proportion of MACE outcomes compared to those with recognised diabetes, although this was not found to be significant in our study. It was postulated by Kosiborod that a higher rate of MACE may have occurred in the non–diabetic cohort due to the presence of subjects with undiagnosed diabetes (particularly with admission BGLs ≥ 13.3 mmol/L) who had not received appropriate treatment for their hyperglycaemia during hospitalisation (i.e. with insulin therapy). As hyperglycaemia is toxic to the ischaemic myocardium, this therapeutic difference may have partially accounted for the disparity between diabetes status and MACE [19]. Through the HI–5 study though, stringent BGL control in patients immediately after an AMI did not improve short-term mortality [13], and as such, other factors may play a more significant role in mediating this disparity over hyperglycaemia alone.

Our study is limited by its retrospective nature. We were reliant on the BGLs recorded from the intensive insulin therapy arm of the HI–5 study only, which limited our sample size. As the HI–5 study was conducted prior to the advent of modern continuous BGL monitoring systems, we relied on hourly fingerprick BGLs, which was not present in the conventional therapy arm. Using patients only on the insulin – dextrose infusion post AMI may have reduced the degree of glycaemic variability captured. Furthermore, the modest number of fingerprick BGLs precluded us from examining more complex measures of glycaemic variability, such as coefficient of variation or mean absolute change in glucose (MAG).

Conclusion

Fluctuating glycaemia in AMI patients is associated with a higher risk of MACE. Further studies are needed to determine whether reducing glycaemic variability during the initial phase following AMI has therapeutic impact.

Author contributions

TYC conceptualised the idea, carried out the post–hoc statistical analysis and contributed to the manuscript. MM & VW contributed to the Discussion section and made constructive criticism to the manuscript. NWC helped with post–hoc statistical analysis and contributed to the manuscript.

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Declaration of Competing Interest

The authors declare they have no conflicts of interests.

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