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Impact of glucose fluctuation and monocyte subsets on coronary plaque rupture

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Abstract *Background and aims:* It remains unclear whether glycemic fluctuation can affect plaque rupture in acute myocardial infarction (AMI). Here we investigate the impact of glucose fluctuation on plaque rupture, as observed by optical coherence tomography (OCT), and monocyte subsets in patients with AMI.
Methods and results: We studied 37 consecutive patients with AMI. All patients underwent OCT examination, which revealed 24 patients with plaque rupture and 13 patients without plaque rupture at the culprit site. Peripheral blood sampling was performed on admission. Three monocyte subsets ($CD14^{+}CD16^{-}$, $CD14^{bright}CD16^{+}$, and $CD14^{dim}CD16^{+}$) were assessed by flow cytometry. Glycemic variability, expressed as the mean amplitude of glycemic excursion (MAGE), was determined by a continuous glucose monitoring system 7 days after the onset of AMI. MAGE was significantly higher in the rupture patients than in the non-rupture patients ($P=0.036$). Levels of $CD14^{bright}CD16^{+}$ monocytes from the rupture patients were significantly higher than those from the non-rupture patients ($P=0.042$). Of interest, levels of $CD14^{bright}CD16^{+}$ monocytes correlated positively and significantly with MAGE ($r=0.39$, $P=0.02$).
Conclusion: Dynamic glucose fluctuation may be associated with coronary plaque rupture, possibly through the preferential increase in $CD14^{bright}CD16^{+}$ monocyte levels.

Introduction

Recent studies have suggested that glycemic variability plays a role in the pathogenesis of atherosclerosis and is an independent risk factor for cardiovascular complications [1]. However, little is known about glucose fluctuation as a possible contributor to coronary plaque instability, especially plaque rupture.

Monocytes in human peripheral blood are heterogeneous. We showed previously that an imbalance in monocyte subsets, namely, a relative increase in $CD14^{+}CD16^{+}$ monocytes, may be relevant to coronary plaque instability, as assessed by 64-slice multidetector computed tomography in patients with stable angina pectoris [2]. We also showed that up-regulation of $CD14^{+}CD16^{+}$ monocytes is associated with plaque rupture in patients with unstable angina pectoris [3]. These results suggest that specific monocyte subsets are involved in the process of coronary plaque instability, leading to plaque rupture.

The purpose of the present study was to investigate the effect of glucose fluctuation on coronary plaque rupture and circulating monocyte subsets in patients with AMI by means of a continuous glucose monitoring system (CGMS).

Methods

Patient population

This study enrolled 37 consecutive patients with acute myocardial infarction (AMI) who underwent optical coherence tomography (OCT). AMI was diagnosed as follows: (i) chest pain within 24 h before admission that lasted for

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>30 min and was not relieved by sublingual nitroglycerin; (ii) ST-segment elevation and/or abnormal Q-wave on an electrocardiogram; and (iii) elevated serum creatine kinase levels. Exclusion criteria were as follows: (i) AMI > 24 h from onset; (ii) history of renal dysfunction requiring dialysis; (iii) evidence of malignant disease; or (iv) unwillingness to participate. All patients received coronary angiography on admission and then underwent percutaneous coronary intervention with coronary stents.

Clinical parameters

The assessed parameters were age, sex, and coronary risk factors (smoking, hypertension, diabetes mellitus, hyperlipidemia, and obesity). The diagnostic criteria for coronary risk factors were as follows. Hypertension: blood pressure $\geq$ 140/90 mmHg and/or a history of antihypertensive medication; diabetes mellitus: fasting plasma glucose $\geq$ 126 mg/dl, casual plasma glucose $\geq$ 200 mg/dl, or a diabetic pattern based on the 75-g oral glucose tolerance test; hyperlipidemia: serum total cholesterol levels > 220 mg/dl or serum triglyceride levels > 150 mg/dl; obesity: body mass index $\geq$ 25 kg/m^2.

Blood sampling and cytometric analysis

Peripheral blood samples were collected from all patients as soon as possible after admission.

Cytometric analysis was performed as described previously [4]. Flow cytometry was performed using a FACSAria™ instrument with BD FACSDiva Software. Monocytes were first gated in a forward scatter/sideward scatter (FSC/SSC) dot-plot, and 2-color fluorescence was measured within the monocyte gate (Fig. 1). $CD14^+CD16^-$ cells were defined as monocytes expressing CD14 but not CD16. $CD14^+CD16^+$ cells were defined as monocytes expressing CD16 and either high levels of CD14 ($CD14^{bright}CD16^+$) or low levels of CD14 ($CD14^{dim}CD16^+$). The recently updated classification of monocyte heterogeneity acknowledges the existence of 3 monocyte subsets, that is, classical monocytes ($CD14^{++}CD16^-$), intermediate monocytes ($CD14^{++}CD16^+$), and non-classical monocytes ($CD14^+CD16^+$) [5]. Therefore, we provided data regarding 3 subsets in this study.

Continuous glucose monitoring

Subcutaneous interstitial glucose levels were monitored over 2 consecutive days using a fourth-generation CGMS (Medtronic iPro2, Medtronic, Northridge, CA) applied to the abdominal area. A sensor was inserted about 7 days after the onset of AMI. Blood glucose was measured using the finger-stick test, at least four times per day (breakfast, lunch, dinner, and bedtime) and the dates were used for the analysis. Standardized meal started on the day of the onset, which contained 1600 kcal (15% protein, 23% fat and 62% glucide).

Assessment of glycemic variability

Intra-day glycemic variability was assessed as the mean amplitude of glycemic excursion (MAGE), which was calculated as described by Service et al. [6] Briefly, the arithmetic mean of the differences between the consecutive peak and nadir values was measured if the differences were greater than the standard deviation (SD) of the mean glucose values. Measurements in the peak-to-nadir or nadir-to-peak directions were determined by the first qualifying excursion.

OCT imaging protocol and analysis

All patients received oral aspirin (162 mg), an intravenous bolus injection of 5000IU heparin before coronary angiography. In patients with thrombolysis in myocardial infarction (TIMI) flow grade 0, I, or II, aspiration thrombectomy was performed using an aspiration catheter before intracoronary imaging. A 0.35 mm OCT catheter (Imaging Wire; LightLab Imaging Inc., Westford, MA) was advanced to the distal end of the culprit lesion. In all cases, the culprit lesion was imaged using the C7-XR™ OCT Intravascular Imaging System (St. Jude Medical, St Paul, MN) and an automatic pullback device at 20 mm/s by the continuous-flushing method.

All OCT images were analyzed using proprietary off-line software by two independent investigators (Y.O. and T.N.). Plaque rupture was identified by fibrous cap discontinuity and cavity formation of the plaque, and the presence of plaque rupture at the culprit lesion was noted.

Cardiovascular magnetic resonance (CMR) imaging protocol and analysis

CMR was performed using a 1.5T clinical scanner equipped with a five-element cardiac phased-array coil for signal reception 7 days after the onset of AMI [6,7]. Late gadolinium enhancement (LGE) imaging was obtained with contiguous short-axis slices of the left ventricle from base to apex 10–15 min after injection of 0.1 mmol/kg gadolinium-diethylenetriamine penta-acid. For an assessment of infarct sizes, the rate of the hyper-enhanced myocardium (>5 SD above the mean of the normal region) by LGE was quantified.

Statistics

All data are expressed as mean $\pm$ SD values, unless stated otherwise. For statistical analysis of plaque rupture, parameters were evaluated by univariate regression. All statistical analysis was performed using the statistical software package SPSS version 11.0 (SPSS Inc., Chicago, IL). Values of $P < 0.05$ were considered significant.

Results

Patient characteristics

Of 51 eligible patients with ST-segment elevation myocardial infarction, 37 consecutive patients were enrolled (Table 1). Reasons for exclusion were as follows: unable to evaluate the culprit lesion by OCT ($n=6$), unable to evaluate the glucose fluctuation ($n=5$) and refusal to participate in the study ($n=3$). The majority of patients ($n=25$, 68%) did not