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Paraoxonase-1 activity and oxidative stress in patients with anterior ST elevation myocardial infarction undergoing primary percutaneous coronary intervention with and without no-reflow

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ABSTRACT

Background: Reperfusion and ischemic injuries are pathogenetic mechanisms of no-reflow. Oxidative stress plays a critical role during ischemia as well as during the reperfusion phase following ST elevation myocardial infarction (STEMI). We sought to investigate the relationship between no-reflow with paraoxonase-1 (PON-1) activity and oxidative stress markers (total antioxidant capacity (TAC), total oxidant status (TOS), oxidative stress index (OSI), lipid hydro-peroxide (LOOH)) in patients with anterior STEMI undergoing primary percutaneous coronary intervention (PCI).

Methods: In this study, 319 consecutive anterior STEMI patients undergoing primary PCI were prospectively included (mean age 56.5 ± 12.5 years). The patients were divided into two groups as normal flow ($n = 231$) and no-reflow ($n = 88$) groups. Serum PON-1 activity was measured spectrophotometrically. TAC and TOS levels were determined by using an automated measurement method. LOOH levels were measured by ferrous oxidation with xylenol orange assay.

Results: PON-1 activity and TAC levels were significantly lower and TOS, OSI and LOOH levels were significantly higher in patients with no-reflow compared to normal flow group ($p < 0.05$, for all). On multivariate logistic regression analysis, PON-1 activity ($\beta = 0.976$, 95% CI = 0.962–0.990, $p = 0.001$) and OSI ($\beta = 1.094$, 95% CI = 1.042–1.148, $p < 0.001$) as well as diabetes, infarction time, thrombus score and initial SYNTAX score were independently associated with no-reflow.

Conclusion: In patients with no-reflow compared with normal flow, oxidants are increased, while serum PON-1 activity and antioxidants are decreased. This result shows that increased oxidative stress has a role in the pathogenesis of no-reflow.

1. Introduction

The no-reflow phenomenon is defined as the inability to reperfuse regions of the myocardium despite removal of a large epicardial coronary artery occlusion [1]. The patients with no-reflow exhibit a higher prevalence of; early postinfarction complications; left adverse ventricular remodeling; late repeat hospital stays for heart failure; and mortality [2]. Ischemic and reperfusion injuries are important pathogenetic mechanisms of no-reflow following ST elevation myocardial infarction (STEMI) [3]. Ischemia results in impaired antioxidant defense and subsequent reperfusion results in an increased concentration of reactive oxygen species (ROS) [3,4].

High-density lipoprotein (HDL) cholesterol exerts cardioprotective properties through its antioxidant activity and anti-inflammatory effects, which is largely maintained by paraoxonase-1 (PON-1) [5]. PON-1 protects lipoproteins against oxidative modification and to hydrolyze hydrogen peroxide, a major ROS produced under conditions of inflammation and atherosclerosis [5].

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Our hypothesis was that oxidative stress parameters and PON-1 activity will be associated with no-reflow phenomenon in patients with STEMI undergoing primary percutaneous coronary intervention (PCI). Therefore, we aimed to investigate PON-1 activity and oxidative stress markers in anterior STEMI patients undergoing primary PCI with and without no-reflow.

2. Methods

2.1. Study population

We prospectively included 319 consecutive patients with anterior STEMI who underwent primary PCI (240 male, 79 female; mean age 56.5 ± 12.5 years) between June 2012 and July 2013. On the basis of post-primary PCI infarct related artery flow, the patients were divided into two groups: no-reflow ($n = 88$) and normal flow groups ($n = 231$). STEMI was defined as resting chest pain lasting ≥30 min, together with new or presumed new ST segment elevation in ≥2 contiguous leads with the cutoff point ≥0.2 mV in anterior leads. The diagnosis was confirmed by coronary angiography in all patients.

Patients with a recent history of myocardial infarction (MI), a previous PCI, a previous coronary artery bypass graft, late presentation (>12 h), unsuccessful primary PCI (residual stenosis >50% in the culprit lesion after procedure), pretreatment with thrombolytic or glycoprotein IIb/IIIa inhibitor therapy before primary PCI, infectious or inflammatory disease, severe liver or renal disease, neoplasm, or hematological disorders were excluded from the study. Patients taking antioxidant drugs such as statins, diuretics, angiotensin-converting enzyme inhibitors (captopril, zofenopril), beta-blocking agents (carvedilol, nebivolol), and vitamins (such as E and C) were excluded from the study. No dietary variation was present between the groups. Patients taking xenobiotics and alcohol were also excluded from the study. Exclusion criteria were applied to all the groups. The Local Ethics Committee approved the study protocol, and each participant provided written informed consent.

After assessment of detailed medical history and a complete physical examination, the baseline characteristics of patients including age, sex, hypertension, hyperlipidemia, diabetes mellitus (DM), current smoking status, family history of coronary artery disease (CAD), body mass index (BMI), and medications were recorded for all patients. Also, the time interval from the onset of symptoms to hospital admission was recorded in all patients. Left ventricle ejection fraction (EF) was measured using Simpson's method according to the suggestions of the American Society of Echocardiography [6].

2.2. Coronary angiography and percutaneous coronary intervention

Urgent diagnostic coronary angiography was performed according to the standard criteria in all patients. To achieve maximal dilatation, each coronary angiogram was preceded by an intracoronary injection of 100 mg nitroglycerine. Significant coronary artery disease was defined as at least 70% luminal diameter stenosis in at least one epicardial coronary artery. Primary PCI procedures were performed using the standard femoral approach with a 7-Fr guiding catheter. All patients were pretreated with loading doses of aspirin (300 mg) and clopidogrel (600 mg); they also received an intravenous bolus of heparin 50 IU/kg. After the guidewire insertion into the infarct related artery (IRA), thromboaspiration (Export™ 6F catheter, Medtronic, Santa Rosa, CA, USA) was performed whenever possible (when the anatomy of the coronary artery – curve and size – allowed it) in all patients with a TIMI Flow 0 and in all patients with a visible thrombus if TIMI Flow was 1 or more. Then, direct stenting was implanted whenever possible; in the remaining cases, balloon pre-dilatation was carried out. Bare-metal stents were mostly used. In each patient treated with tirofiban, it was administered after the primary PCI procedure in the coronary care unit. Baseline and post-primary PCI thrombolysis in myocardial infarction (TIMI) flow grade in IRA and post-PPCI TIMI myocardial perfusion grade (TMPG) were assessed by three independent interventional cardiologists. Intracoronary thrombus in IRA was identified angiographically after wiring of IRA and scored in five grades as described previously [7]. SYNTAX score was calculated as described previously [8].

2.3. The diagnosis of angiographic no-reflow

The diagnosis of no-reflow required the following criteria [2,3]: (a) angiographic evidence of reopening of the occluded coronary artery and successful stent placement with no evidence of flow-limiting residual stenosis (>50%), dissection, spasm, or apparent thrombus; (b) angiographic documentation of a TIMI flow grade of 2 or less, or a TIMI flow grade 3 with a TMPG 0 or 1, at least 10 min after the end of the PCI procedure. A TMPG 0 was defined when contrast failed to enter the vasculature and TMPG 1 was defined when contrast entered slowly, but failed to exit the vasculature [3].

2.4. Blood sampling

Venous blood samples were obtained before primary PCI at admission. Samples were taken from cubital vein into blood tubes and immediately stored on ice at 4 °C. The serum was then separated from the cells by centrifugation at 3000 rpm for 10 min. Serum samples were stored at −80 °C until analysis of lipid parameters, PON-1 activity, lipid hydro-peroxide (LOOH), total oxidant status (TOS) and total antioxidant capacity (TAC).

Blood counts were measured by a Sysmex K-1000 (Block Scientific, Bohemia, New York) autoanalyzer within 5 min of sampling. Plasma triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), glucose, uric acid, and creatinine concentrations were measured with an automated chemistry analyzer (Abbott Aeroset, Minnesota, USA) using commercial kits (Abbott). Activity of creatine kinase MB (CK-MB) was measured with an assay that uses 2 monoclonal antibodies (CK-MB STAT) on an Elecsys 2010 analyzer (Roche Diagnostics, Basel, Switzerland) by electrochemiluminescence immunoassay. Plasma NT-proBNP was measured by electrochemiluminescence (Roche Diagnostics, Basel, Switzerland). For the measurement of the platelet count and mean platelet volume (MPV), samples were analyzed within 20 min after collection using an automated hematology analyzer Sysmex XT 1800i (Roche Diagnostic, Shanghai, China).

2.4.1. Measurement of serum paraoxonase-1 activity (PON-1)

Measurement of serum PON-1 activity was performed in the absence of NaCl (basal activity). The rate of paraoxon hydrolysis (diethyl-p-nitrophenylphosphate) was measured by monitoring the increase of absorbency at 412 nm at 37 °C. The amount of generated p-nitrophenol was calculated from the molar absorptivity coefficient at pH 8, which was 17,000 M^{-1} cm^{-1} [9]. PON-1 activity was expressed as U L^{-1} serum. Coefficient of variation (CV) for measurement of serum PON activity was 2%.

2.4.2. Measurement of lipid hydro-peroxide (LOOH), total oxidant status (TOS), total antioxidant capacity (TAC) and oxidative stress index (OSI)

Serum LOOH levels (as a crucial biomarker of oxidative stress) were measured with the ferrous ion oxidation–xylenol orange (FOX-2) assay as previously described [10]. The TAC and TOS levels