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Role of glycoprotein Ia gene polymorphisms in determining platelet function in myocardial infarction patients undergoing percutaneous coronary intervention on dual antiplatelet treatment

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Abstract

Response variability to antiplatelet treatment has been described and the widespread use of acetylsalicylic acid (ASA) and clopidogrel requires clarification of the residual platelet reactivity (RPR). Various glycoprotein Ia (GpIa) polymorphisms have been investigated, but their influence on platelet reactivity in myocardial infarction (MI) patients undergoing percutaneous coronary intervention (PCI) on dual antiplatelet treatment is not still elucidated.

Aim of this study was to evaluate the effect of C807T, G873A and T837C polymorphisms of GpIa on modulating platelet function in MI patients on dual antiplatelet treatment undergoing PCI.

We measured platelet function by both a point-of-care assay (PFA100) and platelet-rich-plasma aggregation in 289 MI patients undergoing PCI and receiving dual antiplatelet treatment.

Our data show that C807T/G873A polymorphisms, but not T837C, are associated with higher platelet reactivity. Carriers of the 807T/873A allele had significantly higher platelet aggregation values after arachidonic acid (AA) and collagen stimuli and, even if they did not reach the statistical significance, after 2 and 10 μM ADP stimuli; 807T/873A allele carriers had also significantly shorter closure times on PFA100/epinephrine membranes. At the multiple analyses, C807T/G873A polymorphisms resulted an independent risk factor for RPR defined by both AA induced platelet aggregation (OR = 3.0, 95%CI 1.17–7.89, $p = 0.022$) or by PFA100/epinephrine (OR = 4.1, 95%CI 1.53–10.89, $p = 0.005$).

In conclusion, this study shows the 807T/873A allele of the GpIa gene is an independent risk factor for the RPR on dual antiplatelet treatment, and extends, in a larger acute coronary syndrome population, the observation that the 807T/873A allele is associated with higher platelet reactivity.

Keywords: Glycoprotein Ia polymorphisms; Residual platelet reactivity; Aspirin resistance; Antiplatelet treatment; Percutaneous coronary intervention

1. Introduction

Acetylsalicylic acid (ASA) and clopidogrel have become standard therapy in patients undergoing percutaneous coronary intervention (PCI); however, there is a broad variability in response of individual patients to dual antiplatelet treatment [1–5]. Previous studies estimated that adequate antiplatelet effects are not achieved in 5–45% of patients taking ASA and 4–30% of patients taking clopidogrel [1,3–6]. Some studies are available in the literature which investigated the clinical implications of antiplatelet drug effect resistance

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in chronic coronary artery disease (CAD) or stent thrombosis [2,5,7–10]. Recently, we have demonstrated that post-PCI residual platelet reactivity (RPR), the so called ASA resistance, is an independent predictor of 1-year major adverse coronary events in patients with acute myocardial infarction (MI) [11].

Collagen is a major adhesion protein exposed to platelets after blood vessel injury [12]. Interaction between collagen and blood platelets results in their adhesion, activation and aggregation, and finally in the formation of haemostatic plugs [13,14]. Platelets interact with collagen via several platelet surface receptors, and major roles are attributed to glycoprotein Ia/IIa (GpIaIIa or $\alpha_2\beta_1$ integrin) [15,16] as well as glycoprotein VI [17]. GpIa/IIa is the major collagen receptor involved in the early steps of platelet adhesion to collagen under high shear stress [14]. Previous studies showed that GpIa/IIa is activated by various agonists, including thrombin or ADP, and that the activation of GpIa/IIa leads to a different affinity to collagen [13,18].

Several polymorphisms have been described in the cDNA coding the GpIa subunit. The C807T, T837C and G873A polymorphisms are conservative and do not alter the deduced amino acid sequence of the translated protein. The two linked silent GpIa dimorphisms, C807T and G873A, were correlated with a variable expression of the platelet surface receptor: the genotype 807TT/873AA was associated with a higher receptor density and the genotype 807CC/873GG with a lower density, whereas heterozygous individuals expressed intermediate receptor levels [19,20]. Differences in the receptor density directly correlate with the rate of platelet adhesion to collagen under flow conditions [21]. The functional role of the C807T GpIa polymorphism on modulating the response to antiplatelet drugs in patients has been hypothesized in two previous studies: one studying 44 patients undergoing PCI during the first 24 h following clopidogrel loading dose and on ASA treatment for at least 7 days [22], and the other one evaluating 82 CAD patients on dual antiplatelet treatment for >1 month [23]. Scarce data are available on T837C GpIa polymorphism.

Therefore, the aim of this study was to assess the role of the C807T, G873A, and T837C GpIa gene polymorphisms on modulating platelet function and determining antiplatelet drug response in patients on dual antiplatelet treatment.

2. Materials and methods

2.1. Study population

The study population included 289 consecutive patients admitted to the Coronary Care Unit of the Azienda Ospedaliero-Universitaria Careggi, University of Florence with diagnosis of acute MI. Acute MI was diagnosed on the basis of an increase in creatine kinase MB isoenzyme at least twice the upper normal limits (3.6 ng/mL), and/or elevated cardiac troponin I (cTnI) (>0.15 ng/mL) levels with at least one of the following: acute onset of prolonged (≥20 min) typical ischemic chest pain; ST-segment elevation of at least 1 mm in two or more contiguous electrocardiographic leads or ST-depression of ≥0.5 mm, 0.08 s after the J point in ≥2 contiguous leads, or T waves inversion >1 mm in leads with predominant R waves. In 175 patients ST segment elevation MI (STEMI) and in 114 non-ST segment elevation MI (NSTEMI) was diagnosed. All patients underwent coronary angiography performed by the Judkins' technique and primary PCI. Patients were considered to have hypertension if they had been diagnosed as hypertensive according to the European Society of Hypertension/European Society of Cardiology guidelines or were taking antihypertensive drugs. Dyslipidemia was defined according to the Third report of the National Cholesterol Education Program and diabetes according to the American Diabetes Association.

The exclusion criteria included history of bleeding diathesis, platelet count ≤100,000/mm^3, hematocrit ≤30%, creatinine ≥4.0 mg/dL, and glycoprotein (Gp) IIb/IIIa inhibitor use.

Informed written consent was obtained from all patients and the study was approved by the local Ethical Review Board.

2.2. Patient characteristics

Demographic and clinical characteristics of patients are reported in Table 1.

All patients received a loading dose of 300 mg clopidogrel p.o. before the procedure and of 500 mg ASA i.v., followed by 75 mg clopidogrel and 100 mg ASA daily. Unfractioned heparin 70 IU/kg was used during procedure as anticoagulant.

2.3. Blood sampling

Venous blood samples were taken from each patient 24 h after PCI intervention in tubes containing 3.2% trisodium citrate.

Table 1
Demographic and clinical characteristics of studied subjects

Age	67.5 (27–89)
Sex (M/F)	222/67
Hypertension	178 (61.6%)
Smoking habit	139 (48.1%)
Dyslipidemia	200 (69.2%)
Diabetes	61 (21.1%)
Drugs	
β-blockers	179 (61.9%)
Ca-antagonists	48 (16.6%)
Statins	250 (86.5%)
ACE-inhibitors	237 (82.0%)