Association between Endothelial Nitric Oxide Synthase Gene Polymorphism (Glu298Asp) and Coronary No-Reflow Phenomenon in Acute Myocardial Infarction

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Summary

No-reflow phenomenon is an important complication of primary percutaneous coronary intervention. Several variants in the endothelial nitric oxide synthase gene, which reduce endothelial nitric oxide synthase activity, are a risk factor for coronary heart disease. However, its role in no-reflow phenomenon has not yet been revealed. This study aimed to investigate whether there is a relationship between endothelial nitric oxide synthase Glu298Asp gene variant and the development of coronary no-reflow phenomenon in patients with ST elevation myocardial infarction.

The study was conducted among 116 patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction. Group 1 included 52 ST elevation myocardial infarction patients undergoing no-reflow phenomenon as a study group. Group 2 comprised 64 ST elevation myocardial infarction patients without no-reflow phenomenon as a control group. Endothelial nitric oxide synthase was tested using polymerase chain reaction-restriction fragment length variant.

The prevalence of TT genotype of endothelial nitric oxide synthase Glu298Asp gene variant was found to be significantly higher in patients developing coronary no-reflow when compared to those without no-reflow (p = 0.016; 11.54% vs. 1.56%) (OR = 10.85, 95% CI = 1.22–96.39). However, a similar association for the heterozygous GT genotype of endothelial nitric oxide synthase Glu298Asp gene variant was not observed between the two groups.

The results of this preliminary study indicate that there is an association between Glu298Asp variant in endothelial nitric oxide synthase gene and the development of no-reflow phenomenon in ST elevation myocardial infarction. The presence of homozygous TT allele may contribute to tendency to the development of no-reflow phenomenon.

Keywords: coronary no-reflow phenomenon • myocardial infarction • nitric oxide synthase • Glu298Asp • gene variant
INTRODUCTION

Nitric oxide (NO) is a potent vasodilator released by the endothelium, as well as platelets and vascular smooth muscle cells [4, 10, 12]. NO seems to play an important role in the regulation of vascular tone. Although it has a very short half-life, it plays a role in protecting the cardiac vascular network against myocardial damage by inhibiting platelet aggregation and leukocyte adhesion to vascular endothelium [4, 12, 16]. Endothelial NO is synthesized by the enzyme endothelial nitric oxide synthase (eNOS), which is the product of a gene located on chromosome 7q35-q36 [23]. Impaired NO bioactivity plays a major role in the development of endothelial dysfunction, which is thought to be related with atherosclerosis and no-reflow development [11]. It has previously been shown that several variants in this gene that reduce eNOS activity might be a risk factor for atherosclerotic heart disease [4, 11, 24].

One of the most studied eNOS variants has been Glu298Asp variant [10, 15]. The eNOS gene encodes aspartate protein instead of glutamate when a thymine (T) allele is present instead of a guanine (G) allele, which is related to impaired eNOS activity [11]. Numerous studies have indicated that the eNOS gene Glu298Asp variant is associated with coronary artery disease (CAD), premature ST-elevation myocardial infarction, hypertension, metabolic syndrome, impaired coronary collateral development, accelerated carotid atherosclerosis, impaired coronary blood flow and vascular responsiveness to phenylephrine; however, the conclusions have been inconsistent [3, 7, 15, 19, 23].

No-reflow phenomenon is an important complication of primary percutaneous coronary intervention (PPCI), associated with poor clinical outcomes, occurring more frequently in the setting of acute ST-elevation myocardial infarction (STEMI), and it is associated with increased 30-day mortality if not adequately treated [18]. The angiographic no-reflow phenomenon is defined as severely impaired forward coronary flow with a Thrombolysis in Myocardial Infarction (TIMI) flow grade <3 in the absence of residual stenosis, dissection, or thrombosis [18, 25]. The prevalence of no-reflow phenomenon is 2–50%, depending on the definition, recognition methods, and selected patient population [16, 17, 18]. Endothelial dysfunction, microvascular plugging, thrombotic debris, microvascular spasm, cellular edema and reperfusion injury contribute to the development of no-reflow phenomenon [16, 17, 18]. However, its mechanisms have not been definitively described. Intracoronary vasodilator therapy, including dipyridamole, adenosine, verapamil, and nitroprusside have been tested previously for the treatment of no-reflow phenomenon [17, 25, 29].

Genetic structural abnormalities may also contribute the development of no-reflow phenomenon. The TT genotype of the eNOS gene, which leads to endothelial dysfunction, may contribute to the development of no-reflow phenomenon by decreasing NO related vasodilatation [11]. However, the association between the development of no-reflow phenomenon and eNOS variant in the setting of STEMI has not been investigated so far. In the present study, we aimed to investigate whether there is an association between eNOS Glu298Asp gene variant and the development of coronary no-reflow phenomenon during PPCI in patients with acute STEMI.

SUBJECTS AND METHODS

Study population

This observational case-control comparative study was conducted in a tertiary heart center between December 2011 and May 2012. Patients with STEMI who underwent PPCI were included in this study. A total of 116 patients among 998 Caucasian patients who underwent PPCI for STEMI were selected consecutively for the enrollment to the study. The study groups were designed according to the development of no-reflow phenomenon. Group 1 was consisted of 52 STEMI patients undergoing no-reflow phenomenon. Group 2 was comprised of 64 STEMI patients without no-reflow phenomenon for comparison. All patients received similar initial anti-ischemic treatment.

Exclusion criteria were cardiogenic shock, rescue PTCA, intervention on vein grafts, coronary dissection, incomplete lesion dilation, severe heart failure, need for emergent coronary bypass surgery, previous coronary intervention, previous myocardial infarction and severe
renal failure (creatinine >3 mg/dl). All patients provided written informed consent and the study protocol was approved by the ethics committee of the institution in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

DNA extraction and the detection of genetic variant

Genomic DNA was extracted from whole blood samples in EDTA-containing tubes using a commonly applied spin column method [1]. The blood samples collected for genotypic determination were stored at 4°C up to 24 hour until DNA extraction. Genomic DNA was isolated from peripheral blood leukocytes using a QIAamp DNA Blood Mini Kit (Qiagen GmbH, Hilden, Germany). The detection of the Glu298Asp polymorphism (rs1799983) in the eNOS gene was achieved by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Briefly, specific primer pairs were used to amplify a part of the eNOS gene containing the exon 7 by PCR with the following flanking intronic primers: (sense) 5’-CATGAGGGCTAGCCCCAGAC-3’ and (anti-sense) 5’-AGTCAATCCCCGCGTCAC-3’. The PCR amplification was performed in 50 μl reaction mixtures containing 10 μl genomic DNA, 30 μl one step PCR mixture (1 unit Taq polymerase, 10 mM KCl, 10 mM (NH4)2SO4, 20 mM TrisHCl (pH 8.75), 0.1 % Triton X-100, 0.1 mg/ml bovine serum albumin (BSA), 200 mM dNTPs, 2 μl of each primer (BioBasic Inc., Ontario, Canada), and 8 μl DdH.O. PCR was performed by denaturation at 94°C for 30 s, annealing at 60°C for 30 s, and extension at 72°C for 30 s, repeated for 30 cycles. Thereafter, digestion of the amplified DNA was performed using the MboI restriction endonuclease. Only in the presence of a T nucleotide at position 894 (corresponding to Asp 298), but not in the absence of it (wild type), the resulting 206 bp PCR product was cleaved into two smaller fragments of 119 and 87 bp. Digestion fragments were then resolved by electrophoresis on a 2.5% agarose gel stained with ethidium bromide.

Biochemical analysis

Venous blood samples were collected from patients after the procedure. Troponin I levels were recorded during hospitalization. Glucose, creatinine level, and lipid profile were measured for all patients with a Cobas-C 501 biochemical analyzer (Roche Diagnostics, Mannheim, Germany) using Roche kits. Hematological indices were evaluated from complete blood count analyses performed using a Mindray device BC-5800 (Mindray Bio-Medical Electronics Co. Ltd. Shenzhen, China) with the optical laser method.

Coronary angiography

All angiograms were performed with 7 F guiding catheters without side holes at a speed of 15 frames per second. Coronary angiography was carried out by an automatic mechanical injector (ACIST CVi, Bracco Imaging S.p.A., Ferentino, Italy). All observations were performed by an interventional cardiologist who was blinded to the study groups from the same angiographic view at baseline and just after stent implantation, when no-reflow was first recognized. TIMI flow score was defined by the degree of flow into the epicardial artery as follows: TIMI grade 0: complete absence of flow beyond the point of obstruction; grade 1: some contrast material flows distal to the obstruction but complete arterial visualization is not achieved; grade 2: delayed opacification of the entire artery; and grade 3: full prompt visualization of the entire artery [27].

Coronary artery disease scoring

The severity and extent of CAD was evaluated according to the Gensini and Syntax scores. The Gensini score depends on the degree of the coronary artery stenosis and its geographic importance [6]. The degree of luminal narrowing, concentricity, and eccentricity of the plaques were evaluated; 1 point was given for 1–25% stenosis, 2 points for 26–50%, 4 points for 51–75%, 8 points for 76–90%, 16 points for 91–99%, and 32 points for 100% stenosis. Further, each lesion’s points were multiplied by the coefficient given for each principal vascular segment due to the functional significance (the left main coronary artery × 5; the proximal segment of left anterior descending coronary artery (LAD) × 2.5; the proximal segment of the circumflex artery × 2.5; the mid-segment of the LAD × 1.5; the right coronary artery, the distal segment of the LAD, the posterolateral artery, and the obtuse marginal artery × 1; and others × 0.5), and the sum of all of these gave the total score [6]. Scoring was performed by two observers and was then averaged. The Syntax score corresponds to the lesion complexity measured by the coronary tree characteristics, lesion locations, and specifics [6]. The score is measured using the openly accessible web based score calculator (http://www.syntaxscore.com).

Statistical analysis

Statistical calculations were performed with NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) program for Windows. The number of cases in this study was determined with a power of 0.80 and with an α error of 0.05 level at 2-way. Moreover, standard descriptive statistical calculations (mean and standard deviation, median, interquartile range) for the variables indicated a normal distribution, and unpaired t test were used in the comparison of groups. For variables that did not indicate a normal distribution, the Mann-Whitney U test was used in the comparison of groups, and the Chi square test was performed during the evaluation of qualitative data. All variables that were significant in the univariate analyses were included in the multivariate regression analysis. The level of statistical significance was established as p <0.05.
RESULTS

The incidence of no-reflow phenomenon in patients with first STEMI was found to be 5.2% of all patients who underwent PPCI for STEMI in our study period. The patient and control groups were similar in terms of sex, age, diabetes mellitus, hypertension, body mass index, alcohol consumption, and family history of CAD. The baseline characteristics and angiographic parameters of patients are summarized in Table 1. In the control group, current smoking was higher than in no-reflow group (n = 32, 61.5% vs. n = 26, 40.6% p = 0.025). In-hospital mortality was higher in no-reflow group (n = 5, 9.6% vs. n = 0, 0% p = 0.016). Gensini and Syntax scores were lower in control group (64.9 ± 25.3 vs. 47.1 ± 24.8 and 25.1 ± 10.8 vs. 17.9 ± 8.0 p <0.001, p <0.001, respectively). Number, length and diameter of stents used in PPCI procedure were similar between the two groups. Mean left ventricle ejection fraction of the subjects in the no-reflow group was lower than those in control group (51.1 ± 8.8 vs. 41.7 ± 9.4, p <0.001, table 1).

Genotypes and allelic frequencies of the patients are demonstrated in Table 2. The distribution of genotypes in the entire cohort did not differ significantly from that expected under Hardy-Weinberg equilibrium. Twenty-one (40.38%) of the patients in no reflow group were homozygous for the guanine nucleotide (GG genotype), whereas 25 (48.08%) were heterozygous with a GT genotype and 6 (11.54%) were homozygous with a TT genotype. In contrast, 38 (59.38%) of the patients in the control group were homozygous for the G nucleotide (GG genotype), whereas 25 (39.06%) were heterozygous with a GT genotype and 1 (1.56%) was homozygous with a TT genotype. The prevalence of TT genotype was significantly higher in patients with coronary no-reflow in comparison to those without no-reflow (11.54% vs. 1.56%, respectively, p = 0.016). The risk of developing no-reflow in patients with homozygous TT genotype was increased 10.85 fold in the no-reflow group than in the control group (OR: 10.85, 95% CI: 1.22-96.39). However, a similar association for the heterozygous GT genotype was not observed between the two groups (Table 2). The baseline laboratory parameters of the study subjects are given in Table 3. Peak troponin levels were higher in the no-reflow group than in the control group (16.9 ± 15.7 vs. 6.5 ± 8.0, p <0.001). When compared to the control group, plasma glucose levels were significantly higher and plasma low-density lipoprotein (LDL) cho-
The results of the studies indicating that eNOS gene Glu298Asp variant is associated with CAD, STEMI, hypertension, coronary vasospasm, impaired coronary collateral development and impaired coronary blood flow have been inconsistent due to ethnic diversity, differences in age, sample size, population stratification, and environmental factors affecting the genetic structure in their populations [3, 7, 15, 19, 23, 29]. To our knowledge, the association between the development of no-reflow phenomenon during PPCI in the setting of STEMI and eNOS gene variant has not yet been investigated. The present study shows that there is an association between eNOS gene variant and the development of no-reflow phenomenon in patients undergoing PPCI for STEMI.

There is accumulating circumstantial evidence suggesting that endothelial dysfunction contributes to no-reflow phenomenon [5, 18, 24]. Saini et al. investigated the association between eNOS gene variants and endothelial dysfunction in the presence of CAD and plasma NO levels [22]. They indicated that both the plasma endothelin levels and the frequency of the GT allele were higher in patients with CAD than the controls, whereas plasma NO levels were lower in CAD group. They have interpreted the results as suggesting Asp allele might be a risk factor for CAD with endothelial dysfunction was significantly lower in the no-reflow group (p = 0.045 and p = 0.04, respectively). There were no significant differences in terms of the hematological parameters, serum creatinine, or other lipid parameters between the two groups (Table 2). All variables that were significant in the univariate analyzes in Tables 1, 2 and 3 were included in the multivariate regression analysis.

**DISCUSSION**

This comparative analysis of allelic distribution of eNOS gene Glu298Asp variant between developing no-reflow phenomenon and non-developing in patients undergoing PPCI for STEMI demonstrated that the homozygous TT allele was more frequent in patients developing no-reflow phenomenon (p = 0.032; 11.54% vs. 1.56%, respectively) and patients with the homozygous TT allele have more than a tenfold higher risk of developing no-reflow phenomenon as compared to controls. However, a similar association for the heterozygous GT genotype was not observed between the two groups.

### Table 2. The distribution of genotypes and allele frequencies in the study groups

<table>
<thead>
<tr>
<th></th>
<th>No-reflow (n = 52)</th>
<th>Control (n = 64)</th>
<th>p</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eNOS GG</td>
<td>21 (40.4)</td>
<td>38 (59.4)</td>
<td>0.173</td>
<td>1.81 (0.84–3.9)</td>
</tr>
<tr>
<td>eNOS GT</td>
<td>25 (48.1)</td>
<td>25 (39.1)</td>
<td>0.016</td>
<td>10.85 (1.22–96.39)</td>
</tr>
<tr>
<td>eNOS TT</td>
<td>6 (11.5)</td>
<td>1 (1.6)</td>
<td>0.061</td>
<td>2.16 (1.02–4.54)</td>
</tr>
</tbody>
</table>

|                | TT+GT (n = 59.6)  | Control (n = 64) | p     | OR (95% CI) |

Data are presented as n (%), CI: Confidence interval, G: Guanine, OR: Odds ratio, T: Thymine

<table>
<thead>
<tr>
<th></th>
<th>Glucose (mg/dL)</th>
<th>Total cholesterol (mg/dL)</th>
<th>Triglyceride (mg/dL)</th>
<th>LDL cholesterol (mg/dL)</th>
<th>HDL cholesterol (mg/dL)</th>
<th>Creatinine (mg/dL)</th>
<th>Initial troponin (ng/mL)</th>
<th>Maximum troponin (ng/mL)</th>
<th>Leukocyte (x10/μL)</th>
<th>Hemoglobin (g/dl)</th>
<th>Platelet (x10/μL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No-reflow (n = 52)</td>
<td>173.5 ± 95.7</td>
<td>191.3 ± 36.3</td>
<td>134.9 ± 58.5</td>
<td>125.5 ± 33.3</td>
<td>44.9 ± 11.4</td>
<td>0.92 ± 0.31</td>
<td>5.5 ± 8.1</td>
<td>16.9 ± 15.7</td>
<td>12.5 ± 3.9</td>
<td>13.8 ± 2.1</td>
<td>247 ± 64</td>
</tr>
<tr>
<td>Control (n = 64)</td>
<td>141.7 ± 72.4</td>
<td>204.3 ± 47.4</td>
<td>144.4 ± 81.6</td>
<td>140.8 ± 42.1</td>
<td>41.2 ± 10.8</td>
<td>0.84 ± 0.17</td>
<td>3.1 ± 6.5</td>
<td>6.5 ± 8.0</td>
<td>11.8 ± 3.3</td>
<td>13.6 ± 2.2</td>
<td>258 ± 56</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation. LDL = low-density lipoprotein, HDL = high-density lipoprotein.
liaction [22]. A meta-analysis by Li et al. evaluated 23 studies dealing with the Glu298Asp variant and demonstrated that the G allele was lower in patients with different types of CAD than in controls [13]. Likewise, Casas et al. analyzed 26 studies and showed that having a TT allele homozygosity for Asp298 is associated with an increased risk of CAD by 31% [3]. Abdel-Aziz et al. studied the relation between Glu298Asp variant and premature CAD in Egyptians [1]. They concluded that the TT genotype is an independent risk factor for premature CAD. Similarly, Agirbasli et al. investigated eNOS gene variants in Turkish patients with early onset CAD and found that gene-gene and gene-environmental risk factors, including Glu298Asp variant, may predict early onset CAD [2]. Naber et al. tested the effect of Glu298Asp variant on coronary blood flow and showed that coronary vasomotor dysfunction is related with the presence of the T allele [15]. Tian et al. have published a meta-analysis on the associations between eNOS gene Glu298 Asp variant and CAD and their results revealed that eNOS gene Glu298 Asp variant is a risk factor for the development of CAD [26].

Gupta et al. have recently reported that eNOS gene Glu298 Asp variant is associated with coronary slow flow phenomenon (CSFP), and although heterozygous GT + homozygous TT allele are significantly prevalent in patients with CSFP, homozygous TT allele has more significant association with CSFP [8]. They also pointed out that there is a relationship between NO levels and eNOS gene Glu298 Asp variant; NO levels decrease linearly in order of GG, GT, TT [8]. In their model, GT allele was studied together with TT allele, TT allele was more prevalent than GT+TT combination. Our results on TT allele are consistent with their study but do not support the importance of GT allele.

The no-reflow phenomenon is related with poor clinical outcomes [18]. In no-reflow group, mortality rate, Gensini and Syntax scores, and maximum troponin levels were higher than those without no-reflow. Recent studies demonstrated that STEMI patients who developed no-reflow had higher syntax scores [14, 20]. Our results are consistent with these studies. In the pathogenesis of no-reflow phenomenon, the pathogenetic components supported include distal atherothrombotic embolization, ischemic injury, reperfusion injury and susceptibility of the coronary microcirculation to injury [20]. Endothelial NOS may affect the susceptibility of coronary microcirculation to injury via altering the level of NO efficacy.

Our study does have some limitations. The main limitations of our study were its single-centered basis and relatively small patient population size. On the other hand, as genetic variants distribution differs between populations, the homogeneity of the group could be treated as the value of the study. Moreover, we were not able to evaluate the association between NO activity and eNOS gene Glu298 Asp variant. Serum level and the activity of NO could not be studied for the evaluation of endothelial functions due to technical and financial difficulties. Although no-reflow phenomenon is accepted as a multifactorial disorder that may develop during elective or primary PCI, variants in eNOS gene might be a risk factor for the development of the no-reflow phenomenon in STEMI setting. It should be kept in mind that the distribution of eNOS gene variants may differ in populations from various ethnicities. These results support the rationale for further studies with larger sample sizes to investigate the relationship between gene variants and no-reflow phenomenon.

CONCLUSION

The results of this preliminary study indicate that there is an association between Glu298Asp variant in eNOS gene and the development of the no-reflow phenomenon in STEMI setting. The presence of homozygous TT allele may contribute to tendency to the development of no-reflow phenomenon. The screening for the T allele may be useful in predicting no-reflow. Large scale and comprehensive studies are needed to validate these results.

REFERENCES

[2] Agirbasli M., Guney A.I., Ozturhan H.S., Agirbasli D., Ulucan K., Sevinc D., Kirac D., Ryckman K.K., Williams S.M.: Multifactor dimensionality reduction analysis of MTHFR, PAI-1, ACE, PON1 and eNOS gene Glu298 Asp variant in predicting no-reflow. Large scale and comprehensive studies are needed to validate these results.
[8] Gupta M.D., Akkarappaty C., Girish M.P., Kumar R., Rain M., Tyagi S., Qadar Pasha M.A.: Association between the Glu298Asp and 4b/4a polymorphisms of the eNOS gene and Syntax scores, and maximum troponin levels were higher than those without no-reflow. Recent studies demonstrated that STEMI patients who developed no-reflow had higher syntax scores [14, 20]. Our results are consistent with these studies. In the pathogenesis of no-reflow phenomenon, the pathogenetic components supported include distal atherothrombotic embolization, ischemic injury, reperfusion injury and susceptibility of the coronary microcirculation to injury [20]. Endothelial NOS may affect the susceptibility of coronary microcirculation to injury via altering the level of NO efficacy.

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The authors have no potential conflicts of interest to declare.