Plasma Homocysteine Level and Its Genotypes as a Risk Factor for Coronary Artery Disease in Patients Undergoing Coronary Angiography

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Abstract

Aims- Hyperhomocysteinemia has recently been identified as a risk for coronary artery disease (CAD). Some genetic variants such as C677T polymorphism are postulated in this regard. We studied the relation between hyperhomocysteinemia and the above genetic variant and the risk of CAD and also the number of involved vessels.

Methods- In total, there were 90 patients: 45 with angiographically documented CAD and 45 with the clinical manifestations of CAD but negative angiography. The blood homocystein level was measured using the ELISA and C677T polymorphism using the PCR method.

Results- The homocystein level was significantly higher in the case group (p value=0.00), but it did not show any correlation between its level and the extent of CAD. The case group was more homozygote in C677T allele but again it had no relation to the extent of CAD.

Conclusion- Hyperhomocysteinemia acts as a CAD risk factor and whilst its presence increases the risk, it does not predict the extent of it (Iranian Heart Journal 2011; 12 (1):17-21).

Keywords: Hyperhomocysteinemia ■ Genotype ■ Risk factor

Elevated plasma homocysteine levels are known to be associated with a greater risk of coronary artery disease (CAD). Molecular defects (C677T Polymorphism) in the methylenetetrahydrofolate reductase (MTHFR) gene might be associated with hyperhomocysteinemia. The correlation between elevated plasma homocysteine level and its genotypes as a risk factor for CAD and the extent of vessel involvement (single-, two, or three-vessel disease) was the aim of this study.

Homocysteine, produced as an intermediate product in methionine metabolism, is sulfur-containing amino acid with three key enzymes contributing in its metabolism: cystathionine β synthetase, methyltetrahy drofolate homocysteine methyltransferase, and MTHFR.

Methods

According to the clinical manifestation or non-invasive test results compatible with CAD, 90 patients (65 men and 25 women, 25 to 78 years old; mean= 56.2±10.4) who were candidate for
coronary angiography clinically were selected. These patients were admitted to Ekbatan Hospital, Hamedan, IRAN, between 2005 and 2006. The subjects underwent coronary angiography and were divided into two groups (case and control).

The subjects in the case group were divided into three subgroups on the basis of the number of stenotic coronary arteries. The case and control groups were matched in terms of the conventional risk factors of CAD. To rule out the dependency of homocysteine level to renal failure, folic acid consumption, multivitamin therapy, and post-menopausal hormone replacement therapy, these items were considered as excluding criteria.

In the 90 enrolled patients, fasting venous blood sample was drawn and plasma homocysteine level was measured using the ELISA and genotype was analyzed using the PCR methods. The distribution of C677T mutation in MTHFR gene as the most common hereditary risk factor leading to elevated homocysteine levels was thereafter analyzed. Three MTHFR genotypes for C677T mutation (cc, tt, and ct) were assessed using the PCR method. The relation between the C677T genotype of MTHFR and severity of CAD was subsequently assessed via a linear trend test. The quantitative data were analyzed and expressed as mean±SD.

All the patients filled a complete informed consent, and the study was conducted under the supervision of Hamedan University ethics committee in all the aspects.

**Results**

Table I demonstrates that the plasma homocysteine levels in the case and control subjects were 22.3 ± 6.1 and 10.6 ± 5.5, respectively. There was no significant difference between the homocysteine level between the three subgroups of cases in terms of the number of stenotic coronary arteries (p value=0.00, F=36.7, df=3, 19±4.8, 22.5±5.3, 25.7±6.6, respectively).

In 45 subjects of the case group with CAD, the frequencies of homozygote (cc and tt) genotypes in the three subgroups of single- vessel, two-vessel, and three-vessel disease were 38.2%, 35.3%, and 26.5%, whereas the frequencies of heterozygote genotype (ct) were 27.3 %, 27.3%, and 45.5%, respectively.

**Table I. Comparison between average total plasma homocysteine levels in both case and control groups**

<table>
<thead>
<tr>
<th>Coronary artery disease (n=45)</th>
<th>Homocysteine Average(µmol/L)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal and minimal coronary artery disease</td>
<td>22.3±6.1</td>
<td></td>
</tr>
</tbody>
</table>

**Table II. Comparisons between averages total plasma homocysteine levels in both case and control groups**

<table>
<thead>
<tr>
<th>The number of stenotic vessel Coronary artery (n=4)</th>
<th>Homocysteine Average(µmol/L)</th>
<th>P value=0.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal and minimal coronary artery disease</td>
<td>10.6±5.5</td>
<td></td>
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</table>
The assessment of the distributions of c allele in the 45 subjects in the three subgroups in terms of the number of stenotic coronary arteries as single-, two-, and three-vessel disease was 38.6%, 35.7%, and 25.7%, respectively. When the genotype frequency was compared between the patients with different numbers of stenotic coronary arteries, the frequency of homozygote genotypes was not significantly higher in the patients with three-vessel disease (26.5%) than in the patients with single- or two-vessel disease (38.2% and 35.3%, respectively, \( p \) value=0.49). A comparison of the homozygote and heterozygote genotype between every affected subgroup showed that the majority of the patients belonged to the homozygote category (single-vessel disease: 38.2% vs. 27.5%, two-vessel disease: 35.3 vs. 27.3%, three-vessel disease: 26.5% vs. 45.5%).

### Table III. Comparison of genotype’s frequencies (cc, ct, tt) distribution in case group (in terms of the number of stenotic vessels)

<table>
<thead>
<tr>
<th>The number of stenotic vessel</th>
<th>Homozygote (cc,tt genotype)</th>
<th>Heterozygote (ct genotype)</th>
<th><em>P value</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-vessel disease n=15</td>
<td>(38.2%) 13</td>
<td>(27.3%) 3</td>
<td>( p ) value=0.49 ( df=2, hi=1.40 )</td>
</tr>
<tr>
<td>Two-vessel disease n=15</td>
<td>(35.3%) 12</td>
<td>(27.3%) 3</td>
<td></td>
</tr>
<tr>
<td>Three-vessel disease n=15</td>
<td>(26.5%) 9</td>
<td>(45.5%) 5</td>
<td></td>
</tr>
</tbody>
</table>

* Chi-Square

The frequency of c allele in these three mentioned subgroups was 38.6%, 35.7% and 25.7% respectively.

The frequency of t allele in these three mentioned subgroups was 33.3%, 33.3% and 13.2% respectively.

**Discussion**

The role of elevated plasma homocysteine level as a risk factor for CAD and the most common genetic mutation (C677T in MTHFR gene) causing hyperhomocysteinemia were the main purposes...
of this survey. We confirmed that the plasma homocysteine level was significantly higher in subjects with at least one stenotic coronary artery, which is comparable to that in the Framingham study.\textsuperscript{5}

Molecular defects in genes encoding enzymes involved in homocysteine metabolism may account for hyperhomocysteinemia as an independent risk for CAD. The most common polymorphism (C677T) in the MTHFR gene may be associated with hyperhomocysteinemia and CAD in some populations. Homozygous individuals for the allele C677T–MTHFR have significantly higher risk for CAD.

In the past, some studies demonstrated that elevated plasma homocysteine level was in a close association with premature atherothrombosis, leading to cardiovascular events.\textsuperscript{6}

Hyperhomocysteinemia was recently believed to have a key role in premature atherosclerosis and also CAD.\textsuperscript{1, 2, 6, 7} Recent studies have shown that high homocysteine levels are an independent prognostic index for the development of atherosclerosis in dyslipidemic patients.\textsuperscript{3, 4, 5}

High homocysteine levels are related to high blood pressure in the general population,\textsuperscript{6, 7} in diabetics,\textsuperscript{8, 11} and probably in patients with multi-vessel disease.\textsuperscript{9} According to the some studies, the elevated HC level was an independent risk factor for deep vein thrombosis, new stroke, and abortion.\textsuperscript{11, 13, 14, 15, 16}

Active management of hyperhomocysteinemia decreases the mortality rate, revascularization need, and non-fatal myocardial infarction.\textsuperscript{12, 17} It seems to be a positive correlation between the plasma homocysteine level and other known modifiable risk factors of CAD, especially smoking and hypertension.\textsuperscript{4, 10, 11}

Although the precise mechanism of hyperhomocysteinemia as an atherogenic factor has yet to be fully elucidated, various in vitro studies proposed some mechanisms.\textsuperscript{2} Homocysteine has direct toxic effect on cultured endothelial cells, which is prevented by catalyses.\textsuperscript{18, 19, 20} Free radical production during hyperhomocysteinemia plays a major role in endothelial dysfunction.\textsuperscript{21, 22, 23}

Furthermore, homocysteine induces cyclin D and cyclin A expression and stimulates vascular smooth muscle cell proliferation.

It also enhances endothelial cell associated factor 5 activity\textsuperscript{24} and inhibits thrombomodulin surface expression,\textsuperscript{25} protein C activation,\textsuperscript{26} tissue-type plasminogen activator binding,\textsuperscript{26} and anticoagulant heparin sulfate expression in endothelial cells.

It also shows an increase in thromboxane A2 formation in platelets.

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**Conflicts of interest**

None of the authors has any conflict of interest.

**References**


The Effect of Primary Bolus Dose of Pancuronium versus Cisatracurium without Maintenance Dose on Extubation Time in Adult Coronary Artery Bypass Grafting

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Abstract

Background- Given the importance of the effect of muscle relaxants on the extubation time in coronary artery bypass grafting (CABG) patients, we sought to assess the difference in “time to extubation” and “intensive care unit (ICU) length of stay” between the primary bolus doses of Pancuronium and Cisatracurium without using the maintenance dose of them during surgery.

Methods- This double blind clinical trial divided 110 patients into two equal groups receiving either Cisatracurium or Pancuronium. The patients’ surgical and cardiopulmonary bypass variables were evaluated, and the extubation time and ICU length of stay were compared between the two groups.

Results- There was no difference between the two groups regarding the depth of anesthesia, train-of-four (TOF) scores at the beginning of anesthesia, and the surgical and cardiopulmonary bypass variables. However, the Cisatracurium patients were extubated earlier and had a shorter ICU length of stay than the Pancuronium patients.

Conclusion- An appropriate depth of anesthesia facilitates the administration of the induction dose of Cisatracurium, which confers earlier extubation and shorter ICU length of stay by comparison with Pancuronium (Iranian Heart Journal 2011; 12 (1):22 -26).

Keywords: coronary artery bypass grafting ■cisatracurium■ pancuronium■extubation

One of the principal postoperative concerns in patients undergoing cardiac surgery is the time interval between patient entry to the intensive care unit (ICU) and extubation. This is primarily influenced by the anesthetic agents