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Plasma fibrinogen level may predict critical coronary artery stenosis in young adults with myocardial infarction

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Abstract

Background: *This study aims to determine the role of hematological variables in determining critical coronary artery stenosis in young adults with myocardial infarction.*

Methods: *This study includes 76 of 1,804 patients who applied to our hospital between January 2001 and December 2005. All were under 35 years old, diagnosed as acute myocardial infarction with clinical and laboratory findings, and had coronary angiography. Study patients were divided into two groups: those having critical coronary artery lesions (group I) and those having normal coronary arteries (group II). Then we compared these groups for age, sex, body mass index, risk factors, plasma protein C, protein S, antithrombine III and fibrinogen. Student t test, the χ^2 test, Fisher's exact test and Mann Whitney U test were used.*

Results: *There were no differences between the two groups in terms of hypertension ($p = 0.70$), smoking ($p = 0.50$), hyperlipidemia ($p = 0.09$), body mass index ($p = 0.14$), family history ($p = 0.10$), plasma protein C ($p = 0.08$), protein S ($p = 0.35$) or antithrombine III ($p = 0.60$). Plasma fibrinogen levels were significantly higher in group I than in group II ($p = 0.001$).*

Conclusions: *Our study shows that high plasma fibrinogen levels may be used as a predictor of critical coronary artery lesions in young patients with acute myocardial infarction.* (Cardiol J 2009; 16, 4: 317–320)

Key words: myocardial infarction, young patients, hematological variables, predictive value of tests

Introduction

Acute myocardial infarction (AMI) is an irreversible myocardial injury and necrosis caused by serious and long term ischemia. It is generally seen in middle aged men with high risk factors for coronary artery disease. Only 4% of patients with AMI are under 40 years of age [1]. Coronary anatomy is normal in 30% of young AMI patients [2]. The presence of normal coronary anatomy is related to coronary vasospasm, embolism from endocardium or heart vessels, platelet aggregation or spontaneous lysis of thrombus [3]. Due to the high rate of normal coronary angiography in young patients, we wanted to find parameters predicting early coronary artery lesion. So, we aimed to evaluate the relationship between coronary anatomy and risk factors, clinical properties, plasma fibrinogen, protein C, protein S, antithrombine III (AT III) levels to determine coronary artery lesion in patients under 35.

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Methods

Patient population

This study includes 76 of 1,804 patients under 35 years old and admitted to our hospital with a diagnosis of AMI between January 2001 and December 2005. Written informed consent was obtained from all subjects and the study was approved by the local bioethical committee. Patients on anticoagulants or who had hematological and connective tissue diseases were excludued.

AMI is diagnosed where there are at least two of following:

— chest pain longer than 30 minutes which does not respond to nitrates;
— in 12-lead electrocardiography, a new Q wave longer than 40 ms and/or ST segment elevation 0.1 mV on at least two extremity derivations or 0.2 mV on precordial derivation;
— a 1.5 times, or higher, increase in serum creatin-phosphokinase-MB.

Cardiac catheterization

Coronary angiography was performed with Phillips Multidiagnosis C2 device using either the Sones or Judkins technique. Above 50% obstruction in coronary vessel was accepted as critical coronary artery stenosis. Left ventriculography was performed with standard techniques. Study patients were divided into two groups: with critical coronary artery stenosis (group I) and with normal coronary arteries (group II), due to their coronary angiographies.

Analysis of hematological profile

Blood samples were taken four weeks after myocardial infarction. After clear venipuncture of an antecubital vein, the blood was put in tubes containing 0.11 M sodium citrate and centrifuged for 20 minutes at 1000 g. The plasma was stored at –30°C until assayed for proteins C and S and fibrinogen (0–12 months). Assay of protein C, protein S was performed by ELISA (Diagnostica Stago, France) and AT III by chromogenic substrate method (Diagnostica Stago, France). Fibrinogen levels were determined by the method of Clauss (Diagnostica Stago, France). Since fibrinogen levels can be affected by AMI, it was studied after four weeks of AMI.

We evaluated the presence of hypertension (systolic blood pressure; 140 mm Hg and/or diastolic blood pressure; 90 mm Hg and/or receiving antihypertensive agents), hyperlipidemia (serum total cholesterol level; 220 mg/dl, or 5.69 mmol/L, and/or triglyceride level; 150 mg/dL, or 1.70 mmol/L, and/or receiving lipid-lowering agents), diabetes mellitus (plasma glucose; 127 mg/dL, or 7.06 mmol/L, and/or receiving glucose-lowering agents).

Groups were compared for hypertension, diabetes mellitus, hyperlipidemia, smoking, family history, age, sex, body mass index, plasma fibrinogen, protein C, protein S and AT III levels.

Statistical analysis

Quantitative values are expressed as mean ± SD and were compared using unpaired Student t test. The χ^2 test, Fisher's exact test and Mann Whitney U test were used to analyze categorical data. For all tests, $p > 0.05$ was designated nonsignificant, and a value of $p < 0.05$ was considered statistically significant. The Statistical Package for Social Sciences (SPSS) statistical software package (version 10.0, Inc., Chicago, USA) was used to perform all statistical calculations.

Results

Seventy six of 1,804 patients were under 35 years old. All were male, with an average age of 30.2 ± 4.8 years. None had diabetes mellitus. According to the coronary angiography, 47% (group II, n = 36) had normal coronary arteries and 53% (group I, n=40) had critical coronary artery stenosis. In group I, 32 cases had one, six had two and two had three-vessel diseases. There were no significant differences between the two groups in terms of hypertension ($p = 0.70$), smoking ($p = 0.50$), hyperlipidemia ($p = 0.09$), protein C ($p = 0.08$), protein S ($p = 0.35$), AT III ($p = 0.60$), body mass index ($p = 0.14$), or family history ($p = 0.10$). Plasma fibrinogen levels were significantly higher in group I than in group II ($p = 0.001$) (Tables 1 and 2).

Discussion

Our study showed that high plasma fibrinogen levels may be used as a predictor of coronary artery lesions in young patients with AMI. Acute myocardial infarction is generally caused by thrombus arising secondary to the rupture of the atherosclerotic plaque in coronary artery and usually affects adults over 40. Only 4% of AMI patients are under 40 [1, 4]. Young patients have different characteristics in terms of risk factors profile, physiopathological mechanisms, clinical presentation, angiographic findings and prognosis.

Some researchers have claimed that the presence of normal coronary anatomy in young patients

Table 1. Clinical characteristics and prevalence of conventional coronary risk factors in group I and group II; p > 0.05.

Parameters	Group I (n = 40)	Group II (n = 36)
Age	30.6 ± 4.4	31.2 ± 4.8
Hypertension	14 (35%)	10 (28%)
Hyperlipidemia	20 (50%)	14 (39%)
Smoking	32 (80%)	36 (100%)
Family history	12 (30%)	8 (22%)
Body mass index [kg/m^2]	29.1 ± 3.9	28.6 ± 4.0

Table 2. Comparison of hemotological parameters in group I and group II.

Hemotological parameters	Group I (n = 40)	Group II (n = 36)	P
Fibrinogen [mg/dL]	410.8± ± 116.9	298.3± ± 78.2	0.001
Protein C (%, activity)	128 (122–133)	126 (124–130)	> 0.05
Protein S (%, activity)	128 (120–128)	120 (117–124)	> 0.05
Antithrombine III (%, activity)	109 (107–111)	108 (106–110)	> 0.05

with AMI is 17–30% [2, 3]. According to them, normal coronary arteries after AMI is related to coronary vasospasm, embolus arising from endocardium or heart vessels, platelet aggregation, coronary artery lesions invisible by angiography or spontaneously lysised thrombus [5]. In our study, we also found that 47% had normal coronary arteries, 42% had one-vessel, 8% had two-vessel and 3% had three-vessel disease.

Smoking is the most important and commonest risk factor in young patients. It is reported that smoking is a risk factor in 24–56% of patients with AMI over the age of 40 and in 73–90% of patients under 40 with AMI [6]. Smoking is the commonest risk factor in myocardial infarction patients with normal coronary anatomy. Smoking impairs endothelium derived vasodilatory mechanisms and causes vasospasm in coronary arteries [7, 8]. Vasospasm is supposed to be the most important physiopathological mechanism in these patients [9, 10]. Family history is another important risk factor for early coronary artery disease [11]. In our study, we found that smoking and early coronary artery disease positive in 80% and 30% of patients respectively. Clinical presentation of coronary artery disease in young adults is generally AMI, and this may be a consequence of more complex coronary artery lesions [12]. Disorders involving coagulation system should also be considered in the ethiology. Protein S is an endothelium derived protein C cofactor and both proteins function as coagulation inhibitors. Lack of these proteins, AT III and high levels of plasminogen activator inhibitor-1 may be responsible for AMI [13, 14].

In a study comparing young AMI patients to normal healthy cases, there were no significant differences in protein C, protein S, plasminogen, AT III and factor VII levels among the coronary artery lesion group, the normal coronary artery group and the normal healthy group [15]. We studied these haemotological risk factors, but we also could not find any significant difference in protein C, S and AT III levels between our two groups.

Meade et al. [16] first reported an association between hemostatic parameters and cardiovascular death. In their prospective study, they found that people who died of coronary heart disease had higher plasma levels of fibrinogen on presentation compared to the patients who survived. They also showed that the association of cardiovascular mortality with fibrinogen levels was independent of established coronary heart disease risk factors and stronger than the association with serum cholesterol. Lowe et al. [17] reported that levels of fibrinogen were higher in patients with two or three stenosed coronary arteries than in those with a single stenosed artery or no stenosis. Wilhelmsen et al. [18] reported on the synergistic effect of fibrinogen levels and blood pressure on stroke and suggested that high plasma fibrinogen is a risk factor for stroke and myocardial infarction.

Recently it has been demonstrated that plasma fibrinogen is significantly associated with a high quantity of coronary artery calcifications, a marker of preclinical coronary atherosclerosis [19]. Fibrinogen is also involved in a number of mechanisms (endothelial cell injury, platelet aggregation, and plasma viscosity) that play a central role in the formation of thrombi: first, it is an important determinant of platelet aggregation, binding to the platelet membrane glycoprotein receptor IIb/IIIa; secondly, fibrinogen plays a crucial role in the coagulative process since it represents the physiological substrate of thrombin, hyperfibrinogenemia may induce a hypercoagulative state by a procoagulant imbalance, leading to the formation of insoluble fibrin [20, 21]; thirdly, fibrinogen, due to its large and elongated molecular form and to its binding capacity, is the

major determinant of blood viscosity, decreasing microcirculatory blood flow and capillary blood flow velocity, thus favoring leukocyte and red blood cell adhesion with consequent microvascular ischemia.

The importance of hyperfibrinogenemia as a risk factor for atherothrombosis is confirmed by a number of previous studies showing an association between high fibrinogen levels and other risk factors for cardiovascular disease including age, smoking, cholesterol, physical inactivity, arterial hypertension, diabetes [22–24], angiographically determined number and severity of coronary stenosis [25, 26].

Our study found that plasma fibrinogen level in young patients with myocardial infarction and significant coronary artery lesion is higher than young patients with myocardial infarction who have normal coronary arteries.

Limitations of the study

There may be two limitations for this study. Normal coronary arteries were described by coronary angiography; intravascular ultrasonography was not used. Secondly, the number of patients in our study was relatively small.

Conclusions

High plasma fibrinogen levels may be used as a predictor of critical coronary artery stenosis in young patients with AMI. We suggest our findings should be supported by larger studies before being put into practice.

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References

1. Lamm G. The epidemiology of acute myocardial infarction in young age groups. In: Roskamm H ed. Myocardial infarction at young age. Springer-Verlag, Berlin 1981: 5–7.
2. Uhl GS, Farrel PW. Myocardial infarction in young adults: Risk factors and natural history. Am Heart J, 1983; 105: 548–553.
3. Roskamm H, Gohlke H, Sturzenhofecker P. Myocardial infarction at a young age (under 40 years). Int J Sports Med, 1984; 5: 1–10.
4. Fournier JA, Sanchez A, Quero J, Fernandez-Cortacero JA, Gonzalez-Barrero A. Myocardial infarction in men aged 40 years or less: A prospective clinical-angiographic study. Clin Cardiol, 1996; 19: 631–636.
5. Davia JE, Hallal Fj, Cheitlin MD, Gregoratos G, McCarty R, Foote W. Coronary artery disease in young patients: Arteriographic and clinical review of 40 cases aged 35 and under. Am Heart J, 1974; 77: 689–696.
6. Barbash GI, White HD, Modan M et al. Acute myocardial infarction in young - the role of smoking. The Investigators of the International Tissue Plasminogen Activator/Streptokinase Mortality Trial. Eur Heart J, 1995; 16: 313–316.
7. Williams M, Rentieaux N, Low C. Myocardial infarction in young people with normal coronary arteries. Heart, 1998; 79: 191–194.
8. Braunwald E. Coronary spasm and acute myocardial infarction. New possibility for treatment and prevention. N Eng J Med, 1978; 299: 1301–1302.
9. Hosoi T, Koyama Y, Tange S. Acute myocardial infarction due to vasospasm in a 13 year old boy. Jpn Circ J, 1997; 61: 536–542.
10. Takashiba K, Matsuda Y, Hamada Y et al. Recurrence of myocardial infarction related to diffrent vessels in a patient with diffuse coronary artery spasm without underlying severe organic stenosis. Clin Card, 1988; 11: 265–267.
11. Hoit BD, Gilpin EA, Henning H et al. Myocardial infarction in young patients. An analysis by age subsets. Circulation, 1986; 74: 712–721.
12. Klein LW, Agarwal JB, Herlich MB, Leary TM, Helfant RH. Prognosis of symptomatic coronary artery disease in young adults aged 40 years or less. Am J Cardiol, 1987; 60: 1269–1272.
13. Manzar KJ, Padder FA, Conrad AR, Freeman I, Jonas EA. Acute myocardial infarction with normal coronary artery: A case report and review of literature. Am J Med Sci, 1997; 314: 342–345.
14. Hamsten A, de Faire U, Walldius G. Plasminogen activator inhibitor in plasma: Risk factor for recurrent myocardial infarction. Lancet, 1987; 2: 3–9.
15. Dacosta A, Tardy-P B, Isaaz K. Prevalence factor V Leiden (APCR) and other inherited trombophilias in young patients with myocardial infarction and normal coronary arteries. Heart, 1998; 80: 338–340.
16. Meade TW, North WR, Chakrabarti R. Haemostatic function and cardiovascular death: Early results of a prospective study. Lancet, 1980; 1: 1050–1054.
17. Lowe GDO, Drummond MM, Lorimer AR. Relationship between extent of coronary artery disease and blood viscosity. Br Med J, 1980; 1: 673–674.
18. Wllhelmsen K, Svardsudd K, Koraan-Bengaten K, Larsson B, Wolln L, Tibblin G. Fibrinogen as a risk factor for stroke and myocardial Infarction. N Engl J Med, 1984; 311: 501–505.
19. Bielak LF, Klee GG, Sheedy PF, Turner ST, Schwartz RS, Peyser PA. Association of fibrinogen with quantity of coronary artery calcification measured by electron beam computed tomography. Arterioscler Thromb Vasc Biol, 2000; 20; 2167–2171.
20. Folsom AR. Fibrinogen and cardiovascular risk markers. Blood Coagul Fibrinolysis, 1999; 10 (suppl. 1): S13–S16.
21. Di Minno G, Cerbone A, Margaglione M, Vecchione G, Grandone E, Mancini M. Fibrinogen and mechanisms of thrombosis. A difficult link. Eur J Epidemiol, 1992; 8 (suppl. 1): S88––S91.
22. ECAT Angina Pectoris Study Group. Baseline association of haemostatic factors with the extent of coronary risk factors in 3000 patients with angina pectoris undergoing coronary angiography. Eur Heart J, 1993; 14: 8–17.
23. Tataru MC, Schulte H, von Eckardstein A, Heinrich J, Assmann G, Koehler E. Plasma fibrinogen in relation to the severity of arteriosclerosis in patients with stable angina pectoris after myocardial infarction. Coron Artery Dis, 2001; 12: 157–165.
24. Engstrom G, Stavenow L, Hedblad B. Inflammation-sensitive plasma proteins, diabetes, and mortality and incidence of myocardial infarction and stroke. A population-based study. Diabetes, 2003; 52: 442–447.
25. Gil M, Zarebinski M, Adamus J. Plasma fibrinogen and troponin I in acute coronary syndrome and stable angina. Int J Cardiol, 2002; 83: 43–46.
26. Baller D, Miche A, Prohaska W. Fibrinogen and leucocyte counts as a function of the angiographic and clinical degree of coronary artery disease. In: Ernst E, Koenig W, Lowe GD, Meade TW eds. Fibrinogen: A new cardiovascular risk factor. Blackwell, Wien 1992: 207–213.