5A/6A Polymorphism of the Stromelysin-1 Gene and Angiographic Restenosis After Coronary Artery Stenting

Kuan-Rau Chiou[1,4], Sheng-Liang Chung[2], Min-Ji Charng[3,4]*

[1]*Division of Cardiology, Department of Medicine, Kaohsiung Veterans General Hospital,* [2]*Division of Cardiology, Department of Medicine, Lo Tung Poh-Ai Hospital,* [3]*Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, and* [4]*Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.*

Background: Coronary stent deployment is a major advance in interventional treatment, but 20–40% of patients still develop in-stent restenosis (ISR) due to neointimal hyperplasia. Genetic factors play a role in restenosis. This study investigated the frequency of 5A/6A polymorphism in the promoter of the stromelysin-1 gene, and the issue of whether it contributes to restenosis among patients receiving coronary stent in the Chinese population in Taiwan.
Methods: We investigated 344 symptomatic patients after successful coronary stent placement. All patients received repeated angiography after 6 months, or earlier if clinically indicated. Angiographic restenosis was defined as ≥ 50% diameter stenosis at follow-up. Genotyping for stromelysin-1 promoter was based on a polymerase chain reaction technique.
Results: The stromelysin-1 gene promoter genotypes 5A5A, 5A6A, and 6A6A were distributed in 3.5%, 22.7%, and 73.8% of patients, respectively. The frequency of the 6A allele was 0.85. There was no significant difference in angiographic ISR between the non-6A6A and 6A6A groups (28.9% and 37.0%, respectively, $p = 0.165$). However, subgroup analysis revealed a significant difference in patients according to angina status. Among the 5A5A and 5A6A genotype groups, patients with unstable angina had significantly higher ISR rates than those with stable angina (48% vs 21.5%, $p = 0.013$). On the other hand, among patients with stable angina, those with a 6A6A genotype had a higher ISR rate than those with a non-6A6A genotype ($p = 0.029$), making the 6A6A genotype an independent predictor of ISR (odds ratio, 2.57; 95% confidence interval, 1.22–5.41; $p = 0.013$).
Conclusion: There is a low frequency of the stromelysin-1 promoter 5A allele in the Chinese population in Taiwan. How stromelysin-1 5A/6A polymorphism affects ISR appears to be linked to angina status. These results merit further study to identify patients carrying genotypes which put them at increased risk of ISR, and which matrix metalloproteinase inhibitors or drug-eluting stents are more effective for those at risk. [*J Chin Med Assoc* 2005;68(11):506–512]

Key Words: angioplasty, genetics, restenosis, stent, stromelysin-1

Introduction

Percutaneous coronary intervention (PCI) with stent implantation significantly reduces the incidence of complications and restenosis compared with balloon angioplasty alone, via an improved post-procedure luminal diameter and an abrogation of the constrictive remodeling of the artery. However, stent-related arterial injury results in intense inflammatory responses, leading to severe neointimal proliferation and matrix accumulation, which, in 20–40% of patients, ends up as clinically significant in-stent restenosis (ISR).[1–3] Several angiographic and patient-related factors, such as small coronary arteries, lesion complexity, the

*Correspondence to: Dr. Min-Ji Charng, Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: mjcharng@vghtpe.gov.tw • Received: February 17, 2005 • Accepted: September 13, 2005

©2005 Elsevier. All rights reserved.

presence of diabetes mellitus and acute coronary syndrome, have been identified to be associated with ISR. However, these risk factors cannot fully explain the complex process of ISR.[4] Recent information reveals that genetic factors play a role in the initiation or progression of ISR.[5]

The matrix metalloproteinase (MMP) family and their endogenous tissue inhibitors regulate the accumulation of extracellular matrix, and thus contribute to the rate of growth of atherosclerotic plaques.[6] Stromelysin-1, also known as MMP3, is a key member of the MMP family, with wide substrate specificity, degrading collagen types II, IV and IX, proteoglycans, laminin, fibronectin, gelatins and elastin, as well as having a role in activating other MMPs. Its expression is primarily regulated at the level of transcription.[7,8] In addition, animal study revealed that migration and proliferation of vascular smooth cells and neointimal formation after vessel wall injury of rat carotid arteries was substantially inhibited by antisense oligonucleotides to stromelysin-1 mRNA.[9] Thus, stromelysin-1 is a candidate for influencing vascular remodeling, plaque formation and rupture, and restenosis.

A common adenine insertion/deletion polymorphism (5A/6A) at position –1171 of the human stromelysin-1 gene promoter (National Center for Biotechnology Information SNP identification number rs3025039) influences transcription factor binding and stromelysin-1 promoter activity. *In vitro* promoter activity as well as *in vivo* gene expression of the 6A allele has approximately 50% less promoter strength than that of the 5A allele.[10,11] This lower level of proteolytic activity would favor extracellular matrix deposition because of decreased degradation. Three independent studies found that Caucasian patients carrying the 6A6A genotype had more progression of angiographically detectable lesions in documented coronary artery disease.[12–14] In contrast, increased focal expression and activity of MMP-3 by the 5A allele predispose to plaque instability and rupture in the presence of a high atherosclerotic burden associated with acute coronary syndrome.[15,16] Thus, stromelysin-1 genetic variations contribute to heterogeneity in the presentation and natural history of atherosclerosis.[17] However, little information on the Chinese population has been reported. Accordingly, the purpose of this study was to investigate the allele frequency of stromelysin-1 promoter gene polymorphism (5A/6A) and its possible influences on restenosis after coronary stent implantation in the Chinese population in Taiwan.

Methods

Patient population

The study initially had 435 enrolled patients who underwent successful bare metal stent implantation between January 1999 and July 2002. All stents were implanted using high-pressure adjunct balloon angioplasty (≥ 12 atm) to achieve the targeted stent expansion. All subjects received 300–500 mg ticlopidine (or 75 mg clopidogrel) and 100–325 mg aspirin per day after coronary intervention for at least 3 months. All patients gave written informed consent for the intervention, follow-up angiography and genotype determination. Ninety-one patients (21%) who did not repeat angiography systematically because of advanced age, impaired general condition, or patient preference (without symptoms) were excluded. Therefore, a total of 344 patients were included in the final analysis. The study protocol conformed to the Declaration of Helsinki and was approved by our institution's ethics committee.

Determination of stromelysin-1 genotypes

All blood was collected in Vacutainer EDTA tubes in an overnight fasting state. The stromelysin-1 promoter genotype was analyzed by polymerase chain reaction (PCR) amplification of the genomic DNA extracted from lymphocytes of the stored blood. The sense and anti-sense primers were 5'-GGTTCTCCATTCCTT-TGATGGGGGGAAAGA-3' and 5'-CTTCCTGGA-ATTCACATCACTGCCACCACT-3', respectively. The amplification protocol consisted of an initial denaturation segment at 95°C for 5 minutes. After this, each cycle consisted of 3 segments (94°C for 30 seconds, 61°C for 30 seconds and 72°C for 1 minute). The cycle was repeated 30 times, followed by an additional extension at 72°C for 5 minutes. The amplified fragments were cut with endonuclease TthIII I, which can recognize the sequence 5'-GACNNNGTC-3', in which the DNA template contains 5As (but not 6As) at the polymorphic site. These fragments were then electrophoresed in 4% agarose gel and stained with ethidium bromide.

Angiographic assessment

Quantitative computer-assisted angiographic analysis was performed off-line on angiograms obtained just before and immediately after coronary intervention, and at follow-up, using the automated edge-detection system with CAAS II (Pie Medical, Maastricht, The Netherlands). Operators were unaware of the patients' genotypes. Identical

Download English Version:

https://daneshyari.com/en/article/9296214

Download Persian Version:

https://daneshyari.com/article/9296214

Daneshyari.com