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The E4 Allele of Apolipoprotein E is Associated with Increased Restenosis after Coronary Angioplasty

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The aim of this study is to investigate the influence of the E4 allele of apolipoprotein E (apo E) on restenosis after percutaneous transluminal coronary angioplasty (PTCA). The subjects were 171 male patients with more than 75% luminal diameter stenotic lesions of the coronary artery who had undergone an elective initial PTCA. The PTCA was successful in 164 patients, 157 of whom completed a prospective 5 month coronary angiography (CAG) follow up to assess the degree of restenosis after their surgery. Patients with previous coronary artery bypass grafting surgery (CABG), 3 vessel disease, complete obstruction or calcified lesions of the coronary artery, cerebro-vascular disease (CVD), arteriosclerosis obliterans (ASO), and renal failure with hemodialysis were excluded, leaving 105 patients in the analysis. Subjects carrying the E4 allele (n = 22, Phenotype E4/2 = 2, E4/3 = 19, E4/4 = 1 : E4 group) were well matched with non-carriers (n = 83, Phenotype E2/2 = 0, E3/2 = 4, E3/3 = 79 : E3 group) for clinical, and pre-and post-PTCA angiographic features. The restenosis rates were significantly higher in the E4 group than in the E3 group (patient restenosis rate : 59.1 vs 33.7% $p < 0.05$, lesion restenosis rate : 51.8 vs 30.9% $p < 0.05$). These results suggest that the E4 allele is associated with a higher restenosis rate after PTCA.

Key words : Coronary angioplasty, Restenosis, Apolipoprotein E

INTRODUCTION

Apo E is a protein with a molecular weight of about 34000 daltons consisting of 299 amino acids, is synthesized primarily in the liver, and is secreted as a structural component of very low density lipoprotein (VLDL) and high density lipoprotein (HDL). The chylomicrons are synthesized without apo E in the intestine and then acquire apo E as a major protein constituent in the mesenteric and thoracic duct lymph. Apo E serves as a ligand and mediates the binding of these lipoproteins to their receptors. Lipoprotein binding to the receptors initiates the cellular uptake and degradation of the lipoproteins, by which apo E participates in the regulation of the metabolism of several different plasma lipoproteins and also in cholesterol redistribution among various cells in the body. Apo E is also synthesized by a number of different tissues including the brain, spleen, kidney, adrenals, gonads, macrophages, and astrocytic glia. The roles of extrahepatic synthesized apo E are not well understood, but other functions,unrelated to lipid transport, such as the repair of peripheral nerve injury [19], immunoregulation [31, 49], and modulation of cell growth and differentiation, are becoming known. Apo E has three major isoformes (apo E2, apo E3, apo E4) which are determined by three alleles of the Apo E gene at a single locus (ε 2, ε 3, ε 4, respectively). There are six apo E phenotypes, three homozygous (apo E2/2, E3/3, E4/4) and three heterozygous phenotypes (apo E3/2, E4/2 and E4/3), resulting from the expression of any two of the three alleles [72, 73]. The most common phenotype is apo E3/3 and the most common allele is ε 3. Therefore apo E3 is considered to be the parent form of the protein, and apo E2 and apo E4 are variants which differ by amino acid substitution at one or two sites on the 299 amino acid chain of the apo E3 molecule. Regarding the functional and metabolic dif-

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ferences among the apo E isoforms, apo E2 has defective receptor binding activity and is catabolized more slowly than apo E3, while apo E4 has the same receptor binding activity as apo E3, but is catabolized more rapidly than apo E3 [19]. These differences among the apo E isoforms account for the variability in the plasma lipid levels, and so the E alleles are expected to play a role in the pathogenesis of coronary artery disease (CAD). There are numerous reports that individuals carrying the E4 allele (Phenotype E4/2, E4/3, E4/4) have a higher incidence of CAD [36, 45, 60, 63], a younger onset [7, 29] and higher plasma lipids levels [21, 56, 59, 62] as compared with non-carrier (Phenotypes E2/2, E3/2, E3/3), suggesting differences in the development of CAD or hyperlipidemia among the apo E phenotypes.

On the other hand, PTCA introduced by Gruentzig *et al.* [24] has become comparable in use to CABG for coronary artery recirculation. However, a high rate of restenosis within the first 6 months after PTCA, as much as 30–50%, remains the major problem limiting the long-term efficacy of this procedure [40, 48, 57]. Therefore, a number of studies have sought to elucidate the etiology of restenosis [1, 3, 4, 9, 12, 15, 17, 20, 23, 27, 28, 30, 33, 34, 37, 38, 41, 42, 44, 50, 58, 64, 67–69] Then, owing to similarities between restenosis and atherosclerosis, much attention has focused on the role of various clinical, anatomic and procedure-related risk factors for atherosclerosis [1, 3, 4, 9, 15, 17, 20, 23, 27, 28, 30, 33, 34, 37, 41, 44, 50, 58, 64, 67–69], in predisposing to restenosis. A few reports concerning the influence of apo E phenotypes on restenosis after PTCA have been published, but no conclusion has been reached [18, 54, 65, 66].

The present study was undertaken to investigate the influence of the apo E phenotype or E4 allele on restenosis after PTCA.

SUBJECTS AND METHODS

Subjects

Subjects were 171 male patients with CAD, aged 37 to 83 years, and at least one coronary artery with more than 75% luminal diameter stenosis on CAG. The patients had undergone an elective PTCA on a previously untreated native coronary artery at the Tokai University Hospital since April 1994. Patients who had undergone PTCA in an acute phase of myocardial infarction were not included. The PTCA was successful in 164 patients, and 157 of whom completed a prospective 5 month coronary angiography (CAG) follow up. Patients with CABG (n = 2), 3 vessel disease (n = 10), complete occlusion or calcified lesions of the coronary artery (n = 31), cerebro-vascular disease (CVD, n = 1), arteriosclerosis obliterans (ASO, n = 7) and renal failure with hemodialysis (n = 2) were excluded. The remaining 105 patients were used in the analysis. Informed consent was obtained in every case before PTCA.

Methods

Serum lipid and lipoprotein concentrations were determined in fresh serum samples drawn after a 12 hour overnight fast, just before PTCA. Lipid concentrations in whole serum and in lipoproteins separated by ultracentrifugation [26], were determined by enzymatic methods [52], lipoprotein(a) and apolipoprotein concentrations were measured by enzymimmunoassay [47, 70], and Apo E phenotyping was determined by an isoelectric focusing electrophoresis (IEF)-immunoblotting method [10]. Briefly, isolated and delipidated very low density lipoproteins (VLDL) were subjected to IEF using a pH gradient between pH 4 to 7 and apo E isoforms were detected by immunoblotting with an anti apo E antibody.

CAG findings

Luminal diameter stenosis was measured with calipers and expressed as the mean percent stenosis of measurements made on two orthogonal projections. PTCA was considered successful if it reduced stenosis to less than 50% and was not associated with any major complications, such as myocardial infarction or coronary dissection [8]. Restenosis was defined as the loss of more than 50% of the gain attained by PTCA together with a stenosis greater than 50% of the lumen diameter [30, 40, 44].

Satistical evaluations

All results are expressed as mean ± 1 SD. Difference between the means of two groups was analysed by Chi-square analysis and a probability (p) < 0.05 was considered significant.

RESULTS

[1] Patient characteristics

The number of patients with each apo E phenotype were none with E2/2, 5 with E3/2, 128 with E3/3, 2 with E4/2, 34 with E4/3 and 2 with E4/4, to a total of 38 patients with the E4 allele and 133 patients without it. These apo E phenotypes arise from the expression of two of the three alleles, so the relative frequencies of E2(ε 2), E3(ε 3) and E4(ε 4) allele were 2.0% (7/342 alleles), 86.3% (295/342 alleles) and 11.7% (40/342 alleles) respectively (Table 1), which were in accordance with those in healthy volunteers [19].

The 105 patients used in the analysis of the effect of apo E phenotypes on the restenosis rate after PTCA consisted of 22 patients carrying the E4 allele (Phenotype E4/2 = 2, E4/3 = 19, E4/4 = 1 : E4 group) and 83 without the E4 allele (Phenotypes E2/2 = 0, E3/2 = 4, E3/3 = 79 : E3 group).

There were no significant differences between both groups in age, history of previous myocardial infarction and angina pectoris, other cardiovascular risk factors (Table 2), and medications used (Table 3). Serum levels of lipids, lipoproteins and apolipoproteins except lp(a) were higher in the E4 group than in the E3 group, but the differences were not statistically significant (Table

Table 1 Incidence of Apo-E Phenotype and Apo-E Alleles in Patients who underwent PTCA

Phenotype	n (%)
E2/2	0 (0)
E3/2	5 (2.9)
E3/3	128 (74.9)
E4/2	2 (1.2)
E4/3	34 (19.8)
E4/4	2 (1.2)

Allele	n (%)
ε 2	7 (2.0)
ε 3	235 (86.3)
ε 4	40 (11.7)

Table 2 Group Characteristics

	Apo-E3 group	Apo-E4 group	p
No. of cases	n = 83	n = 22	
Age	60.1 ± 6.4	59.1 ± 5.0	ns
Disease			
Angina pectoris	42 (50.6%)	11 (50.0%)	ns
stable	32	8	
unstable	10	3	
Myocardial infarction	41 (49.4%)	11 (50.0%)	ns
Risk factors			
Hypertension	37 (44.6%)	10 (45.5%)	ns
Hyperlipidemia	37 (44.6%)	13 (59.1%)	ns
II a-Type	6	2	
II b	12	5	
IV	19	6	
Diabetes mellitus	12 (14.5%)	4 (18.2%)	ns
Smokers	58 (79.9%)	16 (72.7%)	ns
Family history of CAD	21 (25.3%)	6 (27.3%)	ns

Table 3 Patient Medications

	Nitrate	Ca-blocker	β-blocker	ACE-I	Anti-plate
Apo-E3 group	97%	100%	11%	15%	96%
Apo-E4 group	95%	95%	15%	24%	100%
p	ns	ns	ns	ns	ns

Table 4 Serum levels of lipids, Lipoproteins and Apolipoproteins in Patient Groups

Serum levels (mg/dl)	Apo-E3 group	Apo-E4 group	p
TC	182.6 ± 16.6	188.4 ± 17.2	ns
TG	151.2 ± 48.6	158.2 ± 53.6	ns
HDL-C	40.4 ± 26.2	42.6 ± 36.8	ns
LDL-C	121.2 ± 24.1	123.6 ± 22.2	ns
Lp (a)	34.2 ± 12.1	31.6 ± 14.2	ns
Apo-A1	106.6 ± 17.8	110.4 ± 40.2	ns
B	107.6 ± 31.0	110.5 ± 32.1	ns
E	5.2 ± 4.2	5.3 ± 5.3	ns

Mean ± SD

Table 5 CAG findings in Patients

	Apo-E3 group	Apo-E4 group	p
No. of patients	83	22	
1 vessel disease	53 (63.9%)	12 (54.5%)	ns
2 vessel disease	30 (36.1%)	10 (45.5%)	ns
Advanced lesions (Long segment lesions/ ≧2 lesions on 1 vessel)	22 (26.5%)	6 (27.3%)	ns
No. of Target lesions	94	27	
LAD	57 (60.6%)	14 (51.9%)	ns
Lcx	17 (18.1%)	4 (14.8%)	ns
RCA	20 (21.3%)	9 (33.3%)	ns

CAG = coronary angiography LAD = Left anterior descending artery
Lcx = Left circumflex artery RCA = Right coronary artery

4). Most patients with unstable angina visited our outpatient clinic within 10 days of onset. The mean duration of stable angina was slightly shorter for the E3 group than for the E4 group (4.2 ± 2.3 months vs 5.0 ± 2.1 months), and also the onset of unstable angina to PTCA was shorter for the E3 group than for the E4 group (28.6 ± 18.5 days vs 32.1 ± 16.6 days). However, these differences were not statistically significant.

In the CAG, the E3 group comprised 53 patients with 1 vessel disease (63.9%) and 30 patients with 2 vessel disease (36.1%). On the other hand, the E4 group comprised 12 patients with 1 vessel disease (54.5%) and 10 patients with 2 vessels disease (45.5%).

Although the incidence of 1 vessel disease was slightly higher in the E3 group than in the E4 group, the difference was not significant. There was no difference in the frequency of patients with advanced lesions such as a long-segment lesion or more than 2 stenotic lesions in 1 vessel (26.5% vs 27.3%). The number of target lesions for

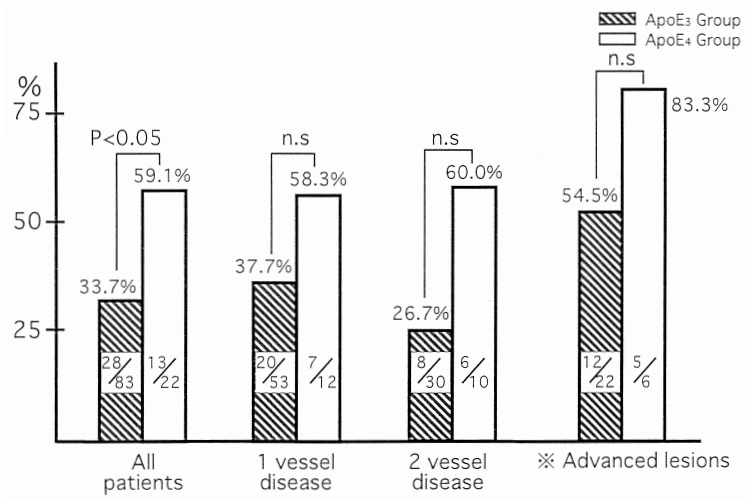

Fig. 1 Restenosis rates in the Apo E3 and E4 groups of Patients
n/n = No. of restenosis cases/all cases
※ Long segment lesions and/or ≧ 2 lesions on one vessel

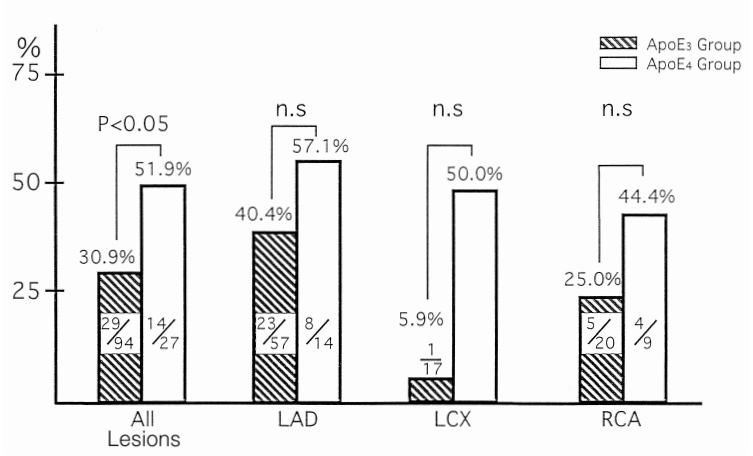

Fig. 2 Lesion restenosis rates in the Apo E3 and E4 groups
n/n = No. of restenosis/all cases

PTCA were 94 in the E3 group and 27 in the E4 group, and their distribution in the coronary artery showed a somewhat higher incidence of LAD in the E3 group, and RCA in the E4 group, but there were no significant differences (Table 5).

[2] Restenosis rate

The mean degree of stenosis before PTCA was 84.6 ± 12.6% in the E3 group and 86.5 ± 11.6% in the E4 group, and those of residual stenosis immediately after PTCA were 19.8 ± 18.4% and 18.9 ± 17.6%, respectively. There were no significant differences in the degree of stenosis in the diameter of the coronary artery either before or after PTCA between both groups.

In the follow-up CAG at 5 months after PTCA, the restenosis rate of the patients was 33.7% (28 of 83 patients) in the E3 group and 59.1% (13 of 22 patients) in the E4 group (Fig. 1), and those of lesions were 30.9% (29 of 94 lesions) in the former and 51.9% (14 of 27 lesions) in the latter (Fig. 2). Both restenosis rates were significantly higher in the E4 group than in the E3 group. The restenosis rates in patients with 1 or 2 vessel disease and also in the lesion on each

Table 6 Characteristics of Patients with and without restenosis

	Restenosis (−)	Restenosis (+)	p
No. of cases	n = 64	n = 41	
age	59.4 ± 4.2	60.7 ± 1.6	ns
Disease			
Angina pectoris	32 (50%)	21 (51.2%)	ns
stable	24	16	
unstable	8	5	
Myocardial infarction	32 (50%)	20 (48.8%)	ns
Risk factors			
Hypertension	30 (46.9%)	17 (41.5%)	ns
Hyperlipidemia	33 (51.6%)	17 (41.5%)	ns
II a-type	5	3	
II b	10	7	
IV	18	7	
Diabetes mellitus	10 (15.6%)	6 (14.6%)	ns
Smokers	44 (68.8%)	30 (73.2%)	ns
Family history of CAD	13 (20.3%)	8 (19.5%)	ns

Table 7 Serum lipids, Lipoproteins and Apolipoprotein levels of Patient groups with and without Restenosis

Serum levels (mg/dl)	Restenosis (−) (n = 64)	Restenosis (+) (n = 41)	p
TC	183.5 ± 16.1	184.3 ± 20.2	ns
TG	152.2 ± 44.8	153.4 ± 52.6	ns
HDL-C	41.6 ± 20.5	39.7 ± 31.4	ns
LDL-C	120.6 ± 22.8	123.4 ± 17.8	ns
Lp (a)	32.5 ± 11.6	35.5 ± 10.3	ns
Apo-A1	108.4 ± 26.6	105.8 ± 22.4	ns
B	106.7 ± 30.5	111.8 ± 33.1	ns
E	5.1 ± 3.3	5.4 ± 3.6	ns

Mean ± SD

branch of the coronary artery were higher in the E4 group than in the E3 group, but there were no significant difference in the rates between the two groups.

[3] Characteristics of patients with or without restenosis

There were no differences between the two patient groups with and without restenosis (41 vs 64 patients) in age, history of CAD, and frequency and average number of risk factors (Table 6), nor in serum levels of lipids, lipoproteins and apolipoproteins (Table 7), excepting a higher frequency of the apo E4 allele in the group with restenosis than in the group without restenosis (Table 8).

DISCUSSION

Although the precise mechanisms of restenosis remain unsolved, they are divided into two categories. The first is caused by elastic recoil of the vessel wall immediately

Table 8 Characteristics of Patients with or without Restenosis

	Restenosis (−)	Restenosis (+)	p
Apo-E phenotype			$p<0.05$
E3 group (E3/2, E3/3)	55 (85.9%)	28 (68.3%)	
E4 group (E4/2, E4/3, E4/4)	9 (14.1%)	13 (31.7%)	
Apo-E alleles			$p<0.025$
$\varepsilon 2$	3 (2.3%)	3 (3.7%)	
$\varepsilon 3$	116 (90.6%)	65 (79.7%)	
$\varepsilon 4$	9 (7.0%)	14 (17.7%)	

after PTCA [12, 51], and the second is caused by intimal thickness due to extensive proliferation of smooth muscle cells as a reparative reaction of the arterial wall against the PTCA injury within 3 to 6 months [2, 61]. Because the latter will determine the long-term efficacy of PTCA, much research has been done which has revealed many different patient-, procedural-, and lesion-related factors for restenosis, as follows:

(a) characteristics of selected subjects (age and sex [16, 37, 64, 69], smoking [22], family history of a juvenile onset of CAD, previous history of myocardial infarction and angina pectoris [17, 28, 30, 41, 44, 64, 69], hypertention [17, 69], diabetis mellitus [3, 69], hyperlipidemia and hyperlipoproteinemia [1, 3, 4, 15, 27, 33, 50, 58, 67, 68], and low high density lipoproteinemia, with severe complications such as CVD, ASO and renal failure [32]).

(b) Characteristics of lesions (sites [30, 40, 44, 64, 69], severity [17, 30, 44, 69], length [28, 64], morphology such as discreate, tubular or diffuse [44], centric or eccentric [27, 44, 64], number of affected vessels [17, 37, 44], and calcification of stenotic sites [44, 64]).

(c) Procedual factors of PTCA (degree of stenosis before and after PTCA, initial dissociation by PTCA, type of catheter used, pressure, duration and number of times of inflation).

Therefore, to investigate the influence of the apo E phenotype or the E4 allele on long-term restenosis after PTCA, these various factors should be thoroughtly taken into consideration.

In the present study, to avoid bias owing to intentional selection or to patient gender, the subjects were limited to 171 male patients with CAD, who had at least one coronary artery with more than 75% stenosis on CAG and had undergone the initial PTCA. The subjects were divided into two groups, with and without the E4 allele (E4 group: 38 patients, E3 group: 133 patients). It is well known that patients with CABG, complete occlusion [28, 30], calcified lesions of the coronary artery [44, 64], three vessel disease [37, 44, 64], and with severe complications such as CVD, ASO and renal hemodialysis, have high restenosis rates. Therefore, an unequal distribution of such patients with a high risk for restenosis between E3 and E4 groups may possibly influence the rate of restenosis, so these patients were excluded with the result that 105 subjects, consisting of 83 patients in the E3 group and 22 patients in the E4 group, were chosen to evaluate the restenosis rates in the present study.

There were no significant differences between the E3 and E4 groups in age, number and frequency of risk factors for atherosclerosis, fasting serum lipids, lipoproteins and apolipoproteins levels, number of affected vessels, the distribution of target lesions, the incidence of patients with either long segment or advanced lesions, and also the degree of stenosis before and after PTCA. The restenosis rates in patients and in lesions were significantly higher in the E4 group than in the E3 group.

Furthermore, the 105 patients were divided into two groups with and without restenosis (41cases vs 64 cases) and compared with each other. There were no significant differences between the two groups in various factors related to the restenosis, except for the higher incidence of the E4 allele in the

restenosis group than in the groups without restenosis. These results suggest that the E4 allele is associated with an increased restenosis rate after PTCA.

To date, there are four reports concerning the relationship between the apo E phenotype or the E4 allele and restenosis with discrepant results. Van Bockmeer *et al.* [65], investigated 290 lesions in 195 patients (163 male, 32 female) who underwent a prospective follow up and angiographic study at 6 months after elective PTCA, and reported that the incidence of the E4 group (Phenotype E4/2, E4/3, E4/4) was somewhat higher in the group with restenosis (59 cases) than in the group without restenosis (91 cases), but the difference was not significant. The incidence of the E4 allele was, however, significantly higher in the former than in the latter (19.5% vs 9.9%) attributable to an excess of E4 homozygotes in the restenosis group. They also reported in another paper [66] that angiotensin converting enzyme (ACE) genotype in non-carriers of the apo E4 allele had no effect, but that the combined ACE (D) and apo E4 carrier state had a 16-fold increase in the odds for restenosis.

In contrast, Samani *et al.* [54], investigated 231 subjects (192 male, 39 female) with successful PTCA for only 1 vessel lesion, and found no increase either in the incidence of the E4 allele (18.4% vs 15.6%) or in the incidence of the E4 allele homozygosity (2/106 vs 5/125, $p < 0.3$) in the restenosis group than in the group without restenosis, by follow-up CAG at 4 months after PTCA. They concluded that the E4 allele did not, either independently or acting synergistically with the ACE (D) allele, increase the risk of restenosis after PTCA. Desmet *et al.* [21] also reported negative results about the relation between the ACE genotype and restenosis after PTCA. In the present study, the ACE genotypes were not determined. Damaraju *et al.* [18] reported that 98 of 206 subjects showed relapse of symptoms or the appearance of abnomalities in the ECG loading test within 3 months after PTCA. In a follow-up CAG, they did not find a significant association between apo E genotypes and the development of restenosis after PTCA (E4/4 + E4/3 + E4/2 in restenosis group : 34%, those in no restenosis group : 27%).

The reason for these discrepant findings are unclear. In all studies, the follow-up CAG was performed 4 to 6 months after the PTCA and the restenosis was assessed by the same criteria [30], and no significant differences were found in the fasting serum lipid levels between the groups with and without the E4 allele, as well as the other studies [3, 4, 66]. These factors, therefore, seem unlikely to provide any explanation for the discrepancies. However, recent studies showing that the postprandial changes in serum lipid levels were different among individuals with different apo E phenotype [71] and that postprandial hyperlipidemia was closely related to the development of CAD [74], seem to deny any effect of postprandial lipid levels on the restenosis rate.

It is possible that the discrepant findings result from differences in the characteristics of the subjects analyzed in each study. In the present study, only male patients with 1 vessel (64%) or 2 vessel disease (36%), without complete obstructive or calcified lesions, or various complications such as CVD and ASO, as mentioned above. On the other hand, the subjects in the studies by Bochxmeer *et al.* [65, 66], or Damaraju *et al.* [18], included patients with 3 vessel disease or complete obstructive lesions, and the subjects in the study by Samani *et al.* [54], consisted of only 1 vessel disease patients, and there were no detailed morphological descriptions of the lesions or their complications in these four studies. So, there is a possibility that the unequal distribution of the patients with a high risk of restenosis in each study obscures the effects of the E4 allele on restenosis.

Although the roles of apo E in restenosis remain unclear, intimal hyperplasia or proliferation of medial smooth muscle cells is a major mechanism responsible for restenosis after PTCA. In addition, intimal hyperplasia or thickening was consistently observed in all patients after PTCA, whether or not restenosis occured. Therefore, the two most important questions are what initiates smooth muscle cell hyperplasia and what determines the degree of hyperplasia, because this should ultimately determine the presence or absence of a hemodynamically significant restenotic lesion.

In the time course of initimal hyperplasia as the major reparative or reactive response of the arterial wall, the intimal and medical

injury due to PTCA is followed by platelet adhesion and aggregation, and thrombus formation, probably resulting in the release of many factors such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and transforming growth factor β (TGF-β) [6, 32, 39, 53]. These growth factors as well as endothelial cell-derived growth factors (EDGF) and macrophage-derived growth factor (MDGF) are involved in division and proliferation of smooth muscle cells (SMCs). The released PDGF and other growth factors may attract SMCs from the media of the artery into the intima and provoke their subsequent proliferation. Those SMCs which are transformed to a synthetic phenotype from a contractile phenotype by these growth factors, lastly synthesize the extracellular matrix (mainly glycosaminoglycans) and cause in intimal hyperplasia. Since intimal hyperplasia reaches a plateau within 3 months, most restenosis occurs within 6 months after PTCA [29, 47, 55]. PDGF may also attract monocytes and neutrophils into the intima. Macrophages derived from monocytes in the intima are deeply involved in the proliferation of SMCs, which is mediated through their secretion of MDGF and apo E.

In this fundamental and inevitably occurring process at the time of PTCA, apo E may no doubt play a role in supplying lipids (especially cholesterol) for membrance biosynthesis in the proliferation of SMCs. In addition to the effects of apo E on lipid levels and composition, there are reports that nonhepatic cells, such as macrophages or astrocytes, also synthesized apo E which could potentially influence restenosis.

The roles of non hepatic synthesized Apo E were become known as follows: Macrophages in sites of injury, attracted by PDGF, synthesize and secrete large quantities of apo E [5]. The apo E binds to glycosaminoglycans, the major components of newly-formed matrix and potent inhibitors of SMCs proliferation and mobility, and thereby weaken their inhibitory activities to result in stimulating SMCs proliferation and mobility. It has also been observed that the E4 allele is not only associated with CAD but also with some degenerative disorders including diabetes mellitus and late-onset of Alzheimer's disease [15, 24]. In Alzheimer's disease, the involvement of apo E4 is not closely related to lipid transport in plasma, but rather to direct binding of apo E to β-amyloid and intracellularly to tau protein.

Furthermore, apo E synthesized by astrocytes at the site of peripheral nerve injury [11] is suggested to bind directly with glycosaminoglycan and to be a neurotropic factor. Besides low density lipoproteins and apo E-containing lipoproteins have a capacity to inhibit or stimulate T lymphocyte activation and proliferation [30, 48], which may be involved in the inflammatry response to restenosis within a week after PTCA.

So, it may be that the different effects of apo E isoforms on restenosis after PTCA are attributable to differences in mechanisms other than lipid transport, especially in their binding capacity to proteoglycan.

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