SCIENTIFIC LETTER

Deletion polymorphism of the angiotensin I converting enzyme gene is a potent risk factor for coronary artery ectasia

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Coronary artery ectasia (CAE) is characterised by irregular, diffuse, saccular, or fusiform dilatation of the coronary arteries. Although the underlying mechanisms are not fully understood, CAE is considered an original form of vascular remodelling in response to atherosclerosis. However, it is not clear why some patients develop CAE while most do not. Experimental data suggest that activation of the renin angiotensin system may lead to an increased inflammatory response in the vessel wall or to an activation of matrix metalloproteinases.^{1,2} In addition, an insertion/deletion (ID) polymorphism of angiotensin converting enzyme (ACE) has been associated with coronary vascular tone³ and the development of aneurysms.⁴ Accordingly, we hypothesised that the gene polymorphism of ACE may be a potential factor influencing the genesis of CAE.

METHODS

We prospectively evaluated 3427 consecutive patients undergoing coronary angiography for the evidence of CAE. Coronary diameters and percent stenosis were measured by using computerised quantitative angiography in a biplane mode (Philips DCI, Eindhoven, Netherlands). CAE was defined as an arterial segment with a diameter of at least 1.5 times the diameter of the adjacent normal coronary artery. If no adjacent normal segment could be identified, the mean diameters of coronary segments in a control group without coronary disease (n = 81) served as normal values.

ACE ID genotype was determined in two groups of patients. Group 1 consisted of 152 patients who were found to have CAE. Group 2 consisted of 158 patients with significant coronary artery disease (CAD) (> 50% stenosis in any of the major epicardial coronary arteries or their branches) but without any evidence of ectasia, matched for sex and age (±2 years) with the patients in group 1. All patients gave written

informed consent for ACE ID genotype determination and coronary angiography.

Genomic DNA was extracted from 10 ml whole blood by standard phenol: chloroform extraction. Polymerase chain reaction conditions were the same as previously described,⁵ except that 64°C was used for annealing temperature and 7% dimethyl sulfoxide was used.

Statistical analyses were performed using SPSS software package (SPSS, Chicago, Illinois, USA), version 8.0 for Windows. Prevalences of alleles and genotypes among cases were counted and compared using a χ^2 test with Hardy-Weinberg predictions. The independent association between the presence of the D allele and CAE was assessed after adjusting for other potential confounding factors using multiple logistic regression analysis. All probabilities were two tailed and $p < 0.05$ was considered significant.

RESULTS

The overall incidence of CAE in our population was 152 out of 3427 (4.4%). Of the 152 patients with CAE, 108 (71%) had coexisting significant CAD, whereas 44 (29%) had either no or non-significant coronary artery stenosis. According to the classification of Markis and colleagues⁶ 32 patients had type 1 (diffuse ectasia of two or three vessels), 26 patients had type 2 (diffuse ectasia in one vessel and discrete in another), 64 patients had type 3 (diffuse ectasia of one vessel only), and 30 patients had type 4 ectasia (localised or segmental ectasia in one vessel). There were no significant differences in baseline characteristics between the patients with CAE (group 1) and

Abbreviations: ACE, angiotensin converting enzyme; CAD, coronary artery disease; CAE, coronary artery ectasia; ID, insertion/deletion

Table 1 Baseline characteristics of study population

	Group 1 (n=152)	Group 2 (n=158)	p Value
Age (years)	59.2 (10)*	58.6 (9)	0.54
Sex, male	117 (77)†	125 (79.1)	0.68
Active smokers	93 (61.2)†	102 (64.6)	0.57
Hypertension	61 (40.1)†	62 (39.2)	0.91
Diabetes mellitus	30 (19.7)†	285 (17.7)	0.67
Family history of CAD	48 (31.5)†	42 (26.6)	0.38
Hypercholesterolaemia	80 (52.5)†	72 (45.6)	0.26
Prior myocardial infarction	66 (43.4)†	73 (46.2)	0.71
Therapy with ACE inhibitors	38 (25)†	48 (30.4)	0.35
Left ventricular EF (%)	54 (11)*	56 (9)	0.31

*Mean (SD).

†Number of patients (%).

ACE, angiotensin converting enzyme; CAD, coronary artery disease; EF, ejection fraction.

Table 2 Characteristics of group 1 patients by ACE genotypes

	II (n=21)	ID (n=49)	DD (n=82)	p Value
Age (years)	62.3 (6.4)*	60.4 (11.1)	57.7 (10.1)	0.11
Sex, male	16 (76.2)†	39 (79.6)	62 (75.7)	0.87
Active smoking	9 (42.9)†	17 (37.8)	36 (45.6)	0.70
Hypertension	9 (42.9)†	19 (42.2)	36 (45.6)	0.93
Diabetes mellitus	2 (9.5)†	6 (13.3)	19 (24.1)	0.17
Family history of CAD	7 (33.3)†	19 (42.2)	33 (41.8)	0.76
Hypercholesterolaemia	11 (52.4)†	23 (51.1)	43 (54.4)	0.93
Prior myocardial infarction	9 (42.8)†	22 (44.9)	35 (42.7)	0.85
Therapy with ACE inhibitors	6 (28.6)†	14 (28.6)	18 (22.0)	0.64
Left ventricular EF	53 (9)*	55 (10)	54 (11)	0.74
Ectasia type				
Diffuse (types 1–3)	17 (81)†	38 (77.6)	67 (81.7)	0.84
Local (type 4)	4 (19)†	11 (22.4)	15 (18.3)	
Coexisting significant CAD	15 (71.4)†	35 (71.4)	58 (70.7)	0.99

*Mean (SD).

†Number of patients (%).

ACE, angiotensin converting enzyme; CAD, coronary artery disease; EF, ejection fraction.

CAD (group 2) (table 1). Within group 1, the parameters indicated in table 1 were similar between 108 patients who had coexisting CAD and 44 patients who did not.

The ACE ID genotype distribution was significantly deviated from Hardy-Weinberg's expectation in group 1 ($\chi^2 = 7.96$, $p < 0.05$) but not in the entire study population ($\chi^2 = 2.59$, $p > 0.05$). Genotype frequencies were significantly different between the two groups, DD genotype being more prevalent in group 1 (21 II, 49 ID, 82 DD in group 1; 31 II, 71 ID, 56 DD in group 2, $p = 0.0046$). Demographic, clinical, and angiographic characteristics of ectatic patients did not vary significantly by ACE genotypes, although the DD allele homozygotes tended to be younger and have a higher prevalence of diabetes mellitus (table 2).

In a multivariate analysis of CAE, we adjusted for arterial hypertension, diabetes mellitus, current smoking habit, family history of CAD, hypercholesterolaemia, left ventricular ejection fraction, prior myocardial infarction, and treatment with ACE inhibitors. The adjusted odds ratios were 2.16 (95% confidence interval (CI) 1.34 to 3.41, $p = 0.0027$) for DD patients versus II/ID patients, and 2.16 (95% CI 1.12 to 4.14, $p = 0.02$) for DD patients versus II patients. The association between ACE DD genotype and CAE was still significant after the elimination of 44 ectatic patients without coexisting significant CAD. The adjusted odds ratios were 2.1 (95% CI 1.28 to 3.48, $p = 0.0033$) for DD patients versus II/ID patients, and 2.14 (95% CI 1.04 to 4.38, $p = 0.037$) for DD patients versus II patients.

DISCUSSION

Although CAE may be congenital or inflammatory in origin, coronary atherosclerosis seems to be the main underlying aetiology since 52–90% of patients with CAE have coexisting stenotic CAD. However, it is not clear why some patients with coronary atherosclerosis develop CAE while most do not. In this study, we showed for the first time that the ACE DD genotype is significantly associated with CAE. Because the great majority of patients with CAE have coexisting CAD, and the DD genotype may be associated with increased incidence of CAD, we chose to use patients with significant CAD as appropriate controls. It is unlikely, therefore, that the increased DD frequency in our ectasia subjects is caused by coexisting CAD. As we did not measure plasma concentration of ACE, our study does not provide the opportunity to corroborate the functional significance of this polymorphism. However, it was repeatedly shown that the D allele of an ID polymorphism is associated with higher plasma ACE concentrations. Accordingly, the deleterious effect of the DD genotype might be attributed to the overexpression of ACE, producing a local increase in angiotensin II in some vascular territories. Angiotensin II may promote development of CAE by contributing to

the inflammatory response in the vessel wall,¹ or may act by altering smooth muscle cell migration, inducing extracellular matrix and matrix metalloproteinase production,² or stimulating reactive oxygen species formation.⁷ In a recent trial, Daugherty and colleagues showed that angiotensin II infusion in apolipoprotein E deficient mice dramatically promoted vascular pathology, including an increase in the extent of atherosclerosis, a change in the nature of lesions and surrounding adventitial tissue, and formation of large aortic aneurysms.¹ On the other hand, non-ACE mediated effects of DD genotype may also be important in some patients.

On the basis of our data, ACE DD genotype seems to be a potent risk factor for the development of CAE. The possible involvement of the renin-angiotensin system in the genesis of CAE raises the question of whether drugs that modulate activity of ACE and/or components of this system may reverse the risk for CAE.

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REFERENCES

- 1 Daugherty A, Manning MW, Cassis LA. Angiotensin II promotes atherosclerotic lesions and aneurysms in apolipoprotein E-deficient mice. *J Clin Invest* 2000;**105**:1605–12.
- 2 Xie B, Laouar A, Huberman E. Fibronectin-mediated cell adhesion is required for induction of 92-kDa type IV collagenase/gelatinase (MMP-9) gene expression during macrophage differentiation. *J Biol Chem* 1998;**273**:11576–82.
- 3 Prasad A, Narayanan S, Wacławski MA, et al. The insertion/deletion polymorphism of the angiotensin-converting enzyme gene determines coronary vascular tone and nitric oxide activity. *J Am Coll Cardiol* 2000;**36**:1579–86.
- 4 Pola R, Gaetani E, Santoliquido A, et al. Abdominal aortic aneurysm in normotensive patients; association with angiotensin-converting enzyme gene polymorphism. *Eur J Vasc Endovasc Surg* 2001;**21**:445–9.
- 5 Shanmugam V, Sell KW, Saha BK. Mistyping ACE heterozygotes. *PCR Methods Appl* 1993;**3**:120–1.
- 6 Markis JE, Joffe CD, Cohn PF, et al. Clinical significance of coronary arterial ectasia. *Am J Cardiol* 1976;**37**:217–22.
- 7 Kheradmand F, Werner E, Tremble P, et al. Role of Rac 1 and oxygen radicals in collagenase-1 expression induced by cell shape change. *Science* 1998;**280**:898–902.