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Angiotensin Converting Enzyme and Angiotensin II Type I Receptor Polymorphisms in Patients with Coronary Aneurysms

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Abstract

Background: Conflicting results have been reported regarding the association of gene polymorphisms in the renin-angiotensin system (RAS) with different aspects of coronary artery disease (CAD), such as myocardial infarction, neointimal hyperplasia or coronary artery vasomotion. Since previous studies have linked angiotensin II to aneurysmal disease, our study hypothesis was that RAS gene polymorphisms may be associated with aneurysm remodeling in response to CAD.

Methods: The study population was selected from a series of 3862 consecutive patients who underwent coronary angiography in our institution. One hundred and thirteen consecutive patients with at least one coronary aneurysm (CA) were compared to 226 randomized control patients without CA. DNA was extracted from white blood cells. The angiotensin-converting enzyme (ACE) I/D and angiotensin type I receptor (AT1-R) A/C polymorphisms were detected using previously published techniques.

Results: The distributions of the three ACE genotypes were similar in both groups: CA: 13%, 46%, and 41% for II, ID, and DD respectively; controls: 18%, 41%, and 41% for II, ID, and DD respectively, $p = 0.45$. The distributions of the three AT1-R genotypes were also similar in both groups: CA: 54%, 41%, and 5% for AA, AC, and CC respectively; controls: 55%, 33%, and 12%, for AA, AC, and CC respectively, $p = 0.08$.

Conclusion: Our results provide further information on the role of RAS polymorphisms on specific mechanisms implicated in CAD. Although an activated RAS may theoretically promote aneurysm formation, the 2 RAS polymorphisms analyzed in this study are not associated with this process in coronary arteries.

Background

Activation of the renin angiotensin system (RAS) plays an important role in the pathogenesis of coronary artery dis-

ease (CAD).

In humans, levels of angiotensin-converting enzyme (ACE) are partly under genetic control [1]; circulating levels of ACE are correlated with an insertion (I) / deletion (D) polymorphism [2]: DD genotypes have higher levels of ACE than either ID or II genotypes [3]. Although the concept that genetic factors may increase the risk of CAD via activation of the RAS is an attractive one, discordant results have been published regarding the association of the ACE I/D polymorphism with myocardial infarction. While the initial study by Cambien et al reported an increased frequency of the DD genotype in patients with myocardial infarction [4], a large prospective study by Lindpaintner et al did not confirm this association [5].

The effects of angiotensin II are exerted through the activation of specific high activity receptors [6]. A polymorphism located in the 3' untranslated region of the type 1 receptor (AT1-R) gene (corresponding to an adenine/guanine substitution at the 1166 nucleotide position of the mRNA) has been described [7]. Although it has been less studied than the ACE I/D polymorphism, discordant results have also been reported regarding the association of the AT1-R polymorphism with myocardial infarction. While Tiret et al reported synergistic effects of ACE and AT1-R gene polymorphisms on the risk of myocardial infarction [8], this was not confirmed in a recent study by Steeds et al [9].

A possible explanation for these discrepancies is that myocardial infarction is the result of a multifactorial process implicating different mechanisms such as plaque progression, vessel remodeling, plaque rupture, thrombosis or vasomotion [10,11]; each of these mechanisms may be affected in one way or another by a given genotype but a clear demonstration of the effect may be difficult if the sole endpoint studied is the occurrence of myocardial infarction. Smaller studies with carefully chosen intermediate end-points may be useful to elucidate the potential impact of RAS polymorphisms on CAD. Previously, we reported the relationships between RAS polymorphisms and several specific mechanisms implicated in the pathogenesis of CAD: the *in vivo* response to methylergonovine was used to study coronary artery vasomotion [12]; restenosis after stent implantation or balloon angioplasty were used as models of neointimal hyperplasia or constrictive remodeling [13,14]. In the present study, we sought to investigate another form of abnormal vessel remodeling in response to CAD: aneurysm formation.

Previous studies have linked angiotensin II to aneurysm formation. In apo E^{-/-} mice, angiotensin II infusion dramatically increased the extent of atherosclerosis and was associated with the formation of large abdominal aortic aneurysms [15]. Different mechanisms may be involved: angiotensin II may promote development of aneurysms

by contributing to the inflammatory response [15,16], altering smooth muscle cell migration [17], or inducing matrix metalloproteinases production [18,19]. Aneurysmal coronary artery disease is characterized by abnormal dilation of a localized or diffuse segment of the coronary arterial tree. Approximately 1 to 5% of the patients with coronary atherosclerosis have coronary aneurysm(s) (CA) [20–23]. In the present study, we investigated whether the ACE and AT1-R gene polymorphisms may be associated with CA. Alleles and genotypes frequencies were compared between 113 patients with atherosclerotic CA and 226 control patients.

Methods

Study Population

The study population was selected from a series of 3862 consecutive patients who underwent coronary angiography in our institution. CA were defined as localized or diffuse coronary dilations that exceeded the diameter of normal adjacent segments by 1.5 times [21]. One hundred and thirteen consecutive patients with evidence of coronary atherosclerosis and at least one coronary aneurysm were selected and constitute the CA group. During the same period, we randomly selected 226 patients (2 : 1 ratio) who presented with coronary atherosclerosis but without CA to form the control group. Patients gave informed consent for the study. We previously reported in the same population the association between functional polymorphisms in matrix metalloproteinase genes and coronary aneurysms [24].

Clinical and Angiographic Data

Epidemiological and clinical characteristics were collected by trained physicians. Coronary angiograms were analysed by two experienced interventional cardiologists. The number of non significant ($\leq 50\%$) or significant ($>50\%$) stenoses was recorded for each patient. The extent of aneurysmal disease (number of segments and vessels diseased per patient) was also noted as was the type (diffuse or focal) of CA. Aneurysmal segment was classified as focal when it involved a discrete portion of a segment with adjacent normal segment within the same segment and diffuse when the entire segment was dilated with no normal vessel within the segment [25]. Representative examples of diffuse and focal CA are shown in Figure 1.

The largest diameter of each aneurysmal vessel was measured by quantitative coronary angiography with use of the CMS system as previously described [26].

Genetic Study

Genomic DNA was extracted from white blood cells by a « salting out » procedure as previously described [27]. The ACE fragment [13] containing the I/D sequence and AT1 receptor fragment containing the A/C -1166 substitution

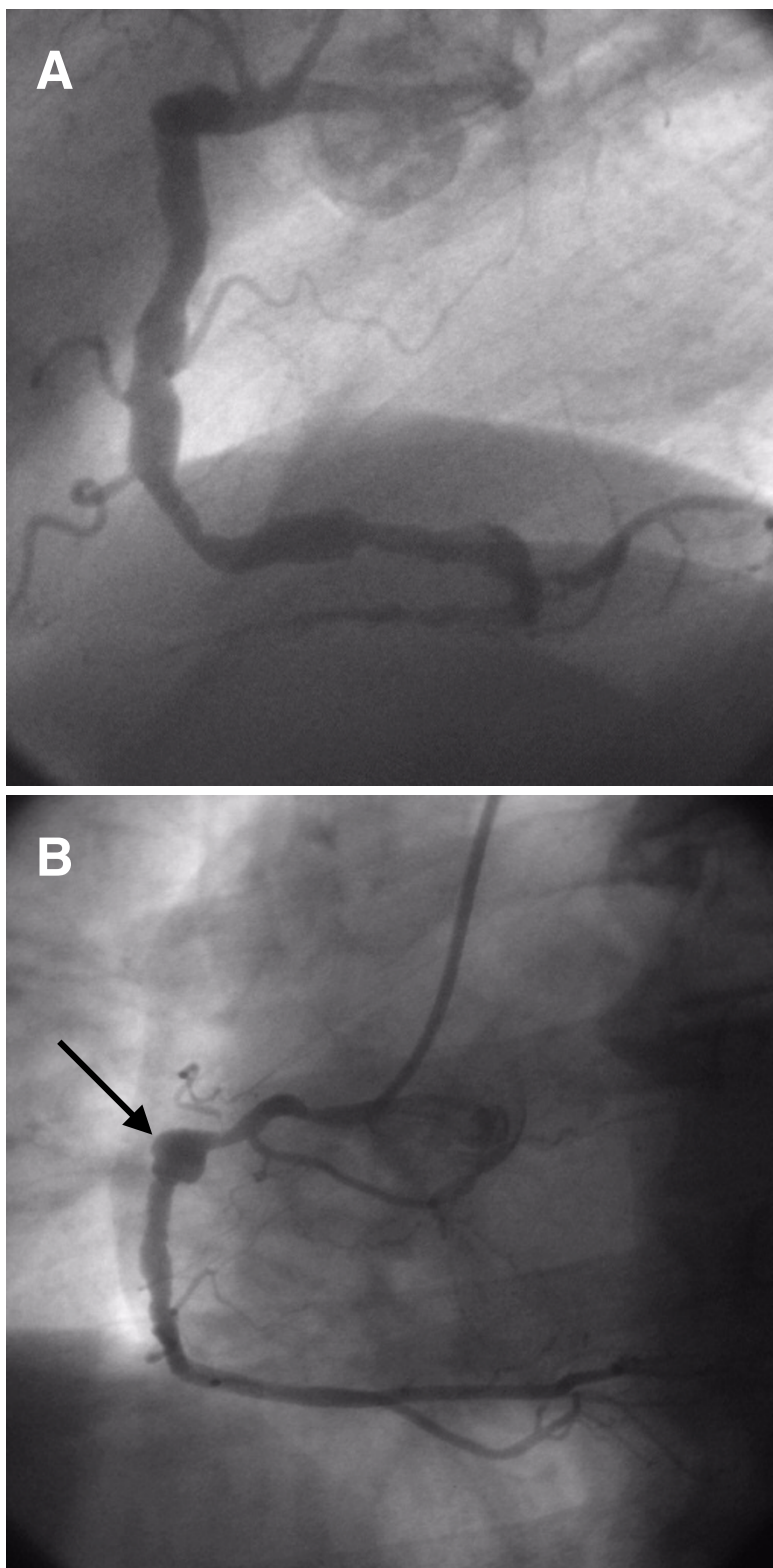


Figure 1
Representative examples of coronary aneurysms: A. Diffuse aneurysmal disease of the right coronary artery. B. A focal coronary aneurysm of the mid-portion of the right coronary artery (arrow)

Table 1: Clinical and angiographic characteristics in CA and control patients as a function of the ACE I/D polymorphism.

	CA (n = 113)			Controls (n = 226)		
	II (n = 15)	ID (n = 52)	DD (n = 46)	II (n = 41)	ID (n = 92)	DD (n = 93)
Age, years	63 ± 13	64 ± 10	60 ± 13	64 ± 11	61 ± 11	62 ± 11
Body Mass Index, kg/m ²	28.4 ± 5	27.3 ± 4	27.6 ± 4	27.3 ± 4	27.8 ± 12	26.6 ± 4
Male gender, %	93	92	87	73	83	81
Smoking, %	80	77	80	63	76	67
Hypercholesterolemia, %	87	79	80	88	71	75
Hypertension, %	40	40	48	46	53	47
Diabetes, %	13	13	20	24	27	23
Previous myocardial infarction, %	73	67	67	56	59	44
History of aortic aneurysm, %	7	4	11	2	0	0
Number of stenotic lesions, %						
- Non significant	0	6	7	15	9	7
- Single-vessel	13	30	28	24	35	37
- Two-vessel	60	42	43	37	32	31
- Three-vessel	27	22	22	24	25	25
Coronary aneurysm(s) location, %						
- Left Main	0	4	13	NA	NA	NA
- Left Anterior Descending Artery	60	52	50	NA	NA	NA
- Circumflex	67	34	35	NA	NA	NA
- Right Coronary Artery	67	74	72	NA	NA	NA
Number of vessel(s) with CA, %						
- 1	33	56	52	NA	NA	NA
- 2	40	28	35	NA	NA	NA
- 3	27	16	13	NA	NA	NA
Type of aneurysm(s), %						
- Diffuse	93	79	78	NA	NA	NA
- Focal	7	21	22	NA	NA	NA

[12] were amplified by Polymerase Chain Reaction (PCR). The ACE and AT1 receptor A/C polymorphisms were detected as previously described [12].

Statistical Analysis

Statistical analysis was conducted with SAS software, version 6.12 (SAS Institute Inc., Cary, NC). Mean values ± SD were calculated for quantitative data. The quantitative variables were compared between groups with use of unpaired Student *t* tests. Qualitative variables were compared by the Pearson's χ^2 -test, or the Fisher's exact test when necessary.

Results

The baseline characteristics are presented in Tables 1 and 2. Except for male gender (CA group: 90%, control group: 80%; $p = 0.02$), previous myocardial infarction (CA group: 68%, control group: 52%; $p = 0.005$) and an history of aortic aneurysm (CA group: 7%, control group: 0.4%; $p = 0.0003$) which were more frequent in the CA group, the baseline characteristics were similarly distributed in both groups. Forty eight percent of the patients had aneurysmal involvement of more than one coronary vessel. The most frequent location of CA was the right cor-

onary artery. In most cases, this involvement was classified as diffuse. The maximal diameter of the aneurysmal segments was 6.6 ± 1.2 mm.

Regarding ACE I/D genotypes, there was no statistically significant difference in the baseline characteristics both in the CA group and in the control group (Table 1). The distributions of the three genotypes were similar in both groups: CA: 13%, 46%, and 41% for II, ID, and DD respectively; controls: 18%, 41%, and 41% for II, ID, and DD respectively; $p = 0.45$. The proportions of D allele were 64% in the CA group and 62% in the control group; $p = 0.58$.

Regarding AT1 receptor A/C genotypes, there was no statistically significant difference in the baseline characteristics both in the CA group and in the control group (Table 2). The distributions of the three genotypes were similar in both groups: CA: 54%, 41%, and 5% for AA, AC, and CC respectively; controls: 55%, 33%, and 12%, for AA, AC, and CC respectively; $p = 0.08$. The proportions of C allele were 26% in the CA group and 29% in the control group; $p = 0.36$.

Table 2: Clinical and angiographic characteristics in CA and control patients as a function of the AT1 receptor A/C polymorphism.

	CA (n = 113)			Controls (n = 226)		
	AA (n = 61)	AC (n = 46)	CC (n = 6)	AA (n = 123)	AC (n = 75)	CC (n = 28)
Age, years	61 ± 13	64 ± 11	63 ± 7	61 ± 11	61 ± 12	64 ± 9
Body Mass Index, kg/m ²	27.2 ± 4	28.4 ± 4	26 ± 6	27.7 ± 10	26.4 ± 5	27.3 ± 5
Male gender, %	90	91	83	80	81	75
Smoking, %	80	78	67	67	75	71
Hypercholesterolemia, %	80	83	67	75	73	86
Hypertension, %	41	43	67	54	41	54
Diabetes, %	16	13	33	26	19	36
Previous myocardial infarction, %	70	72	17	54	53	39
History of aortic aneurysm, %	10	4	0	0	0	4
Number of stenotic lesions, %						
- Non significant	6	4	0	6	11	22
- Single-vessel	22	29	67	32	37	32
- Two-vessel	45	51	0	33	31	32
- Three-vessel	27	16	33	29	21	14
Coronary aneurysm(s) location, %						
- Left Main	7	7	17	NA	NA	NA
- Left Anterior Descending Artery	47	60	50	NA	NA	NA
- Circumflex	33	49	17	NA	NA	NA
- Right Coronary Artery	72	73	67	NA	NA	NA
Number of vessel(s) with CA, %						
- 1	60	40	0	NA	NA	NA
- 2	27	38	50	NA	NA	NA
- 3	13	22	50	NA	NA	NA
Type of aneurysm(s), %						
- Diffuse	80	80	83	NA	NA	NA
- Focal	20	20	17	NA	NA	NA

Discussion

CA is a relatively rare manifestation of CAD. In the present study, 2.9% of patients undergoing coronary angiography had CA; previous studies have reported rates ranging between 1 and 5% [20–23]. The exact mechanisms by which CA may occur in response to atherosclerosis are unknown but histological and clinical studies suggest that processes similar to those implicated in abdominal aortic aneurysms (AAA) may be involved [22]. Experimental studies have linked angiotensin II to aneurysm formation. Nishijo et al observed that angiotensin II stimulated aneurysm formation in hypertensive transgenic mice that overproduce angiotensin II [28]. Recently, Daugherty et al found that continuous perfusion of angiotensin II was associated with the formation of large AAA in atherosclerotic apoE^{-/-} mice with a dose-response effect [15]. Moreover, angiotensin II-induced AAA development was significantly reduced by doxycycline, a broad spectrum MMP inhibitor [19]. Furthermore, Huang et al showed that ACE inhibition reduced the rate of spontaneous rupture of the internal elastic lamina of the abdominal aorta [29] and Liao et al reported total inhibition of elastase-induced AAA in a rat model by treatment with 3 different ACE inhibitors [30].

In humans, limited data are available regarding the implication of the RAS in aneurysm formation; however, genetic association studies may provide interesting information. Discordant results have been reported regarding the ACE I/D polymorphism and abdominal aortic aneurysm. Although Hamano et al failed to show any positive correlation between this polymorphism and the occurrence of AAA [31], a recent study by Pola et al suggested that the ACE DD genotype may be a risk factor for AAA in normotensive patients [32]. In the present study, the distribution of the ACE I/D genotypes were similar in the CA and the control groups, suggesting that the ACE I/D polymorphism is not an important determinant of CA formation. To the best of our knowledge, the association of the AT1-R genotype with AAA has never been specifically analyzed. In the present study, the distribution of the AT1-R genotypes were similar in the CA and the control groups, suggesting that the AT1-R polymorphism is not an important determinant of CA formation.

Study Limitations

The interpretation of negative results may be limited by a relatively small sample size. With a statistical power of 80% and a significant value of 0.05, the sample size of this

study allowed us to detect a 11% difference in the frequency of the ACE D allele and a 10% difference in the frequency of the AT1-R C allele. However, the 113 patients with CA were prospectively recruited by a systematic analysis of 3862 consecutive angiography procedures; the design of larger studies would imply a multicentric recruitment. Finally, this was an angiographic study; as shown by Maehara et al, the use of intravascular ultrasound may allow a better analysis of aneurysmal segments [33].

Conclusions

Epidemiological studies have suggested a link between RAS polymorphisms and CAD [4–8]. Our results provide further information on the role of RAS polymorphisms on specific mechanisms implicated in CAD. We [14] and others [34] previously reported that the ACE I/D polymorphism was associated with neointimal hyperplasia in response to coronary stent implantation. We also showed that the AT1-R polymorphism (but not the ACE I/D polymorphism) was associated with coronary artery vasoconstriction in response to methylergonovine [12]. By contrast, the ACE I/D and AT1-R polymorphisms are not associated with restenosis of coronary arteries after balloon angioplasty [13], a process which is mainly related to constrictive vessel remodeling [35]; in the present study, we focused on another form of vessel remodeling, aneurysm formation, which again was not associated with either the ACE I/D or the AT1-R polymorphisms. Although an activated RAS may theoretically promote aneurysm formation via mechanisms such as an induction of metalloproteinases [18] or an increased inflammation [15], the 2 RAS polymorphisms analyzed in this study are not associated with this process in coronary arteries.

Competing interests

We have no competing interests to disclose for this paper

Authors' contributions

NL, CB and PA participated in the design of the study and performed the statistical analysis. NL, XH and NH carried out the molecular genetic studies. NL, JML and CB participated in the selection of patients and in angiographic analyses. NL and CB drafted the manuscript. All authors approved the final version of the manuscript.

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