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Relation between angiotensin-converting enzyme II genotype and atrial fibrillation in Japanese patients with hypertrophic cardiomyopathy

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Abstract Atrial fibrillation (AF) occurs in about 20% of patients with hypertrophic cardiomyopathy (HCM). HCM patients with AF have an increased risk for clinical decline and thromboembolism. In addition, AF is known to be associated with the atrial renin-angiotensin system (RAS). However, the relation between AF and the RAS in HCM has not been investigated. We genotyped the insertion/deletion (I/D) polymorphism of the angiotensin-converting enzyme (*ACE*) gene in 138 HCM patients (26 with AF, 112 with sinus rhythm). Distribution of the *ACE* genotypes (DD, ID, and II) among the total HCM patients was 15%, 46%, and 38%. AF was documented in 3 patients with the DD genotype, 7 with the ID genotype, and 16 with the II genotype ($P < 0.03$ vs. sinus rhythm group). The odds of AF were 3.2-fold greater in patients with the II genotype than in those with the other genotypes ($P = 0.009$, 95% confidence interval = 1.3–7.8). Kaplan-Meier curves examining the time to the first documented AF event showed a significant difference between genotypes during the follow-up period (mean 116 months, $P < 0.05$). These findings suggest that the II genotype of the *ACE* gene is a significant risk factor for AF in patients with HCM.

Key words Hypertrophic cardiomyopathy · Atrial fibrillation · Angiotensin-converting enzyme · Renin-angiotersin system · Polymorphism

Introduction

Atrial fibrillation (AF) is known to occur in 20% of patients with hypertrophic cardiomyopathy (HCM) (Maron et al. 2000). In addition, patients with HCM have markedly impaired left ventricular diastolic function (Rosing et al. 1979; Hamada et al. 2001). Thus, AF leads to clinical decline in patients with HCM because of the loss of atrial contribution to filling of the hypertrophied and stiff left ventricle. Moreover, the coagulation system is markedly activated in HCM (Yamamoto et al. 1995). Therefore, patients with AF have a markedly increased risk of clinical decline and thromboembolism (Hamada et al. 1985; Shigematsu et al. 1995).

The renin-angiotensin system (RAS) is known to play a very important role in many cardiovascular diseases (Marian et al. 1993; Raynolds et al. 1993; Lechin et al. 1995; Lindpaintner et al. 1995; Yoneya et al. 1995; Pfeufer et al. 1996; Malik et al. 1997; Tabara et al. 2001) and to influence occurrence of thromboembolism (González Ordóñez et al. 2000). Circulating levels of angiotensin-converting enzyme (ACE) are linked to a 287-base pair insertion/deletion (I/D) polymorphism in intron 16 of the *ACE* gene, which accounts for 50% of serum ACE level variability (Rigat et al. 1990). In addition, plasma ACE activity is significantly higher in individuals with the D allele than in individuals with the I allele (Rigat et al. 1990).

However, the relation between AF and the ACE I/D polymorphism has not been fully investigated. Thus, the purpose of this study was to determine the relation between *ACE* genotypes and the occurrence of AF in patients with HCM.

Patients and methods

Study population

Analyses of DNA and measurement of plasma atrial natriuretic peptide (ANP) levels and brain natriuretic peptide (BNP) levels were performed between March 2000 and August 2000 on blood samples of patient volunteers. The study protocols were approved by the Ethics Committee of Ehime University School of Medicine, and written and informed consent was obtained from each subject.

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One hundred thirty-eight patients diagnosed with HCM at Ehime University Hospital between 1977 and 2000 were enrolled in this study. Of these patients, 26 were diagnosed with AF and 112 were diagnosed with sinus rhythm (SR); thus, there were two groups of study patients. HCM was diagnosed on the basis of echocardiographic criteria defined as the presence of left ventricular hypertrophy in the absence of other causes for hypertrophy. Patients were excluded from this study if they had undergone cardiac surgery. These patients also met the definition and classification proposed by the 1995 World Health Organization/International Society and Federation of Cardiology Task Force (Richardson et al. 1996). Age at initial clinical evaluation ranged between 13 and 75 years (mean 52 ± 13 years). Age at the most recent evaluation ranged between 14 and 91 years (mean 63 ± 13 years). The total follow-up period ranged between 8 and 276 months (mean 128 ± 85 months).

Echocardiographic study

M-mode and two-dimensional echocardiography were performed in all patients via an SSD 870 or 9000 imaging system (Aloka, Tokyo, Japan) with a 2.5- or a 3.5-MHz transducer. M-mode echocardiograms were recorded on a strip-chart recorder at a paper speed of 50 mm/s. From the M-mode echocardiographic study, the following conventional variables were measured according to the criteria of the American Society of Echocardiography: left atrial dimension (LAD) at end-systole, interventricular septal thickness and left ventricular posterior wall thickness at end-diastole (IVST and PWT), left ventricular dimensions at end-diastole and end-systole (LVDd and LVDs), and percent fractional shortening (%FS).

Measurement of plasma ANP and BNP levels

Plasma ANP and BNP levels were determined as reported previously (Hamada et al. 1998). Normal plasma ANP and BNP values in our institution are <43.0 pg/ml and <17.0 pg/ml, respectively.

Determination of *ACE* genotypes

Genomic DNA was extracted from peripheral blood samples with an extraction kit (Qiagen, Hilden, Germany). Gene polymorphisms of ACE I/D were determined by standard methods (Lindpaintner et al. 1995). In brief, the I/D polymorphism of the *ACE* gene was identified by polymerase chain reaction (PCR) amplification performed with a set of oligonucleotide primers flanking the polymorphic site in intron 16 (5′-GCC CTG CAG GTG TCT GCA GCA TGT-3′ and 5′-GGA TGG CTC TCC CCG CCT TGT TCT C-3′). To avoid mistyping, each sample found to have the DD genotype was subjected to a second, independent round of PCR amplification with a primer pair that recognized an insertion-specific sequence (5′-TGG GAC CAC AGC GCC CGC CAC TAC-3′ and 5′-TCG CCA GCC CTC CCA TGC CCA TAA-3′). *ACE* genotypes of patients with HCM were compared with those of healthy Japanese subjects that have been reported elsewhere (Tabara et al. 2001).

Statistical analysis

All statistical analyses were performed on a personal computer with SPSS Version 10.0J for Windows (SPSS, Inc., Chicago, IL, USA). Summary data are expressed as mean ± SD values. To test for Hardy-Weinberg equilibrium, the expected genotype numbers were calculated from the allele frequencies, and deviation from the observed genotype numbers was determined by chi-square test. To analyze differences between D allele carriers and noncarriers, the ID and DD genotypes were pooled into one group. Because of the non-normal distribution of most parameters, differences between the AF group and the SR group were tested by Mann-Whitney *U* test. Association between polymorphisms and case/control status was tested by logistic regression analysis controlling for age, gender, and other variables. Odds ratios (ORs) were estimated with 95% confidence intervals as measures of risk. Kaplan-Meier curves were constructed to examine time to the first AF event and compared by log-rank test. A probability value of less than 0.05 was considered statistically significant.

Results

Characteristics of the study population

Characteristics are shown per group in Table 1. No significant differences in age, sex ratio, body mass index, systolic and diastolic blood pressures, LVDd, LVDs, %FS, and IVST + PWT were found between the two groups. Significant differences in the follow-up period, LAD, ANP, BNP, and incidence of thromboembolism were detected between the two groups.

Documentation of AF

The AF group consisted of 18 patients with chronic AF (defined as AF sustained for >6 months) and 8 with paroxysmal AF (lasting for >1 h but not persisting for 6 months). Age at the first documented AF was 59 ± 10 years. AF was present in 4 patients at initial clinical evaluation. Twenty-two patients developed AF 12 to 216 months (median 93 ± 61 months) after the diagnosis of HCM. The onset of AF was associated with thromboembolic episodes in 15 of 26 (58%) patients. In addition, thromboembolic events might have occurred during the first documented episode of paroxysmal AF in 4 of 8 patients (50%) diagnosed with paroxysmal AF. Cerebral embolism occurred in 14 (93%) of 15 patients with thromboembolism. There was no significant difference in the incidence of thromboembolism between patients with paroxysmal AF (50%) and those with chronic

Table 1. Clinical data per study group

	Total HCM patients (n = 138)	AF group (n = 26)	SR group (n = 112)
Age at the most recent evaluation (years)	63 ± 13	66 ± 10	62 ± 14
Age at initial evaluation (years)	52 ± 13	53 ± 9	52 ± 14
Duration of follow-up (months)	128 ± 85	159 ± 81*	121 ± 84
Male sex (%)	104 (75%)	22 (85%)	82 (73%)
Body mass index	24 ± 4	24 ± 3	24 ± 4
Systolic blood pressure (mmHg)	129 ± 19	124 ± 19	130 ± 19
Diastolic blood pressure (mmHg)	76 ± 11	74 ± 10	77 ± 11
HOCM	33 (24%)	5 (19%)	28 (25%)
HNCM	105 (76%)	21 (81%)	84 (75%)
LAD (mm)	40 ± 8	46 ± 8*	38 ± 7
IVST + PWT (mm)	23 ± 5	23 ± 3	22 ± 5
LVDd (mm)	47 ± 5	48 ± 3	47 ± 5
LVDs (mm)	30 ± 6	32 ± 5	29 ± 6
%FS (%)	37 ± 9	35 ± 7	38 ± 9
ANP (pg/ml)	67 ± 76	101 ± 77*	59 ± 73
BNP (pg/ml)	223 ± 296	379 ± 314*	187 ± 281
Thromboembolism	15 (11%)	15 (58%)*	0
Treatment			
Beta-blocker	56 (41%)	13 (50%)	43 (38%)
Calcium antagonist	105 (76%)	22 (85%)	83 (74%)

Values are mean ± SD
HCM, Hypertrophic cardiomyopathy; AF, atrial fibrillation; SR, sinus rhythm; HOCM, hypertrophic obstructive cardiomyopathy; HNCM, hypertrophic nonobstructive cardiomyopathy; LAD, left atrial dimension; IVST, interventricular spetal thickness; PWT, posterior wall thickness; LVDd, left ventricular dimension at end-diastole; LVDs, left ventricular dimension at end-systole; FS, fractional shortening; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide
* $P < 0.05$ Mann-Whitney U test (vs. SR group)

Table 2. Frequencies of ACE genotypes in HCM patients

Genotype and allele frequencies	Healthy Japanese (n = 205)	HCM (n = 138)	AF group (n = 26)	SR group (n = 112)
DD	27 (13%)	21 (15%)	3 (12%)*	18 (16%)
ID	95 (46%)	64 (46%)	7 (27%)*	57 (51%)
II	83 (41%)	53 (38%)	16 (62%)*†	37 (33%)
DD + ID	122 (59%)	85 (62%)	10 (38%)†	75 (67%)
D allele	0.36	0.38	0.25*	0.42
I allele	0.64	0.62	0.75*	0.58

Numbers are number of patients. Percentages are shown in parentheses
ACE, Angiotensin-converting enzyme; all other abbreviations as in Table 1
* $P < 0.03$, † $P < 0.01$ by chi-square test

AF (61%). None of the patients in the SR group had systemic thromboembolism.

Frequencies of alleles and genotypes

The PCR results were evaluated by two independent investigators. All ambiguous samples were analyzed a second time. Table 2 shows distribution of the *ACE* genotypes and allele frequencies in the 138 study patients. Frequencies of the *ACE* genotypes were virtually identical to those predicted by Hardy-Weinberg equilibrium. Distribution of the respective *ACE* genotypes in the AF group and in the SR group was in Hardy-Weinberg equilibrium. There was a significant difference in the distribution of *ACE* genotypes between the AF and SR groups, however (chi-square = 7.36; $P < 0.03$).

In addition, in a dominant D allele model (DD and ID genotypes vs. II genotype), there was a significant difference in genotypes between the AF group and the SR group (chi-square = 7.25; $P < 0.01$). However, in a recessive D allele model (DD genotype vs. ID and II genotypes) there was no significant difference in *ACE* genotypes between the AF and SR groups.

Risk factors for AF

Table 3 shows ORs for AF in patients with HCM determined by logistic analysis. The odds of AF occurring in patients with the II genotype were 3.2-fold greater in the univariate model and 4.8-fold greater in the multivariate model than that in patients with the ID or DD genotypes.

Table 3. Odds ratios for AF in patients with HCM

	Univariate model		Multivariate model	
	Odds ratio (95% confidence interval)	*P* value	Odds ratio (95% confidence interval)	*P* value
Age	1.03 (0.99–1.06)	0.17		
Male sex	2.01 (0.64–6.32)	0.23		
Body mass index	1.02 (0.90–1.15)	0.80		
HOCM	0.71 (0.25–2.07)	0.54		
II genotype (vs DD + ID)	3.24 (1.34–7.84)	0.009	4.80 (1.45–15.9)	0.01
LVDd	1.07 (0.99–1.17)	0.11		
LVDs	1.07 (1.00–1.14)	0.06		
%FS	0.96 (0.91–1.01)	0.09		
IVST + PWT	1.03 (0.94–1.11)	0.55		
LAD	1.17 (1.09–1.25)	<0.0001	1.16 (1.07–1.26)	0.001
ANP	1.00 (1.00–1.02)	0.04	1.01 (1.00–1.02)	0.003
BNP	1.00 (1.00–1.00)	0.01		

Odds ratios determined by logistic regression analysis
Abbreviations as in Table 1 and Table 2

Probability of remaining free of AF

For 134 patients without evidence of established AF at initial evaluation, Kaplan-Meier curves examining the time to the first event of documented AF showed that the probability of remaining free of AF was significantly lower in patients with the II genotype than in patients with the DD genotype or the ID genotype ($P < 0.05$; Fig. 1 A) or when considering the DD and ID genotypes together ($P = 0.01$; Fig. 1 B).

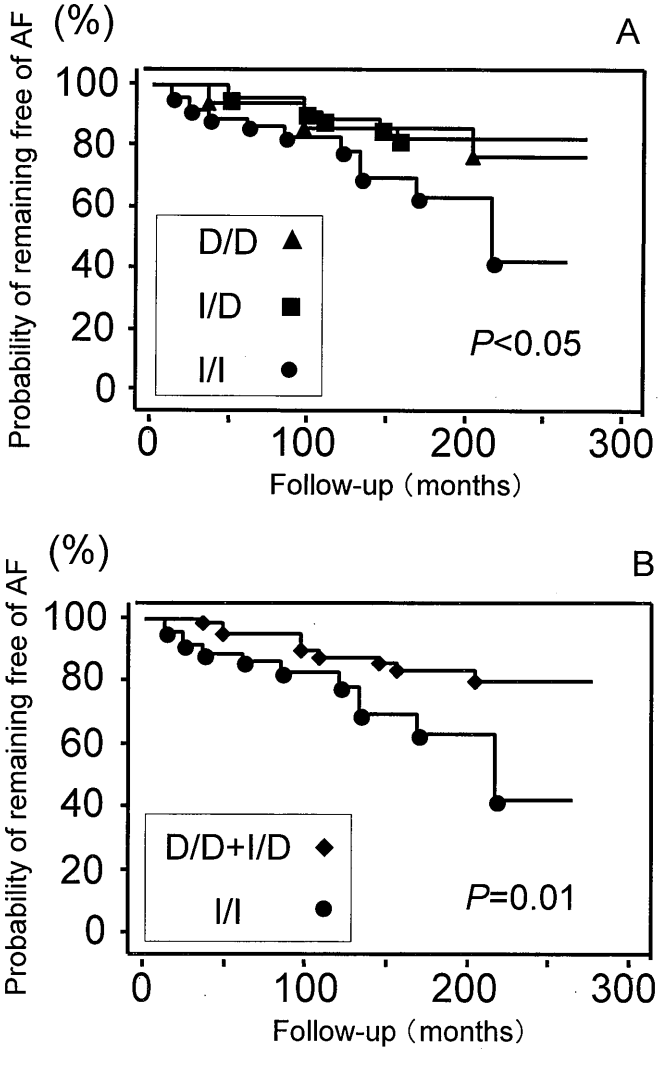

Fig. 1A,B. Percent cumulative probability (Kaplan-Meier estimates) of remaining free of atrial fibrillation (AF) during the follow-up period in study patients without evidence of established AF at initial evaluation

Discussion

Our study is the first to show a relation between the ACE I/D polymorphism and AF in patients with HCM. Our results indicate that the II genotype may be a risk factor for development of AF in Japanese patients with HCM. Moreover, our results suggest that the *ACE* gene plays an important role in the occurrence of AF in patients with HCM.

AF in patients with HCM

Several investigators (Spirito et al. 1992; Cecchi et al. 1995; Shigematsu et al. 1995; Higashikawa et al. 1997; Maron et al. 2000) have reported the occurrence of AF in 10% to 28% of patients with HCM 7 to 10 years after initial diagnosis. The incidence of AF in the present study (19%) was almost identical to that of these previous studies. In our study, 23% of the AF group had left ventricular obstruction, which was not significantly different from that of the SR group. In addition, there was no significant difference in IVST + PWT between the AF and SR groups. Duration of the follow-up period, which means an increase in age of patients, may be one of determinants for AF. Spirito et al. (1992) reported that chronic AF occurred most often in the nonobstructive type HCM with relatively mild ventricular hypertrophy. Previously, we reported that the functional

chamber-size of the left ventricle in patients with HCM was closely related to the size of left atrium and left ventricular end-diastolic pressure (Shigematsu et al. 1995). Thus, the severity of left ventricular diastolic dysfunction may be another factor for AF. Recently, we reported that the class Ia antiarrhythmic drug cibenzoline can attenuate the left ventricular pressure gradient (Hamada et al. 1997) and directly improve left ventricular diastolic dysfunction in HCM (Hamada et al. 2001). Thus, the chronic effect of cibenzoline on left ventricular diastolic function may lessen the risks for AF.

Recent studies (Pedersen et al. 1999; Goette et al. 2000; Nakashima et al. 2000) suggest that AF is associated with activation of the atrial RAS. According to these findings, the DD genotype is associated with activation of the RAS and is likely to be a risk factor for AF. However, our results do not support this hypothesis in patients with HCM. To our knowledge, there is no report associating the ACE polymorphisms and AF in patients with cardiovascular disease. In patients with lone AF, distribution of the *ACE* genotypes is not statistically different from that of healthy volunteers (Yamashita et al. 1997).

Allele frequencies of the *ACE* gene

Our study showed that the frequency of the D allele was 0.38 in Japanese patients with HCM, as observed in previous reports (Yoneya et al. 1995; Tabara et al. 2001). However, the D allele frequency of Japanese HCM patients was markedly lower than that of Caucasian HCM patients (Marian et al. 1993; Pfeufer et al. 1996). Although several studies (Marian et al. 1993; Yoneya et al. 1995; Pfeufer et al. 1996) showed that the D allele occurred at a higher frequency in HCM patients than in control subjects, the allele frequency of our HCM patients did not differ significantly from that of previously reported healthy Japanese (Tabara et al. 2001).

ACE I allele and deterioration toward AF

The exact mechanisms by which AF tends to develop in patients with the II genotype remain to be determined. The RAS has an important role in cardiovascular homeostasis (Malik et al. 1997). It regulates sodium balance and intravascular volume and, in addition, interacts with other blood pressure control mechanisms including the sympathetic nervous system and baroreflexes (Reid 1992). Patients with HCM usually have small left ventricular cavity size due to hypertrophy, and thus, reduction of intravascular volume seems to be related to hypotension. In addition, exercise hypotension due to inappropriate peripheral vasodilation was demonstrated in patients with HCM (Frenneaux et al. 1990). Therefore, activation of the RAS may be more protective to maintain intravascular volume and systemic circulation in HCM patients. In fact, ACE inhibition in patients with HCM is known to aggravate hemodynamics (Kyriakidis et al. 1998) and lead to hypotension and excessive systolic emptying (Topol et al. 1985). Patients with the II genotype may be in a circulatory ACE inhibitory state. Thomson et al. (1998) suggested that hypotension during central volume unloading might provide an additional or alternate trigger for arrhythmia in some patients with HCM. Thus, a systemic irritable condition associated with an ACE inhibitory state in HCM patients may be related to the high occurrence of AF in patients with the II genotype.

Study limitations

We did not measure plasma levels of renin, ACE, angiotensin II, or bradykinin in evaluating RAS. We did not evaluate the left ventricular function at the patient's initial visit to our hospital. Therefore, we could not evaluate changes in left ventricular hemodynamics. The number of patients in our study was relatively small; therefore, these findings could have resulted from a spurious or chance association. Our results should be compared with those of longitudinal studies in various populations. Further molecular, biological, and clinical studies are needed to clarify the relation between ACE polymorphism and AF in patients with HCM.

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