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AT_1 Receptor A/C^{1166} Polymorphism Contributes to Cardiac Hypertrophy in Subjects With Hypertrophic Cardiomyopathy

Arthur P.R.M. Osterop, Marcel J.M. Kofflard, Lodewijk A. Sandkuijl, Folkert J. ten Cate, Rob Krams, Maarten A.D.H. Schalekamp, A.H. Jan Danser

Abstract**—**The development of left ventricular hypertrophy (LVH) in subjects with hypertrophic cardiomyopathy (HCM) is variable, suggesting a role for modifying factors such as angiotensin II. We investigated whether the angiotensin II type 1 receptor (AT_1-R) A/C^{1166} polymorphism, the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism, and/or plasma renin influence LVH in HCM. Left ventricular mass index (LVMI) and interventricular septal thickness were determined by 2-dimensional echocardiography in 104 genetically independent subjects with HCM. Extent of hypertrophy was quantified by a point score (Wigle score). Plasma prorenin, renin, and ACE were measured by immunoradiometric or fluorometric assays, and ACE and AT_1-R genotyping were performed by polymerase chain reactions. The ACE D allele did not affect any of the measured parameters except plasma ACE ($P<0.04$). LVMI was higher ($P<0.05$) in patients carrying the AT_1-R C allele (190 ± 8.3 g/m^2) than in AA homozygotes (168 ± 7.2 g/m^2), and similar patterns were observed for interventricular septal thickness (23.0 ± 0.7 versus 21.6 ± 0.7 mm) and Wigle score (7.0 ± 0.3 versus 6.3 ± 0.3). Plasma renin was higher ($P=0.05$) in carriers of the C allele than in AA homozygotes. Multivariate regression analysis, however, revealed no independent role for renin in the prediction of LVMI. Plasma prorenin and ACE were not affected by the AT_1-R A/C^{1166} polymorphism, nor did the ACE and AT_1-R polymorphisms interact with regard to any of the measured parameters. We conclude that the AT_1-R C^{1166} allele modulates the phenotypic expression of hypertrophy in HCM, independently of plasma renin and the ACE I/D polymorphism. **(*Hypertension*. 1998;32:825-830.)**

Key Words: renin ■ cardiomyopathy ■ hypertrophy ■ receptors, angiotensin ■ angiotensin-converting enzyme

Hypertrophic cardiomyopathy (HCM) is characterized by idiopathic myocardial hypertrophy. HCM occurs as a familial disorder, with an autosomal dominant pattern of inheritance, as well as in sporadic clinical presentation. Currently, 6 genes (β-myosin heavy chain, cardiac troponin T, α-tropomyosin, cardiac myosin binding protein-C, cardiac essential light chain-1, and cardiac regulatory light chain) have been identified that may cause HCM.[1–5] Patients with identical gene mutations display variable clinical manifestations or even fail to express the disease.[6–8] Other factors, genetic as well as environmental, may therefore modify the phenotypic expression of the mutated gene.

It is now generally believed that angiotensin (Ang) II, formed by angiotensin-converting enzyme (ACE) from Ang I, is not only a potent vasoconstrictor but also an important modulator of cardiac hypertrophy.[9,10] ACE inhibition induces regression of cardiac hypertrophy, independent of load, and prevents dilatation and remodeling of the ventricle after myocardial infarction (MI).[11–14] Cardiac ACE levels are increased after MI,[11,15,16] as well as during pressure overload–induced left ventricular hypertrophy (LVH).[17] The ACE levels in the human heart are in part determined by the so-called insertion/deletion (I/D) polymorphism, with subjects with the DD genotype having higher tissue ACE levels than subjects with II or ID genotypes.[18] According to some[19–21] but not all[22,23] studies, the frequency of the D allele is higher in patients with HCM. Moreover, the extent of hypertrophy in subjects with HCM is influenced by the ACE I/D polymorphism,[20,22,23] suggesting that Ang II may modify the phenotypic expression of hypertrophy in HCM. The latter association may depend on the underlying gene mutation, since it was found only in subjects with mutations in the Arg 403 codon of the β-myosin heavy chain gene.[23]

Ang II exerts most of its known cellular actions through the angiotensin II type 1 receptor (AT_1-R).[24] Recently, the C allele of a polymorphism located in the 3′ untranslated region

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of the AT_1-R gene (corresponding to an adenine/cytosine [A/C] substitution at the 1166 position) has been shown to increase synergistically the risk of MI in subjects carrying the ACE D allele.[25]

It was the aim of the present study to investigate whether the AT_1-R C allele influences the extent of hypertrophy in HCM, eg, through an interaction with the ACE D allele. Because cardiac angiotensin generation depends largely on kidney-derived (pro)renin taken up from the circulation,[26–28] we also studied the relationship between plasma (pro)renin, cardiac hypertrophy, and the AT_1-R C allele in subjects with HCM.

Methods

Patients

One hundred sixteen patients with HCM (aged 21 to 81 years; median, 47 years) visiting the Hypertrophic Cardiomyopathy Clinic at the Thorax Center of the Academic Hospital "Dijkzigt" between December 1994 and January 1997 for routine follow-up were included in the study. HCM had been diagnosed on the basis of echocardiographic criteria showing a nondilated, hypertrophied left ventricle (any wall thickness >15 mm) in the absence of known causes of LVH such as systemic hypertension or valvular disease.[29] From each patient, a peripheral venous blood sample was collected for measurement of plasma prorenin, renin, and ACE and for the extraction of genomic DNA. Patients using ACE inhibitors (n=7) were excluded from the study because of interference with the measurement of plasma ACE. Of the remaining 109 subjects, 41 had a sporadic form of HCM and 50 had at least 1 other affected first-degree family member. The family history of HCM was unknown in 18 patients. To avoid potential bias introduced by the presence of genetically dependent samples (relatives), we randomly selected 1 patient per family. This resulted in a final cohort of 104 genetically independent patients, of whom 30 were receiving a β-adrenergic antagonist, 44 a calcium channel blocker, and 8 a diuretic.

The study was approved by the internal review board, and patients gave informed consent.

Echocardiographic Methods

Two-dimensional echocardiography was performed with commercially available equipment (Toshiba Sonolayer SSH-140A System). The heart was visualized in a number of cross-sectional planes using standard transducer positions, and images were recorded on videotape for off-line analysis. Echocardiographic analysis was performed by 2 physicians who were blinded to the results of the genotyping studies.

Interventricular septal thickness (IVS) was measured in diastole from the parasternal short-axis view at the level of the papillary muscles. The magnitude of LVH was determined by calculating left ventricular mass (LVM, g) according to the method described by Devereux et al[30]: $LVM=0.8(1.04[(IVS+LVED+LVPW)^3-LVED^3])+0.6$ g, where LVED is the left ventricular end-diastolic diameter and LVPW is the end-diastolic thickness of the posterior wall. LVM was indexed (LVMI, g/m^2) to body surface area (BSA).

Systolic anterior motion (SAM) of the anterior leaflet of the mitral valve was assessed from the 2-dimensional images and graded as 0 (absent), 1+ (mild [minimal mitral-septal distance >10 mm during systole]), 2+ (moderate [minimal mitral-septal distance ≤10 mm during systole]), or 3+ (marked [brief or prolonged contact between the mitral valve and septum]).[31]

Peak LV outflow tract gradient at rest was estimated using the modified Bernoulli equation, $P=4V^2$, where P is the pressure gradient and V is the velocity determined by Doppler echocardiography.

Because the echocardiographic measurement of LVMI may not truly reflect the extent of hypertrophy and the involvement (or lack thereof) of the distal (apical) half of the septum or lateral wall, the extent of hypertrophy was also assessed by a semiquantitative point score method developed by Wigle et al.[32] A maximum of 10 points are given: 1 to 4 points for septal hypertrophy based on magnitude of thickness, 2 points for extension of hypertrophy beyond the level of the papillary muscles (basal two thirds of septum), 2 points for extension of hypertrophy to the apex (total septal involvement), and 2 points for extension of hypertrophy into the lateral wall.

Biochemical Measurements

Blood (5 mL) was collected into tubes containing trisodium citrate (final concentration in blood, 0.026 mol/L). The blood was centrifuged at 3000*g* for 10 minutes at room temperature, and plasma was stored in 1-mL aliquots at −70°C. Shortly before assay, the samples were rapidly thawed and kept at room temperature. All assays were performed in duplicate.

Immunoreactive renin was quantified in 200 μL plasma with an immunoradiometric assay kit (Nichols Institute), following the methods proposed by Derkx et al.[33] Prorenin was activated nonproteolytically by incubation with the renin inhibitor remikiren, and its concentration was calculated by subtracting the level of renin from that of total renin (ie, the level obtained after activation). The renin and prorenin levels are expressed as milliunits per liter, using the international human kidney renin standard MRC 68/356 (Medical Research Council, National Institute of Biological Standards and Control, London, UK) as a reference. The normal range in plasma is 8 to 55 mU/L for renin and 88 to 390 mU/L for prorenin.[33]

ACE activity was measured with a commercial kit (ACE Color, Fujirebio); its normal range in plasma is 7 to 20 U/L.[34]

Genetic Analysis

Peripheral leukocytes, obtained after centrifugation of 5 mL blood (see Biochemical Measurements), were used to isolate genomic DNA in H_2O using the QIAamp Bloodkit (Qiagen Inc). DNA concentrations varied from 25 to 50 ng/μL.

The determination of the ACE gene I/D polymorphism was based on the triple-primer polymerase chain reaction (PCR) method described by Evans et al.[35] This method, which avoids mistyping of ID as DD,[36] was modified into 2 separate PCRs. The first PCR encompassed the entire I/D region. Using the sense oligonucleotide primer 5′-GCTGGAGACCACTCCCATCCTTTCT-3′ and the antisense primer 5′-TAGACCTCCACGAGTCCCCTGCAT-3′, 2 fragments of 493 bp and 781 bp were amplified corresponding to the D and I alleles, respectively. In the other PCR, an insertion-specific sense primer, 5′-TGGGATTABPCAGGCGTGATACAG-3′, was used with the above-mentioned antisense primer. This PCR amplified a 460-bp fragment corresponding to the I allele. PCR reactions were performed on 2 μL genomic DNA in a final volume of 25 μL containing 0.4 nmol/L of each primer, 1.5 mmol/L $MgCl_2$, 75 mmol/L Tris-HCl (pH 9.0), 20 mmol/L $(NH_4)_2SO_4$, 0.01% (wt/vol) Tween 20, 0.2 mmol/L of each dNTP, and 0.5 U Goldstar DNA polymerase (Eurogentec Inc). The amplification profile included an initial denaturation at 96°C for 3 minutes and 35 cycles of denaturation at 96°C for 30 seconds, annealing at 60°C for 15 seconds, and extension at 72°C for 60 seconds with a final extension time of 10 minutes. The PCR products were separated by electrophoresis on 3% agarose gels and visualized by ethidium bromide staining.

The AT_1-R gene A/C^{1166} polymorphism was determined using PCR, spanning the polymorphic site, and subsequent fluorescent sequence analysis of the PCR product. The sense primer in the PCR was extended at the 5′ site, with a nucleotide stretch homologous to the sequence analysis primer (−28M13Rev) shown in italics, 5′-*AGGAAACAGCTATGACCAT*GACATGTTCGAAACCTGTCCAT-AAAG-3′, and the antisense primer was 5′-CGGTTCAGTCC-ACATAATGC-3′. These primers allowed the amplification of a genomic DNA segment of 139 bp that contained the polymorphic site 88 bp downstream from the sequencing primer. Reactions were performed on 1 μL genomic DNA in a final volume of 15 μL containing 0.2 nmol/L sense primer, 0.4 nmol/L antisense primer, 1.5 mmol/L $MgCl_2$, 75 mmol/L Tris-HCl (pH 9.0), 20 mmol/L $(NH_4)_2SO_4$, 0.01% (wt/vol) Tween 20, 0.2 mmol/L of each dNTP, and 0.5 U Goldstar DNA polymerase (Eurogentec Inc). The ampli-

TABLE 1. Genotype Frequencies of ACE and AT_1-R Genes in HCM Patients

ACE Genotype	AT_1-R Genotype, n			Sum (%)
	AA	AC	CC	
II	15	6	3	24 (23%)
ID	33	21	3	57 (55%)
DD	9	12	2	23 (22%)
Sum (%)	57 (55%)	39 (38%)	8 (8%)	104 (100%)

fication profile included an initial denaturation at 96°C for 3 minutes and 35 cycles of denaturation at 96°C for 30 seconds, annealing at 50°C for 15 seconds, and extension at 72°C for 60 seconds with a final extension time of 10 minutes. After completion of the PCR, 6 μL was used to perform sequence analysis reactions using the fluorophore-labeled "−28M13Rev DYEnamic ET-primer" and the "DYEnamic direct cycle sequencing kit with 7-deaza dGTP" according to the instructions of Amersham International. The sequence reaction products were separated by electrophoresis in polyacrylamide gels and analyzed in an ABI Prism 377 automatic DNA sequencer (Perkin-Elmer Corp) using the accompanying software.

Statistical Analysis

Data are expressed as counts, mean±SEM, or as median and range. Statistical analysis was performed with the SPSS 7.0 statistical package. The Hardy-Weinberg equilibrium was tested by a χ^2 test. To analyze differences between carriers of the C or D allele and the noncarriers, we collapsed the AC and CC genotypes and the ID and DD genotypes into 2 groups (AC+CC and ID+DD, respectively). Because of a nonnormal distribution of most parameters, differences between carrier and noncarrier groups were tested by the Mann-Whitney *U* test. Univariate and multivariate regression analyses were conducted to determine the percentage of explained variance in LVMI that is accounted for by the genotypes of the candidate modifier genes and other variables. Both polymorphisms were tested as codominant 0, 1, or 2 ordinal variables (presence of 0, 1, or 2 C or D alleles). In the multivariate regression analysis, the 2 polymorphisms, gender (male=0, female=1), age, peak LV outflow tract gradient, and plasma renin concentration were considered independent variables. Plasma prorenin, plasma ACE, and SAM were excluded from this analysis because of their physiological interrelationship with plasma renin, ACE genotype, and peak LV outflow tract gradient, respectively. These interrelationships were consolidated by respective high correlations: plasma renin (r=0.680, P<0.001), ACE genotype (r=0.389, P=0.003), and peak LV outflow tract gradient (r=0.766, P<0.001).

Results

The distributions of the ACE I/D and the AT_1-R A/C^{1166} genotypes in 104 genetically independent HCM patients are shown in Table 1. The frequencies of the ACE I and D alleles (0.50 and 0.50, respectively) and the AT_1-R A and C alleles (0.74 and 0.26, respectively) were similar to previously reported numbers in normal white populations.[18,25,37,38] Genotype frequencies were in agreement with Hardy-Weinberg equilibrium.

Table 2 lists the characteristics of the HCM patients according to ACE I/D genotype. No differences with regard to gender, age, BSA, or any of the cardiac parameters were found between carriers of the D allele and subjects with the II genotype. Plasma renin and prorenin levels (Table 2), as well as the percentage of patients taking β-adrenergic antagonists, calcium channel blockers, or diuretics (data not shown), were also similar in II and ID+DD patients. In accordance with previous studies,[39,40] plasma ACE activity was highest in DD subjects and intermediate in ID subjects. Regression analysis showed that the ACE genotype accounted for 15.1% of the variability in plasma ACE activity (r=0.389, P=0.003).

Table 3 lists the characteristics of the HCM patients according to AT_1-R A/C^{1166} genotype. The percentage of patients taking β-adrenergic antagonists, calcium channel blockers, or diuretics did not differ between AA and AC+CC patients (data not shown). Gender, age, BSA, and peak LV outflow tract gradient were not associated with the AT_1-R A/C^{1166} polymorphism. However, LVM, LVMI, and plasma renin were significantly higher in subjects carrying 1 or 2 C alleles than in AA homozygotes, and similar patterns were observed for IVS and Wigle score. Regression analysis

TABLE 2. Characteristics of HCM Patients According to ACE I/D Genotype

Parameter	ACE Genotype			*P*
	II (n=24)	ID (n=57)	DD (n=23)	ID+DD vs II
Gender, M/F	14/10	36/21	15/8	0.632
Age, y	49.8±3.3	46.2±2.0	48.0±2.8	0.358
BSA, m^2	1.80±0.05	1.85±0.02	1.88±0.04	0.159
IVS, mm	22.0±0.9	22.3±0.7	22.3±1.1	0.956
LVM, g	326.5±22.2	331.1±14.1	315.2±18.4	0.923
LVMI, g/m^2	182.5±11.9	180.3±8.1	167.0±8.3	0.725
Wigle score, 1–10	6.8±0.4	6.6±0.3	6.5±0.6	0.743
SAM, 0/1+/2+/3+*	4/1/7/9	11/9/11/22	5/4/8/4	0.369
Gradient, mm Hg	55.8±9.4	47.6±5.4	36.1±7.9	0.395
Prorenin, mU/L	156 (86–1339)	173 (47–813)	141 (28–299)	0.540
Renin, mU/L	20.7 (7.8–202)	21.0 (3.0–85)	20.3 (3.0–54)	0.383
ACE, U/L	8.7±0.5	9.9±0.4	11.2±0.5	0.038

Values are counts, mean±SEM, or median (range). Mann-Whitney *U* test was used to test for differences between the ID+DD and II subjects. Gradient indicates peak LV outflow tract gradient; Wigle score, semiquantitative point score assessing the extent of hypertrophy.

*SAM could not be determined in 9 patients.

TABLE 3. Characteristics of HCM Patients According to AT_1-R A/C[1166] Genotype

	AT_1-R Genotype			*P*
Parameter	AA (n=57)	AC (n=39)	CC (n=8)	AC+CC vs AA
Gender, M/F	33/24	29/10	3/5	0.288
Age, y	48.6±2.1	45.7±2.1	47.4±6.9	0.332
BSA, m^2	1.84±0.03	1.88±0.03	1.75±0.06	0.796
IVS, mm	21.6±0.7	22.9±0.7	23.4±2.3	0.111
LVM, g	306.2±12.5	350.1±16.2	356.5±49.3	0.010
LVMI, g/m^2	167.9±7.2	186.5±8.1	205.4±30.3	0.010
Wigle score, 1–10	6.3±0.3	6.9±0.3	7.3±0.8	0.109
SAM, 0/1+/2+/3+*	7/8/14/23	12/5/8/10	1/1/4/2	0.045
Gradient, mm Hg	53.1±5.5	37.8±6.4	43.6±16.6	0.078
Prorenin, mU/L	161 (28–741)	147 (48–1339)	228 (86–813)	0.627
Renin, mU/L	17.0 (3.0–55)	22.7 (3.0–202)	24.6 (10.2–85)	0.054
ACE, U/L	10.2±0.4	9.6±0.4	9.9±0.8	0.225

Values are counts, mean±SEM, or median (range). Mann-Whitney *U* test was used to test for differences between the AC+CC and AA subjects. Gradient indicates peak LV outflow tract gradient; Wigle score, semiquantitative point score assessing the extent of hypertrophy.

*SAM could not be determined in 9 patients.

showed that the AT_1-R genotype accounted for 4.3% of the variability of LVM ($r=0.208$, $P=0.034$), 4.5% of the variability of LVMI ($r=0.213$, $P=0.031$), and 4.2% of the variability of plasma renin ($r=0.204$, $P=0.037$). SAM was lower in carriers of the C allele, but regression analysis revealed no relationship between AT_1-R genotype and SAM ($r=0.152$, $P=0.138$).

Using a 2-factor ANOVA, no interaction was observed between the ACE D allele and the AT_1-R C allele with regard to any of the measured parameters.

Plasma renin, plasma prorenin, and the sum of plasma renin and plasma prorenin (plasma total renin) did not correlate with LVM, LVMI, or any of the other cardiac parameters (data not shown).

Multivariate regression analysis showed that age, peak LV outflow gradient, and the AT_1-R A/C[1166] polymorphism, but not gender, plasma renin, or the ACE I/D polymorphism, were significant predictors of LVMI (Table 4).

Discussion

The present study shows that the AT_1-R genotype influences the magnitude of LVH in subjects with HCM. LVM and LVMI were significantly higher in patients carrying the C allele than in AA homozygotes, and a similar pattern was observed for IVS and Wigle score, the latter being a semiquantitative score reflecting the extent of cardiac hypertrophy.[32] No relationship with SAM and peak LV outflow tract gradient was observed. Interestingly, plasma renin but not plasma prorenin was higher in subjects carrying the C allele than in AA homozygotes.

TABLE 4. Multivariate Regression Analysis of Factors With Potential Effect on LVMI

Parameter	β	SEM	*P*
Gender (male=0, female=1)	7.045	11.015	0.524
Age, y	−0.898	0.356	0.013
ACE genotype, No. of D alleles	−8.103	8.039	0.316
AT_1-R genotype, No. of C alleles	20.645	8.569	0.018
Renin, mU/L	−0.159	0.247	0.521
Gradient, mm Hg	0.276	0.134	0.043

Gradient indicates peak LV outflow tract gradient.

The AT_1-R A/C[1166] polymorphism is located at the 5′ site of the 3′ untranslated region of the gene. This polymorphism is probably not functional but might be in linkage equilibrium with an unidentified functional variant affecting the structure or function of the AT_1-R (or adjacent unknown genes). Tiret et al[25] have speculated that the downregulation of the AT_1-R gene in response to Ang II is altered in subjects with the C allele. Such altered downregulation, which is most likely tissue-specific,[41–44] would not only offer an explanation for our findings on cardiac hypertrophy but it might also explain the increased renin levels in patients carrying the C allele, since Ang II stimulates cardiac hypertrophy[9,45] and regulates renin release[46,47] via AT_1-R. In line with our findings, Hein et al[48] recently showed that overexpression of the AT_1-R in the mouse leads to an increase in cardiac mass and myocyte hypertrophy.

The C allele has been associated with hypertension,[38,49] aortic stiffness,[50] the development of coronary artery stenosis,[51] and coronary artery vasoconstriction.[52] The frequency of the C allele in the HCM subjects of the present study was similar to that reported previously in the general population.[25,50] Thus, the AT_1-R A/C[1166] polymorphism is not associated with HCM as such but rather modulates the phenotypic expression of hypertrophy in subjects with HCM. Such modulation might explain why individuals with the same HCM mutation show a significant variability in the magnitude of LVH.[6–8]

The ACE I/D polymorphism has also been reported to account for some of the variability of LVMI in HCM subjects.[20,22] This could not be confirmed in the present study, although our data do support the previously described association between plasma ACE and ACE genotype.[39,40] It is possible that the influence of the ACE genotype in HCM

subjects depends on the specific disease gene mutation.[23] We did not determine the underlying gene mutations in our HCM patients. The presence of different sarcomeric gene mutations in our population, however, might offer an explanation for the lack of association between ACE genotype and LVH in the present cohort. It might also explain why Brugada et al[53] did not find an association between the AT_1-R C allele and cardiac hypertrophy in their patients. In addition, the HCM patients selected by Brugada et al had a less severe form of HCM (wall thickness ≥13 mm) than those selected in the present study (wall thickness >15 mm). This may have enhanced our chance of finding a significant association between hypertrophy and the AT_1-R C allele.[23]

Theoretically, the high tissue ACE levels found in DD subjects[18] might lead to high tissue Ang II levels and thereby enhance the AT_1-R C allele-related effects on hypertrophy. Such synergy has been described for the risk of MI.[25] Any interaction between the AT_1-R C allele and the ACE D allele, however, will be obscured by the elevated plasma renin levels found in HCM patients carrying the C allele. High plasma renin levels, via uptake of renin by the heart,[26,27,54] will also lead to high cardiac Ang II levels. Thus, cardiac Ang II levels may already be high in AC and CC subjects independently of the ACE gene polymorphism, and this could explain the lack of interaction between the 2 gene polymorphisms of the renin-angiotensin system in the present study.

Recently, plasma renin activity was found to correlate positively with LVM in healthy young adults.[10] One may therefore argue that the elevated plasma renin levels in subjects carrying the C allele are the underlying reason for the relationship between the C allele and cardiac hypertrophy. However, plasma renin did not correlate with either LVM or LVMI in the present study, and multivariate regression analysis revealed no independent effect of plasma renin after correction for AT_1-R genotype. Thus, it appears that in HCM subjects, other factors related to the AT_1-R A/C^{1166} polymorphism (eg, cardiac AT_1-R density) are more important determinants of cardiac hypertrophy than plasma renin.

In addition to the AT_1-R A/C^{1166} polymorphism, age and peak LV outflow gradient were also independent predictors of LVMI. Both associations have been reported before.[55–59] LVMI decreases with age, most likely because progressive wall thinning occurs gradually over time in HCM patients.[55,56] Mitral leaflet-septal contact determines the magnitude of the pressure gradient in the LV outflow tract, and more marked SAM of the mitral valve is associated with an augmentation of LVH.[55–59]

In conclusion, the results of this study support a modulating role for the AT_1-R A/C^{1166} polymorphism in the development of LVH in patients with HCM, independent of age, gender, peak LV outflow gradient, plasma renin, and the ACE I/D polymorphism.

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