Journal of Human Hypertension (1997) 11, 595–597

Left ventricular hypertrophy, blood pressure and ACE genotype in untreated hypertension

J Mayet[1,2], KPJ O'Kane[3], R Elton[4], HA Johnstone[3], M Shahi[2], MA Ozkor[1], AV Stanton[1], NR Poulter[1], PS Sever[1], RA Foale[2], DJ Webb[3] and SAMcG Thom[1]

[1]*The Peart-Rose Clinic and* [2]*Department of Cardiology, St Mary's Hospital, Imperial College of Science, Technology and Medicine, London;* [3]*Department of Medicine, Western General Hospital;* [4]*Medical Statistics Unit, University of Edinburgh, UK*

It has been suggested that the deletion polymorphism of the angiotensin-converting enzyme (ACE) genotype may be important in the development of left ventricular hypertrophy (LVH). In order to test this hypothesis we investigated the interaction between blood pressure (BP), LVH and ACE genotype in 86 previously untreated hypertensive patients. Each underwent two-dimensional and Doppler echocardiography and ACE genotyping.

There were no significant differences in BP, the parameters of left ventricular structure (including left ventricular mass index) or diastolic function between the three genotype groups. Additionally, there were no significant differences in the relationship between systolic BP and left ventricular mass index among the three genotype groups (II genotype, $r = 0.46$, $P = 0.02$; ID genotype, $r = 0.42$, $P = 0.01$; DD genotype, $r = 0.34$, $P = 0.10$; F = 0.38).

In contrast to some previous studies, we have found in this group of previously untreated hypertensive subjects no evidence to suggest that the deletion polymorphism of the ACE genotype is important in the development of LVH.

Keywords: left ventricular hypertrophy; hypertension; ACE genotype

Introduction

Left ventricular hypertrophy (LVH) in essential hypertension is a potent independent risk factor for an increased cardiovascular morbidity and mortality.[1] Previous studies have found a weak association between clinic blood pressure (BP) and LVH.[2] Twenty-four hour ambulatory BP is a closer correlate of left ventricular mass than clinic values,[2,3] but it is clear that other non-haemodynamic factors must also play a role in determining LVH.[4] It has been suggested that genetic factors exert an important influence on the genesis of LVH.[4] Angiotensin II has been shown to cause myocyte proliferation[5] and non-myocyte growth.[6] Angiotensin–converting enzyme (ACE) produces angiotensin II from its relatively inactive precursor, angiotensin I. An insertion/deletion polymorphism in the gene encoding for ACE has been shown to account for almost half of the variance in plasma ACE concentration.[7] Deletion homozygotes have higher plasma, and presumably tissue, ACE concentrations.[8] The increased ACE activity associated with the deletion polymorphism could therefore be a mechanism for the development of LVH *via* increased cardiac angiotensin II.

Our hypothesis in performing the present study was that in hypertensive patients increased plasma, and presumably tissue, ACE concentrations in subjects who carry the ACE gene polymorphism deletion allele would confer an increased tendency to develop LVH directly or through an interaction with BP.

Correspondence: Dr J Mayet, Department of Cardiology, St. Mary's Hospital, Praed Street, Paddington, London W2 1NY, UK

Subjects and methods

Eighty-six otherwise healthy subjects with essential hypertension were studied, none of whom had previously received antihypertensive therapy. Each patient underwent two-dimensional and Doppler echocardiography with a phased array sector scanner (General Electric Pass II, 3.3 MHz transducer). Interventricular septal wall thickness (IVS), posterior wall thickness (PWT) and left ventricular internal diameter (LVID) were measured from the left ventricular short axis view with two-dimensionally guided echocardiography. Left ventricular mass index (LVMI) was calculated using Devereux's method.[9] The ratio of the peak flow velocity of the early filling wave to peak flow velocity of the atrial wave (E/A ratio) and the isovolumic relaxation time (IVRT) were measured as previously described.[10] ACE genotype was determined using the polymerase chain reaction as described by Rigat *et al*.[11] Determination of ACE genotype was possible in 83 of the 86 samples.

Results

For the group as a whole, LVMI was significantly related to systolic and diastolic BP ($r = 0.38$, $P < 0.01$; $r = 0.40$, $P < 0.01$, respectively). Addition-

Table 1 Patient characteristics and haemodynamic and structural parameters for each of the ACE genotype groups

	II	*ID*	*DD*
Number (%)	23 (28%)	36 (43%)	24 (29%)
Male/Female	14/9	25/11	17/7
Caucasian/ Afro–Carribean/ Oriental	8/15/0	20/15/1	12/11/1
Age (years)	49 ± 2	50 ± 3	47 ± 3
Reported duration of hypertension (months)	22 ± 6	35 ± 8	36 ± 8
Systolic blood pressure (mm Hg)	164 ± 4	167 ± 4	164 ± 4
Diastolic blood pressure (mm Hg)	96 ± 3	98 ± 2	97 ± 2
Heart rate (beats/min)	67 ± 3	65 ± 2	70 ± 3
IVS (cm)	1.1 ± 0.05	1.2 ± 0.04	1.1 ± 0.04
LVID (cm)	4.7 ± 0.08	4.9 ± 0.10	5.0 ± 0.09
PWT (cm)	1.1 ± 0.05	1.1 ± 0.04	1.1 ± 0.04
LVMI (g/m^2)	130 ± 7	134 ± 7	132 ± 8
E/A ratio	1.07 ± 0.10	1.07 ± 0.09	1.03 ± 0.07
IVRT (ms)	104 ± 6	102 ± 4	96 ± 6

No differences are statistically significant.

ally, systolic BP was related to both E/A ratio and IVRT ($r = -0.33$, $P < 0.01$; $r = 0.30$, $P < 0.05$, respectively). The relationships between diastolic BP and E/A ratio and IVRT were also significant ($r = -0.26$, $P = 0.04$; $r = 0.36$, $P < 0.01$, respectively). The three allelic groups were similar with regard to age, sex ratio, duration of hypertension and BP (Table 1). However, there was a higher proportion of black subjects homozygous for the insertion allele, although this was not statistically significant ($\chi^2 = 2.88$, 2 d.f.). Measurements of left ventricular structure and diastolic function were similar among the groups (Table 1).

Figure 1 shows the regression lines of LVMI on systolic BP for each genotype. There was no significant difference in the slope of the regression lines for the three different genotype groups (II genotype, $r = 0.46$, $P = 0.02$; ID genotype, $r = 0.42$, $P = 0.01$; DD genotype, $r = 0.34$, $P = 0.10$; analysis of covariance $F = 0.38$, 2 and 79 d.f.). This remained true after adjusting for the effects of age, sex and ethnicity on the relationships.

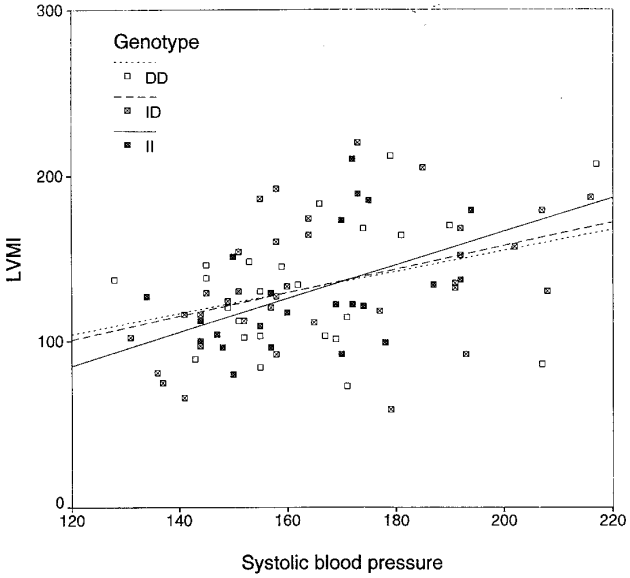

Figure 1 The relationship between systolic BP (mm Hg) and LVMI (g/m^2) for each of the three ACE genotype groups.

When parallel lines were fitted with intercepts linearly related to the number of D genes, the confidence intervals for the increase in LVMI per additional D gene adjusted for systolic BP was –8.8, +10.9 g/m^2.

Discussion

Systolic and diastolic BP were independent of ACE genotype in the present study, in keeping with previous observations[12,13] and it would thus seem that ACE genotype is not important in determining the severity of hypertension.

Left ventricular structural and functional parameters were similar among the groups. Systolic BP, but not ACE genotype, was positively related to LVMI in all groups. Our hypothesis in this study was that the deletion allele, associated with higher plasma, and presumably tissue ACE concentrations,[7] would be a risk factor for the development of LVH. The deletion allele has been shown in a large population study[14] to be a risk factor for electrocardiographic LVH in normotensive men, but not in normotensive women or hypertensive subjects of either sex. However, electrocardiographic assessment is limited by its poor sensitivity for detecting LVH. The most significant study using echocardiography is that reported from the Framingham population; in 2439 subjects they found no relationship between ACE genotype and LVH.[15] In contrast to this, smaller studies from Iwai and colleagues[16] found the deletion allele to be linked with LVH measured by echocardiography in a heterogeneous population with a wide variety of cardiac diseases, and Gharavi and colleagues,[17] who reported a similar finding in a racially-mixed, purely hypertensive group of 67 patients. However, a further Australian study in 72 hypertensive patients found no relationship between ACE genotype and LVH.[18] In addition to these, a previous study in a Caucasian Scottish group of 85 patients with essential hypertension,[19] although finding no differences in LVH between genotype groups, concluded that the effect of systolic BP on LVMI is expressed only in the presence of the deletion allele. These findings conflict with those of the present study in which a positive relationship between systolic BP and LVMI was observed in all subjects, including those homozygous for the insertion allele.

One limitation of this study is the ethnic mix of the population. However, when Afro–Carribeans and Caucasians are analysed separately, the results are similar to that of the combined group. A second limitation relates to the sample size. In this group of 86 patients the possibility that LVMI differs by up to 20 g/m^2 cannot be excluded.

In conclusion, in this population of untreated subjects with essential hypertension no association was found between the ACE gene and LVH.

References

1 Levy D *et al*. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Study. *N Engl J Med* 1990; **322**: 1561–1566.
2 Rowlands DB *et al*. Assessment of left ventricular mass and its reponse to antihypertensive treatment. *Lancet* 1982; **1**: 467–470.
3 Drayer JM, Weber MA, De Young JL, Brewer DD. Long-term monitoring in the evaluation of antihypertensive therapy. *Arch Intern Med* 1983; **143**: 898.
4 Frohlich ED *et al*. The heart in hypertension. *New Engl J Med* 1992; **327**: 998–1008.
5 Morgan HE, Baker KM. Cardiac hypertrophy. Mechanical, neural and endocrine dependence. *Circulation* 1991; **83**: 13–25.
6 Weber KT *et al*. Pathological hypertrophy with fibrosis: the structural basis for myocardial failure. *Blood Press* 1992; **1**: 75–85.
7 Rigat B *et al*. An insertion/deletion polymorphism in the angiotensin 1-converting enzyme gene accounting for half the variance of serum enzyme levels. *J Clin Invest* 1990; **86**: 1343–1346.
8 Costerousse O, Allegrini J, Lopez M, Alhenc-Gelas F. Angiotensin I converting enzyme in human circulating monuclear cells. Genetic polymorphism of expression in T-lymphocytes. *Biochem J* 1993; **290**: 33–40.
9 Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: Anatomic validation of the method. *Circulation* 1977; **55**: 613–618.
10 Mayet J *et al*. Ventricular arrhythmias in hypertension: in which patients do they occur? *J Hypertens* 1995; **13**: 269–276.
11 Rigat B, Hubert C, Corvol P, Soubrier F. PCR detection of the insertion/deletion polymorphism of the human angiotensin converting enzyme gene (DCP) (dipeptidyl carboxylase). *Nucleic Acids Res* 1992; **20**: 1433.
12 Harrap SB *et al*. The angiotensin-converting enzyme gene and predisposition to high blood pressure. *Hypertension* 1993; **21**: 455–460.
13 Schmidt S *et al*. Polymorphism of the angiotensin 1 converting enzyme gene is apparently not related to high blood pressure: Dutch hypertension and offspring study. *J Hypertens* 1993; **11**: 345–348.
14 Schunkert H *et al*. Association between a deletion polymorphism of the angiotensin-converting-enzyme gene and left ventricular hypertrophy. *N Engl J Med* 1994; **330**: 1634–1638.
15 Lindpainter K *et al*. Absence of association or genetic linkage between the angiotensin-converting-enzyme gene and left ventricular mass. *N Engl J Med* 1996; **334**: 1023–1028.
16 Iwai N, Ohmichi N, Nakamura Y, Kinoshita M. DD genotype of the angiotensin-converting enzyme gene is a risk factor for left ventricular hypertrophy. *Circulation* 1994; **90**: 2622–2628.
17 Gharavi AG *et al*. Deletion polymorphism of the angiotensin-converting enzyme gene is independently associated with left ventricular mass and geometric remodelling in systemic hypertension. *Am J Cardiol* 1996; **77**: 1315–1319.
18 West MJ *et al*. Renin and angiotensin-converting enzyme genotypes in patients with essential hypertension and left ventricular hypertrophy. *Clin Exp Pharm Physio* 1994; **21**: 207–210.
19 Prasad N *et al*. The relationship between blood pressure and left ventricular mass in essential hypertension is observed only in the presence of the angiotensin-converting enzyme gene deletion allele. *Q J Med* 1994; **87**: 659–662.