

Association of ACE genotype and predominantly diastolic hypertension: a preliminary study

Pablo Martín Jiménez,* Cecilia Conde,* Ana Casanegra,† Cesar Romero,* Aldo Hugo Tabares,† Marcelo Orías #

Key words:
pulse pressure,
hypertension,
angiotensin-
converting
enzyme,
genetic,
angiotensin II

* Institute for Medical
Research Mercedes y
Martín Ferreyra (INIMEC-
CONICET),
Córdoba,
Argentina.

† Vascular Medicine
Hospital Privado,
Córdoba,
Argentina

*Nephrology Section
Natorto Alledde,
Córdoba,
Argentina.

Correspondence to:
Marcelo Orías,
Friuli 2434 CC 389,
5016 Córdoba,
Córdoba, Argentina.
Tel: +11 54 351 426
9278
Fax: +11 54 351 426
9278
E-mail: orias@
uolsinetis.com.ar

Accepted for publication
5th February 2007

JRAAS 2007;8:42–44

Abstract

Background. The insertion/deletion (I/D) angiotensin-converting enzyme (ACE) polymorphism has been established as a cardiovascular risk factor in some populations, but the association with essential hypertension is controversial. Predominantly diastolic hypertension (PDH), or narrow pulse pressure hypertension, has been shown to have increased peripheral resistance. Because a DD genotype has been associated with higher plasma ACE levels and angiotensin II activity, we genotyped PDH patients for ACE I/D polymorphism. **Methods.** Ninety-three patients with systolic blood pressure (BP) < 140 mmHg systolic and diastolic BP > 90 mmHg, or BP > 140/90 mmHg with a pulse pressure < 45 mmHg, were defined as PDH. The II, ID and DD genotype variants of ACE were characterised by the triple primer nested-PCR method. Results were compared to 75 normotensive control individuals. Statistical significance was assessed by the Chi square test. **Results.** The genotype distribution among PDH patients was II=20 (21.5%), ID=34 (36.5%), DD=39 (42%), while the distribution among normotensive controls was II=16 (21.4%), ID=42 (56%), DD=17 (22.6%). The difference in genotype distribution between PDH patients and controls was significant ($p<0.02$). ACE allele frequencies in PDH patients and controls were D=0.60, I=0.40 and D=0.51, I=0.49, respectively, statistically non-significant (ns). **Conclusion.** These results suggest an association between ACE genotype DD and predominantly diastolic hypertension.

Introduction

Hypertension (HTN) is a worldwide hazard that contributes to many cardiovascular deaths each year. In pursuit of its pathophysiology, it has become clear that HTN is a syndrome rather than a single disease. Many efforts have been made to recognise homogeneous subgroups (intermediate phenotypes) within essential HTN, but this strategy has been of limited success.¹

We believe that pulse pressure patterns may help better define intermediate phenotypes, therefore hypertensive patients can be classified as having isolated systolic hypertension (ISH),

isolated diastolic hypertension (IDH), or systo-diastolic hypertension (SDH). Although recognised many years ago, ISH has recently become a well-characterised entity. Its contribution to cardiovascular mortality is prominent and large randomised clinical trials have demonstrated that different drug regimens can reduce mortality.^{2,3} ISH is marked by increased arterial stiffness. A less well-defined entity is IDH. This narrow pulse pressure pattern of high BP is usually seen in younger patients and has been defined as a low morbidity-mortality disease.⁴ These patients have increased peripheral resistance and a relatively higher stroke volume than those with ISH.⁵

SDH is the most common elevated blood pressure (BP) pattern⁶ and is usually a combination of pulse pressure subtypes with normal pulse pressure, decreased pulse pressure (higher diastolic relative to systolic BP) or increased pulse pressure (higher systolic relative to diastolic BP). We believe that isolated diastolic and systo-diastolic narrow pulse pressure hypertensive patients represent a clinical continuum of narrow pulse pressure HTN and therefore it is arbitrary to divide them into different groups. We refer to this novel phenotypic group as “predominantly diastolic hypertension” (PDH).

Angiotensin-converting enzyme (ACE) is a zinc metallopeptidase that converts angiotensin I (Ang I) into the vasoactive peptide Ang II, and inactivates bradykinin. The complete amino acid sequence deduced from the complementary desoxyribonucleic acid (cDNA) contains 1,306 residues,⁷ and the DNA sequence contains a polymorphism consisting of the presence or absence of a 250-bp fragment. The absence of the segment constitutes a deletion (D) and its presence, an insertion (I).⁸

The I/D ACE genotype has been established as a cardiovascular risk factor in selected populations, but the association with essential hypertension is controversial.⁹⁻¹¹ ACE DD genotype has been associated with half the variance in ACE plasma levels^{8,12} and increased levels of Ang II could play a role in enhancing peripheral resistance.

Table 1

ACE polymorphism frequency in predominantly diastolic hypertensive patients and normotensive controls.

	Controls	PDH
Patients (male)	75 (30)	93 (55)
Age±SD	48±19	41±10.1
Average BP mmHg	112/69	134/98
BMI±(SD) kg/m ²	24±3.8	24±6
II (%)	16 (21.4)	20 (21.5)
ID (%)	42 (56)	34 (36.5)
DD (%)	17 (22.6)	39 (42)

A significant difference was encountered between the hypertensive and the control groups; DD vs. ID vs. (p<0.02).

Considering the hypothesis that the ACE DD genotype may participate in the PDH phenotype, the purpose of this preliminary study was to investigate an association between the ACE I/D polymorphism in PDH patients.

Methods

Study population

A total of 93 PDH patients and 75 normotensive individuals were recruited from the outpatient clinic of a university-affiliated tertiary care institution from November 2002 to December 2005. All patients willing to participate in the study and those who met inclusion criteria during the recruitment period were enrolled.

PDH patients were defined as those with systolic BP < 140 mmHg and diastolic BP > 90 mmHg, or BP > 140/90 mmHg with a pulse pressure < 45 mmHg¹³ on two separate clinic visits.

BP was measured in duplicate on the left arm with a mercury column sphygmomanometer after five minutes rest in the seated position. Systolic (SBP) and diastolic BP (DBP) values were determined by the first and fifth Korotkoff phases, respectively. Pulse pressure is the difference between the SBP and DBPs. Body height and weight were used to calculate body mass index (BMI: weight [in kilograms] divided by height [in metres] squared).

The control group was composed of normotensive individuals aged 60 and older. Subjects with normal BP aged less than 60 were included if both their parents and known relatives did not have HTN by the age of 60.

Patients with known secondary HTN, renal insufficiency or nephropathy were excluded, as were patients receiving antihypertensive medications. The II, ID and DD genotype variants of ACE were characterised by the triple primer nested-PCR method.¹⁴

Arcus Quickstat (Biomedical version 1.2) software was used to perform all statistical analysis. ACE genotype percentages were evaluated by a two-sided *t* by *c* Chi square test and a value of p<0.05 was considered statistically significant.

All patients signed informed consent. The consent form and the protocol were approved by the local Institutional Review Board.

Results

The ACE I/D allele distribution encountered in hypertensive patients (55 males, mean age 41±10.1 years; BMI 24±6; average BP 134/98 mmHg) was: II=20 (21.5%), ID=34 (36.5%), DD=39(42%). The distribution in the control group I/D polymorphism (30 males; mean age 48±19 years; BMI: 24±3.8; mean BP 112/69 mmHg) was: II=16 (21.4%), ID=42 (56%), DD=17 (22.6%). The difference in genotype distribution between PDH patients and controls was significant (p<0.02) (see table 1). ACE I/D allele frequencies in PDH patients and controls were D=0.60, I=0.40 and D=0.51, I=0.49, respectively, p=0.27 (ns).

Discussion

Our results suggest an association between the ACE DD genotype and PDH. Despite the fact that this study lacks a sufficient number of patients to conclusively validate this observation, we believe the results may indicate a true association. Ang II, produced by conversion of Ang I by the ACE enzyme, is one of the most potent vasoconstrictors known to date, the ACE I/D gene polymorphism contributes to the variation in circulating plasma ACE levels and the DD genotype is associated with higher ACE levels.^{8,11} Also, because DBP correlates more closely to peripheral resistance in younger patients⁵ and brachial pulse pressure is inversely related to peripheral resistance,^{15,16} hypertensive patients with low pulse pressure have increased systemic vascular resistance. Therefore, the DD genotype may explain the high peripheral vascular resistance observed in IDH (and probably in PDH) patients. However, the hypothesis that PDH DD patients have increased ACE levels and increased peripheral resistance will need to be confirmed by studies that evaluate ACE levels and cardiovascular haemodynamics.

While recognising that this study was underpowered,¹⁷ several interesting observations can be made. We believe that PDH may represent a new subgroup of essential hypertensive patients. This novel low pulse pressure subgroup combines patients with IDH (e.g., BP of 130/100 mmHg) and those with SDH that have a higher DBP relative to their SBP (e.g. 140/100 mmHg, 150/110, 160/120). Although this

group may be disputed as arbitrary, one can speculate that patients with a narrow pulse pattern may have a more homogeneous genetic background. Supporting the previous statement is the fact that a division between IDH and SDH with a relatively elevated diastolic pressure is based on the epidemiology and treatment of hypertension, not etiology or pathophysiology.¹⁸ Furthermore, clinical follow-up of PDH patients demonstrates that isolated diastolic hypertensive patients often evolve into a systo-diastolic pattern with a narrow pulse pressure.¹⁹

When dealing with genetic hypertension associations, a considerable amount of effort has to be placed in obtaining normotensive controls. Selection of normotensive control groups in hereditary diseases that increase in prevalence with ageing is difficult. The majority of hypertension studies define normotensive individuals as those currently with BP below 140/90 mmHg or not taking antihypertensive medications. This potential selection bias does not take into account whether the subject will become hypertensive in the future and is especially relevant when young patients are included in normotensive control groups. Also, because HTN has an important hereditary basis, an extensive effort should be made to rule out a family history of HTN. Therefore, for the purpose of this study, individuals with normal BP below age 60 were considered normotensive if a detailed history indicated that their parents (aged 60 and older) and other first-degree relatives also had normal BP. Subjects older than 60 years were considered normotensive after two separate normal clinic BP measurements.

Finally, we believe that this paper highlights the need for encountering embedded essential HTN phenotypes that may have a more homogenous genetic background. Failure in the recognition of intermediate phenotypes may be one of the reasons why associations of genetic variants in unselected hypertensive populations have given ambiguous results.

Conclusion

These results suggest an association between the DD ACE polymorphism and a novel low pulse pressure/predominantly diastolic subgroup of essential hypertensive patients.

This study was partially supported by grants from Fundación Para el Progreso de la Medicina and Fundación Antorchas.

References

1. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. *Cell* 2001;**104**:545-56.
2. SHEP, Cooperative, Research, Group. Prevention of stroke by antihypertensive drug treatment in older persons

with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991;**265**:3255-64.

3. Staessen J, Fagard R, Thijs L *et al*. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension: the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 1997;**350**:757-64.
4. Hozawa A, Ohkubo T, Nagai K *et al*. Prognosis of isolated systolic and isolated diastolic hypertension as assessed by self-measurement of blood pressure at home. The Ohasama study. *Arch Intern Med* 2000;**160**:3301-06.
5. Galarza C, Alfie J, Waisman G *et al*. Diastolic pressure underestimates age-related hemodynamic impairment. *Hypertension* 1997;**30**:809-16.
6. Owens P, Lyons S, O'Brien E. Ambulatory blood pressure monitoring in the hypertensive population: patterns and prevalence of hypertensive subforms. *J Hypertens* 1998;**16**:1735-45.
7. Soubrier E, Alhenc-Gelas F, Hubert C *et al*. Two putative active centers in human angiotensin I-converting enzyme revealed by molecular cloning. *PNAS* 1988;**85**:9386-90.
8. Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier E. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *J Clin Invest* 1990;**86**:1343-6.
9. Jeunemaitre X, Lifton R, Hunt S, Williams R, Lalouel J. Absence of linkage between the angiotensin converting enzyme locus and human essential hypertension. *Nat Genet* 1992;**1**:72-5.
10. Staessen J, Wang J, Ginocchio G *et al*. The deletion/insertion polymorphism of the angiotensin converting enzyme gene and cardiovascular-renal risk. *J Hypertens* 1997;**15**:1579-92.
11. Mostafa Zaman M, Yoshiike N, Date C *et al*. Angiotensin converting enzyme genetic polymorphism is not associated with hypertension in a cross-sectional sample of a Japanese population: The Shibata Study. *J Hypertens* 2001;**19**:47-53.
12. Tiret L, Rigat B, Visvikis S *et al*. Evidence, from combined segregation and linkage analysis, that a variant of the angiotensin-converting enzyme (ACE) gene controls plasma ACE levels. *Am J Hum Genet* 1992;**51**:197-205.
13. Schillaci G, Verdecchia P, Borgioni C, Ciucci A, Porcellati C. Predictors of diurnal blood pressure changes in 2042 subjects with essential hypertension. *J Hypertens* 1996;**14**:1167-73.
14. Ueda S, Heeley R, Lees K, Elliott H, Connell J. Mistyping of the human angiotensin-converting enzyme gene polymorphism: frequency, causes and possible methods to avoid errors in typing. *J Mol Endocrinol* 1996;**17**:27-30.
15. Safar M, Laurent S, Safavian A, Pannier B, London G. Pulse pressure in sustained essential hypertension: a haemodynamic study. *J Hypertens* 1987;**5**:213-18.
16. Segers P, Stergiopoulos N, Westerhof N. Quantification of the contribution of cardiac and arterial remodeling to hypertension. *Hypertension* 2000;**36**:760-5.
17. Castellano M. Diogenes in the 2000s: searching for hypertension genes. *J Hypertens* 2004;**22**:1081-3.
18. Chobanian A, Bakris G, Black H *et al*. The seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. The JNC 7 report. *JAMA* 2003;**289**:2560-72.
19. Franklin SS, Pio JR, Wong ND *et al*. Predictors of new-onset diastolic and systolic hypertension: The Framingham Heart Study. *Circulation* 2005;**111**:1121-7.