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Angiotensin I-converting enzyme insertion/deletion polymorphism and adrenergic response to exercise in hypertensive patients

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
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Summary

Background: The insertion/deletion ACE polymorphism (ACE I/D) regulates different levels of circulating and tissue ACE activities, which may induce diverse adrenergic responses to physiological stimuli. The aim of this study was to evaluate the influence of the ACE I/D polymorphism on the adrenergic response to isotonic exercise in middle-aged hypertensive patients.

Material/Methods: Submaximal exercise (on a treadmill, using the Naughton protocol at 75% of maximal heart rate) was performed in 34 patients homozygous for the ACE I/D polymorphism (ACE II and ACE DD) with untreated essential hypertension (II = 19, DD = 15). Plasma venous adrenaline and noradrenaline were measured at rest and at submaximal exercise.

Results: Plasma ACE activity was significantly higher in the hypertensive patients carrying the ACE DD genotype compared with the ACE II group. Left atrium size, as well as LV dimensions, mass, and function, were similar in both groups. Total exercise time, baseline and 75% maximal heart rate (MHR) and blood pressure were similar in both groups. Baseline plasma adrenaline and noradrenaline levels were similar in both groups and increased significantly ($p<0.05$) by ca. 300% at submaximal exercise without differences between groups.

Conclusions: The presence of the D allele on the ACE gene in middle-aged hypertensive patients determines higher circulating ACE activity but not increased sympathetic activity in response to submaximal exercise.

key words: **angiotensin converting enzyme polymorphism • angiotensin • catecholamines • adrenergic system • hypertension • exercise**

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BACKGROUND

The angiotensin I-converting enzyme (ACE) (kininase II, EC 3.4.15.1) converts the decapeptide angiotensin I to the vasoactive octapeptide angiotensin II (Ang II), degrades bradykinin, and inactivates angiotensin-(1-7) [1]. In this way, the activity of this enzyme may control the circulating and tissue levels of Ang II and contribute to the regulation of vascular tone, and may also have effects on cardiac mass and structure.

In Caucasian populations, as well as in Chilean normotensive individuals, an insertion/deletion (I/D) polymorphism of the ACE gene determines almost half the variance of circulating ACE activity [2–4]. Higher levels of circulating ACE are associated with the presence of the deletion allele, and may be implicated in increased cardiovascular and renal morbidity [5–7]. In humans, this polymorphism could be a marker for a linkage disequilibrium, which presumably – though the sequence variant is unidentified – modulates the expression of the ACE gene in such a way that the deletion allele is associated with higher ACE activity in plasma, T lymphocytes and the heart [3,8,9]. This polymorphism, associated with differing levels of ACE, is also present in hypertensive patients [10,11], but it is not clear whether there is an association with hypertension [12] or with the development of left ventricular hypertrophy (LVH) in these patients. In one study [13], hypertensive patients with the ACE DD genotype were found to be less likely to show regression of LVH when treated with ACE inhibitors than were patients with other ACE genotypes.

On the other hand, there are also synergistic interactions between the adrenergic and the renin-angiotensin systems. This is particularly relevant in hypertension, where the activation of one system may stimulate the activity of the other. The I/D ACE polymorphism regulates different levels of circulating and tissue ACE activities, and this may induce diverse adrenergic responses to typical physiological stimuli. This aspect of the issue has not been addressed in hypertensive patients to date.

For the purposes of the present study we evaluated the influence of ACE polymorphism on the adrenergic response to isotonic exercise in middle-aged hypertensive patients. Submaximal exercise (on a treadmill, using the Naughton protocol at 75% of maximal heart rate) was performed by patients with untreated essential hypertension.

MATERIAL AND METHODS

This prospective study was approved by the Research Commission of the Hospital Clínico, Pontificia Universidad Católica de Chile. The participants were consecutive hypertensive subjects (blood pressure >140/90 mm Hg, measured twice with a mercury manometer on two different days in sitting position after at least 5 minutes of sitting rest without ingestion of caffeine or food for 30 minutes prior to measurement), homozygous for the II or DD ACE polymorphism, who had not received antihypertensive drugs for at least 2 weeks before being enrolled in our study. Blood pressure (BP) was recorded as the mean of three measurements in sitting position, taken every 1 min.

Table 1. Clinical characteristics of the patients with different ACE genotypes.

	II group (n=19)	DD group (n=15)
Age (years)	54±6	53±5^{NS}
Gender (Females/Men)	15/4	8/7
Body Weight	67±10	69±10^{NS}
Body Mass Index (Kg/m^2)	26±3	26±2^{NS}
Serum creatinine (mg/dL)	0.9±0.1	0.9±0.1^{NS}
Hematocrit (%)	41±3	42±3^{NS}
Sodium (mEq)	143±2	142±2^{NS}
Potassium (mEq)	4.3±0.4	4.2±0.3^{NS}
Plasma ACE activity (U/mL)	18±4	31±8*

Mean±standard deviation; * p<0.001 vs the II ACE genotype group;
NS – not significant vs. the II group

These hypertensive patients, in stages I or II, ranged in age from 45 to 60 years. All were native-born Chileans, of middle socioeconomic status (Graffar scale 2 to 4), non-obese (body mass index (BMI) < 28 kg/m^2) and non-diabetic. These criteria were selected to control for sociogenetic influences and for the effects of body mass and diabetes on blood pressure and LV mass [14]. Patients with a clinical history of angina, myocardial infarction, stroke or secondary hypertension were excluded. In 21 of 34 patients the diagnosis of hypertension was recent (< 1 month). In 13 patients the duration of hypertension was 71±21 months. Demographic characteristics and laboratory results pertaining to these patients are shown in Table 1.

ACE I/D polymorphism was determined in DNA extracted from circulating leukocytes and amplified by polymerase chain reaction (PCR) as previously described [4]. Briefly, after the subjects had given written informed consent (approved by the Research Commission of the Hospital Clínico, Pontificia Universidad Católica de Chile), one blood sample was obtained and placed in a tube containing EDTA. The blood was then centrifuged at room temperature, the supernatant was removed, and the cells were resuspended in sterile NaCl 0.9% and re-centrifuged. The pellet was washed and resuspended in 1 mL of DNAzol® (Gibco BRL, NY, USA). DNA was precipitated by adding ethanol; the pellet was dried, resuspended in 8 mM NaOH and incubated at 50°C for 20 min [4].

The DNA was amplified by PCR [15] in a Techne thermal cycler (Cambridge, UK). The reaction mixture contained PCR buffer, 1.5 mM $MgCl_2$, 200 µM dNTPs, 1 U Taq polymerase (Gibco BRL, NY, USA), the sense oligonucleotide primer:
5' CTGGAGACCACTCCCATCCTTTCT 3' (ACE1, Eurogentecs, France) and the antisense primer:
5' GATGTGGCCATCACATCCGTCAGAT 3' (ACE2, Eurogentec, France) and DNA (50–200 ng). The amplification cycles were as follows: one cycle at 94°C for 5

min, then 30 cycles each (1 min at 94°C; for denaturation), 1 min at 60°C (for annealing) and 1 min at 72°C (for extension). The amplification products were mixed with bromophenol blue, incubated at 65°C and resolved by agarose gel electrophoresis. The gel was stained with ethidium bromide, visualized and photographed in an UV transilluminator. The PCR products corresponded to 190 and 490-bp fragments in the presence of the deletion and the insertion, respectively [4].

In order to measure plasma ACE activity, another blood sample was obtained in a chilled heparinized tube (after overnight fasting). The sample was then centrifuged within 3 h at 4°C. Plasma was stored in liquid nitrogen and processed within 4 weeks. The method used was based on spectrofluorimetric determination of histidyl-L-leucine (HL) using Z-phenyl-histidyl-leucine (Bachem Bioscience Inc, USA) as ACE substrate [16–18]. Briefly, 50 µL of plasma was incubated for 20 min at 37°C. Then 100 µL of cold trichloroacetic acid (10%) was added to stop the reaction. The samples were then centrifuged at 4°C, and the supernatants were neutralized by addition of NaOH and o-phthaldialdehyde solution. The samples were again incubated at 37°C for 10 min and the reaction was stopped with 2 M HCl. Fluorescence was measured within 60 min in an Aminco–Bowman spectrofluorimeter (λ excitation = 365 nm, λ emission = 500 nm). The readings were interpolated in a calibration curve and the amount of HL formed during the incubation time was calculated. ACE activity was expressed as U/mL (1 U = nmol HL produced in 20 min in 0.05 mL). All determinations were performed in duplicate. With this method we have previously observed intra-assay and inter-assay coefficients of variation of 1% [19].

Echocardiographic measurements were obtained, at the same time as blood sampling, with a 3.5 Mhz transducer operated by one echocardiographer using an Aloka SSD 875 instrument. The echocardiographic testing was blinded for the clinical condition and genotype of the patients. All measurements were performed according to the recommendations of the American Association of Echocardiography (ASE) [20], measuring 3–5 consecutive cardiac cycles. The following variables in the parasternal short axis were measured: interventricular septal thickness (IVSpTh) and posterior wall thickness (PWTh), end diastolic (EDD) and end systolic dimension (ESD). With these variables, left ventricular (LV) mass and LV mass index were calculated according to the formula developed by Devereux and modified by the ASE [21].

Progressive isotonic exercise was performed on a treadmill according to a modified Naughton protocol. The exercise studies were performed in a blind fashion for the examiners. Exercise was stopped when 75% of the maximal heart rate appropriate for age and sex was reached [22,23]. Before the exercise test was started, blood samples were taken from a brachial vein from subjects in supine position after a resting period of 30 min, in order to determine the plasma concentrations of noradrenaline (NA) and adrenaline (A). Samples were taken again at the time 75% maximal heart rate was attained. Catecholamines were measured using a radioenzymatic technique (Biotrak Kit, Amersham Pharmacia Biotech, UK) [22,23].

Statistical analysis

The results achieved are presented as means ± SD. The unpaired t-test or non-parametric Mann-Whitney test were used, as well as 2 factor ANOVA (using genotype and rest/exercise condition as factors) and chi square tests. Linear regression analysis was also performed. A p value less than 0.05 was considered statistically significant.

RESULTS

Thirty four homozygous hypertensive patients were consecutively evaluated (II = 19 and DD = 15). The clinical characteristics and laboratory results are shown on Table 1. Arterial blood pressure (systolic/diastolic) was 159±15/95±6 and 160±18/98±10 mmHg in the II and DD groups respectively (difference not significant), whereas plasma ACE activities were significantly higher in the hypertensive patients carrying the DD genotype when compared with the II group (Table 1).

No differences were observed between the two genotypes in LV dimensions (left atria, end systolic, end diastolic), LV mass and function (Table 2). When broken down by gender, both genotypes were similar in terms of LV mass.

The total exercise time, baseline as well as 75% maximal heart rate (MHR) and blood pressure were similar in both groups (Table 3). Baseline plasma adrenaline levels were

Table 2. Cardiac dimensions, LV mass and systolic function in the ACE genotypes.

	II group (n=19)	DD group (n=15)
Left atrial dimension (mm)	36±4	36±4^{NS}
LV End diastolic dimension (mm)	47±5	48±4^{NS}
LV End systolic dimension (mm)	31±5	29±3^{NS}
Interventricular septum thickness (mm)	10±2	10±2^{NS}
LV posterior wall thickness (mm)	10±2	10±2^{NS}
LV Mass (g)	165±43	181±49^{NS}
LV Mass Index (g/m^2)	86±20	91±18^{NS}
LV Shortening fraction (%)	34±11	39±4^{NS}

Mean±standard deviation; NS – not significant vs, the II group

Table 3. Submaximal exercise responses in both ACE genotypes.

	II group (n=19)	DD group (n=15)
Exercise time (sec)	605±243	705±210^{NS}
Resting heart rate (bpm)	79±10	83±16^{NS}
Heart rate at 75% MHR (bpm)	127±5	127±5^{NS}
DBP at 75% MHR (mm Hg)	94±10	98±11^{NS}
SBP at 75% MHR (mm Hg)	170±15	173±19^{NS}

Mean±standard deviation. MHR – maximal heart rate;
DBP – diastolic blood pressure; SBP – systolic blood pressure;
NS – not significant vs. the II group

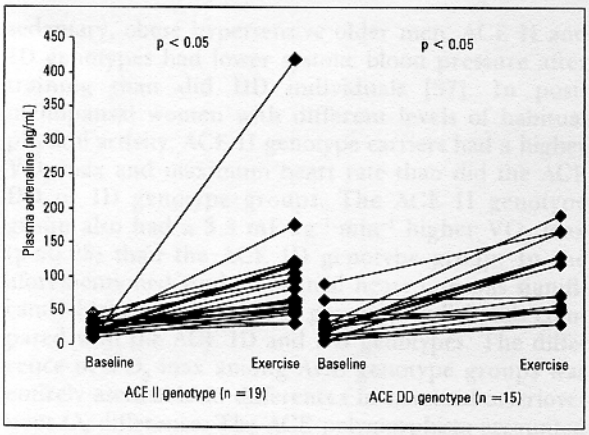

Figure 1. Plasma venous adrenaline (black rhomboids) concentrations at rest (Baseline) and at submaximal exercise (Exercise, 75% of the maximal heart rate) in hypertensive patients with the II (n=19) and DD (n=15) ACE genotypes. In both groups a significant ($p<0.05$), but similar increase in adrenaline was observed.

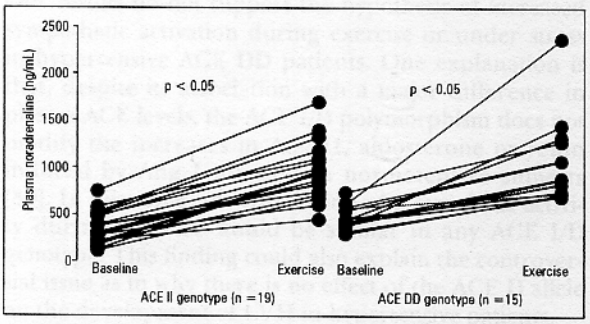

Figure 2. Plasma venous noradrenaline (black circles) concentrations at rest (Baseline) and at submaximal exercise (Exercise, 75% of the maximal heart rate) in hypertensive patients with the II (n=19) and DD (n=15) ACE genotypes. In both groups a significant ($p<0.05$), but similar increase in noradrenaline was observed.

25±11 and 31±22 pg/mL in the II and DD patients, respectively (NS). These levels increased significantly ($p<0.05$) in both groups by 300% at submaximal exercise, without differences between the 2 groups (Figure 1).

Baseline plasma NA levels were 336±181 and 334±125 pg/mL in the II and DD patients, respectively (NS). These levels increased significantly ($p<0.05$) at submaximal exercise by 270 % in both genotypes without differences between groups (Figure 2).

No significant correlations were observed between LV dimensions, LV mass, plasma ACE or blood pressure with plasma cathecolamines at rest or during exercise.

DISCUSSION

In the present study no effect of I/D ACE genotype was observed on the sympathetic response to submaximal exercise in hypertensive patients.

Ang II and sympathetic activity

Experimental data from both animal models and human subjects suggest that activation of the renin-angiotensin system stimulates sympathetic activity. Ang II stimulates the release of NA from cardiac sympathetic nerves [24], enhances NA spillover during sympathetic activation (in conscious rabbits) [25], and increases NA release from atria by acting on the Ang subtype 1 receptors in the guinea pig isolated atria [26].

In humans, forearm venous NA and forearm NA spillover increased significantly after intrabrachial arterial Ang II infusions [27]. A pharmacodynamic interaction has been suggested [28] between NA and Ang II, which acts synergistically, possibly at a postsynaptic site, to maintain systolic blood pressure. Nevertheless, it has also been observed in humans that Ang II infusion at subpressor doses has no effect on heart rate or plasma NA responses to stimulation of the sympathetic nervous system [29].

Ang II and sympathetic activity during exercise

The effect of the renin-angiotensin system on sympathetic activation induced by exercise has been assessed in several studies. In normal volunteers exercised at approximately 25 and 65% of their maximal O_2 consumption, the ACE inhibitor enalapril did not attenuate the NA spillover response to exercise, leading to the conclusion that prejunctional Ang II receptors do not appear to facilitate NE release [30]. In another study, captopril during isometric handgrip exercise blunted the increase in mean arterial pressure, but not in systemic NA spillover [31].

In patients with hypertension or heart failure, however, adrenergic responses to exercise as assessed by plasma catecholamines are enhanced [22,32,33]. ACE inhibitors decrease the excessive adrenergic response to exercise in patients with hypertension [34] or with heart failure [23] as well as myocardial overflow of NA at peak exercise in patients with chronic heart failure [35].

These findings suggest that, in hypertensive or heart failure patients, but not in healthy persons, there is enhanced stimulation of the adrenergic response by the renin-angiotensin system.

These physiological observations led us to hypothesize that genetically increased ACE activity in hypertensive patients could stimulate higher sympathetic activity during exercise. There have been a few studies assessing the effect of the ACE I/D polymorphism on exercise, but ours is the first study to specifically address the effect of this polymorphism on the adrenergic response to exercise in hypertensive patients.

I/D ACE polymorphism and exercise

The development of LVH in young males with physical training has been shown to be strongly associated with ACE genotype and the presence of the D allele [36]. In

sedentary, obese hypertensive older men, ACE II and ID genotypes had lower systolic blood pressure after training than did DD individuals [37]. In postmenopausal women with different levels of habitual physical activity, ACE II genotype carriers had a higher VO_2 max and maximum heart rate than did the ACE DD or ID genotype groups. The ACE II genotype group also had a 3.3 $mL \cdot kg^{-1} \cdot min^{-1}$ higher VO_2 max ($p<0.05$) than the ACE ID genotype group. In the aforementioned study, maximal heart rate was significantly higher in the ACE II genotype individuals compared with the ACE ID and DD genotypes. The difference in VO_2 max among ACE genotype groups was entirely ascribable to differences in maximal arteriovenous O_2 difference. The ACE polymorphism accounted for 17% of the variation in maximal a-vDO_2 in these women due to genotype-dependent differences in maximal a-vDO_2; this was unrelated to maximal stroke volume and maximal cardiac output [38]. In these studies no assessment of the sympathetic responses to exercise has been reported.

Our results do not support the hypothesis of increased sympathetic activation during exercise or under stress in hypertensive ACE DD patients. One explanation is that, despite its association with a major difference in plasma ACE levels, the ACE I/D polymorphism does not modify the increases in Ang II, aldosterone or renin induced by Ang I infusion in normotensive subjects [39]. In this sense, the stimulation of sympathetic activity during exercise would be similar in any ACE I/D genotype. This finding could also explain the controversial issue as to why there is no effect of the ACE D allele on the development of LVH in hypertensive patients.

CONCLUSION

The presence of the D allele on the ACE gene in middle-aged hypertensive patients determines higher circulating ACE activity but not increased sympathetic activity to submaximal exercise.

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REFERENCES:

1. Ferrario CM: Angiotensin formation and degradation. In: Izzo JL and Black HR (editors): Hypertension Primer, Second Edition. American Heart Association. Lippincott Williams & Wilkins, Baltimore, USA, 1999; 21-22
2. Rigat B, Hubert C, Ahlenc-Gelas F et al: 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: 1343-1346
3. Tiret L, Rigat B, Visvikis S et al: Evidence, from combined segregation and linkage analysis, that a variant of the angiotensin I-converting enzyme (ACE) gene controls plasma ACE. Am J Hum Genet, 1992; 51: 197-205
4. Jalil JE, Piddo AM, Cordova S et al: Prevalence of the angiotensin I-converting enzyme insertion/deletion polymorphism, plasma ACE activity and left ventricular mass in normotensive Chilean population. Am J Hypertension, 1999; 12: 697-704
5. Cambien F, Costerousse O, Tiret L et al: Plasma level and gene polymorphism of angiotensin-converting enzyme in relation to myocardial infarction. Circulation, 1994; 90: 669-676
6. Marian AJ, Yu Q-T, Workman R, Greve G, Roberts R: Angiotensin-converting enzyme polymorphism in hypertrophic cardiomyopathy and sudden cardiac death. Lancet, 1993; 342: 1085-1086
7. Marre M, Jeunemaitre X, Gallois Y et al: Contribution of genetic polymorphism in the renin-angiotensin system to the development of renal complications in insulin-dependent diabetes. J Clin Invest, 1997; 99: 1585-1595
8. Costerousse O, Allegrini J, Lopez M, Alhenc-Gelas F: Angiotensin I-converting enzyme in human circulating mononuclear cells: genetic polymorphism of expression in T-lympocytes. Biochem J, 1993; 290: 33-40
9. Danser AHJ, Schalekamp MADH, Bax WA et al: Angiotensin-converting enzyme in the human heart. Effect of the deletion /insertion polymorphism. Circulation, 1995; 92: 1387-1388
10. Bonithon-Kopp C, Ducimetiere P, Touboul P-J et al: Plasma angiotensin-converting enzyme activity and carotid wall thickening. Circulation, 1994; 89: 952-954
11. Higashimori K, Zhao Y, Higaki J et al: Association analysis of a polymorphism of the angiotensin converting enzyme gene with essential hypertension in the Japanese population. Biochem Biophys Res Commun, 1993; 191: 399-404
12. O'Donnell CJ, Lindpaintner K, Larson MG et al: Evidence for association and genetic linkage of the angiotensin-converting enzyme locus with hypertension and blood pressure in men but not women in the Framingham Heart Study. Circulation, 1998 12; 97: 1766-72
13. Kohno M, Yokokawa K, Minami M et al: Association between angiotensin-converting enzyme gene polymorphisms and regression of left ventricular hypertrophy in patients treated with angiotensin-converting enzyme inhibitors. Am J Med, 1999; 106: 544-549
14. Valenzuela CY, Acuña MP, Harb Z: A socio-genetic cline in Chilean population. Rev Med Chile, 1987; 115: 295-299
15. Rigat C, Hubert C, Corvol P, Soubrier F: PCR detection of the insertion/deletion polymorphism of the human angiotensin converting enzyme gene (DCP 1) (dipeptidyl carboxypeptidase 1). Nucleic Acids Research, 1992; 20: 1433
16. Piquilloud Y, Reinharz A, Roth M: Studies on the angiotensin converting enzyme with different substrates. Biochim Biophys Acta, 1970; 206: 136-142
17. Friedland J, Silverstein E: A sensitive fluorimetric assay for serum angiotensin-converting enzyme. Am J Clin Pathol, 1976; 66: 416-424
18. Cushman DW, Cheung MS: Spectrophotometric assay and properties of the angiotensin-converting enzyme level by direct radioimmunoassay. Biochem Pharmacol, 1971; 20: 1637-1638
19. Jalil JE, Ocaranza MP, Piddo AM, Jalil R: Reproducibility of plasma angiotensin-converting enzyme activity in human subjects determined by fluorimetry with Z-phenylalanine-histidyl-leucine as substrate. J Lab Clin Med, 1999; 133: 501-506
20. Sahn DJ, De Maria A, Kisslo J, Weyman A: Recommendations regarding quantitation in M - Mode echocardiography: results of a survey of echocardiographic measurements. Circulation, 1978; 58: 1072-1083
21. Devereux RB, Alonso DR, Lutas EM et al: Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol, 1986; 57: 450-458
22. Jalil JE, Corbalán R, Chamorro G et al: Respuesta adrenérgica al ejercicio dinámico leve en sujetos sanos y en pacientes con insuficiencia cardíaca crónica. Rev Med Chile, 1988; 116: 216-221
23. Corbalán R, Jalil JE, Chamorro G, Casanegra P: Effects of captopril versus milrimone therapy in modulating the adrenergic nervous system response to exercise in congestive heart failure. Am J Cardiol, 1990; 65: 644-649

24. Blumberg AL, Ackerly JA, Peach MJ: Differentiation of neurogenic and myocardial angiotensin II receptors in isolated rabbit atria. Circ Res, 1975; 36: 719-726

25. Noshiro T, Shimizu K, Way D et al: Angiotensin II enhances norepinephrine spillover during sympathetic activation in conscious rabbits. Am J Physiol, 1994; 266: 1864-71

26. Brasch H, Sieroslawski L, Dominiak P: Angiotensin II increases norepinephrine release from atria by acting on angiotensin subtype 1 receptors. Hypertension, 1993; 22: 699-704

27. Clemson B, Gaul L, Gubin SS et al: Prejunctional angiotensin II receptors. Facilitation of norepinephrine release in the human forearm. J Clin Invest, 1994; 93: 684-691

28. Seidelin PH, Coutie WJ, Pai MS et al: The interaction between noradrenaline and angiotensin II in man: evidence for a postsynaptic and against a presynaptic interaction. J Hypertens Suppl, 1987; 5: 121-4

29. Seidelin PH, Coutie WJ, Struthers AD: The effect of angiotensin II on endogenous noradrenaline release in man. Br J Clin Pharmacol, 1987; 24: 699-704

30. Leuenberger U, Gaul L, Noack H et al: Angiotensin-converting enzyme inhibition and the norepinephrine spillover response to dynamic exercise. J Appl Physiol, 1996; 81: 1138-42

31. Lang CC, Stein CM, He HB, Wood AJ: Angiotensin converting enzyme inhibition and sympathetic activity in healthy subjects. Clin Pharmacol Ther, 1996; 59: 668-74

32. Corbalan R, Kunstmann S, Garayar B et al: Lack of modulation of the adrenergic response to exercise in essential hypertension during diltiazem therapy. Circulation, 1989; 80: 1607 (abstract)

33. Cody RJ, Kubo SH, Laragh JH, Atlas SA: Cardiac secretion of atrial natriuretic factor with exercise in chronic congestive heart failure patients. J Appl Physiol, 1992; 73: 1637-1643

34. Grossman E, Messerli FH, Oren S et al: Disparate cardiovascular response to stress tests during isradipine and fosinopril therapy. Am J Cardiol, 1993; 72: 574-579

35. Mulligan IP, Fraser AG, Lewis MJ, Henderson AH: Effects of enalapril on myocardial noradrenaline overflow during exercise in patients with chronic heart failure. Br Heart J, 1989; 61: 23-28

36. Montgomery HE, Clarkson P, Dollery CM et al: Association of angiotensin converting enzyme gene I/D polymorphism with change in left ventricular mass in response to physical training. Circulation, 1997; 96: 741-747

37. Hagberg JM, Ferrell RE, Dengel DR, Wilund KR: Exercise training-induced blood pressure and plasma lipid improvements in hypertensives may be genotype dependent. Hypertension, 1999; 34: 18-23

38. Hagberg JM, Ferrell RE, McCole SD et al: VO2 max is associated with ACE genotype in postmenopausal women. J Appl Physiol, 1998; 85: 1842-1846

39. Lachurie ML, Azizi M, Guyene T-T et al: Angiotensin-converting enzyme gene polymorphism has no influence on the circulating renin-angiotensin-aldosterone system or blood pressure in normotensive subjects. Circulation, 1995; 91: 2933-2942