

Is there relationship between the A1166C polymorphism of the angiotensin II receptor AT₁ and plasma renin activity, insulin resistance and reduction of blood pressure after angiotensin-converting enzyme inhibitor therapy?

Jerzy Głuszek, Karolina Jankowska

Chair and Clinic of Hypertensiology, Angiology and Internal Diseases, Medical University, Poznań, Poland

Abstract: Objectives. The aim of this study was to assess the relationship between the A1166C polymorphism of the angiotensin AT₁ receptor gene and reduction of blood pressure and pulse pressure in patients with mild and moderate arterial hypertension. Moreover, we sought to investigate the impact of insulin resistance and plasma renin activity on blood pressure reduction following treatment with perindopril depending on the A1166C polymorphism of the AT₁ receptor gene. **Patients and methods.** The study included 64 patients with mild-to-moderate essential hypertension, with a mean age of 40.5 ± 16.4 years. Before and after treatment with angiotensin-converting enzyme inhibitors (ACEI) blood pressure measurement with a traditional method and ambulatory blood pressure monitoring were performed and blood samples were taken for laboratory investigation. **Results.** The A1166C genotype distribution was: AA 53.1% in 34 patients, AC 43.8% in 28 patients, CC 3.1% in 2 patients. There were no statistically significant differences in the magnitude of blood pressure reduction and pulse pressure after treatment with perindopril between genotypes. Only in patients with genotype AA insulin resistance correlated with body mass index and only in these patients we observed a significant correlation between plasma renin activity and reduction of diastolic blood pressure. There was an inverse correlation between insulin resistance and reduction of systolic blood pressure only in patients with genotype AC. **Conclusions.** The A1166C polymorphism of the AT₁ receptor gene is not associated with reduction of blood pressure after treatment with ACEI in patients with essential hypertension. There is a negative correlation between plasma renin activity and reduction of diastolic blood pressure only in patients with genotype AA. There is an inverse correlation between insulin resistance and systolic blood pressure only in patients with AC genotype.

Key words: A1166C polymorphism of the AT₁ receptor gene, hypertension, insulin resistance, plasma renin activity, pulse pressure

INTRODUCTION

Blood pressure is, to a large extent, genetically determined. However, apart from several rare types caused by mutations of particular genes, primary hypertension is considered a multigenic disease. Studies have not shown a major impact of ge-

netic polymorphisms associated with renin-angiotensin-aldosterone system on the hypertension incidence. However, Nałogowska-Głońska et al. [1] observed an increased risk of pregnancy-induced hypertension in patients carrying the angiotensin II AT₁ receptor CC genotype. Recently, interest has been aroused by studies regarding the value of the reduction of blood pressure by hypotensive drugs, depending on individual genetic polymorphisms which may be associated with the pathogenesis of essential hypertension [2-6]. Admittedly, most of those studies did not show a significant impact of polymorphisms of those genes on the hypotensive response during pressure-lowering therapy, but it was observed that cardiovascular complication incidence increased in DD homozygote patients compared to patients with II geno-

Correspondence to:

Professor Jerzy Głuszek, MD, PhD, Katedra i Klinika Hipertensjologii, Angiologii i Chorób Wewnętrznych, Uniwersytet Medyczny im. Karola Marcinkowskiego, ul. Długa 1/2, 61-848 Poznań, Poland, phone: +48-61-854-90-90, fax: +48-61-852-94-72, e-mail: jerzygluszek@o2.pl

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type of the angiotensin-converting enzyme (ACE) gene [7]. Jankowska [3] also demonstrated that pulse pressure reduction was significantly higher in DD homozygote patients than in ACE II and ID carriers. Angiotensin II acts on the vascular system by means of AT_1 receptor. Therefore, receptor gene polymorphisms might be significant for efficiency of essential hypertension treatment. The results of the studies published to date that concerned the impact of the A1166C polymorphism of the AT_1 receptor gene on blood pressure reduction following hypotensive therapy, are contradictory [8-10]. The relation between the pulse pressure and the polymorphism has not been analyzed either. Papers assessing relations between the A1166C polymorphism of the AT_1 receptor gene and insulin resistance are scarce, and the relationship has not been studied in hypertension patients [11,12].

It has not been evaluated whether the A1166C polymorphism has an impact on variability of insulin resistance during treatment with an angiotensin-converting enzyme inhibitor (ACEI). In the case of the ACE insertion/deletion (I/D) polymorphism, it is well known that the plasma ACE activity is approximately 60% higher in DD homozygotes than in II homozygotes, which, however, might not translate into plasma renin activity [13,14]. The level of plasma renin activity compared with the A1166C polymorphism of the AT_1 receptor gene in hypertensive patients and the impact of plasma renin activity on blood pressure reduction caused by angiotensin convertase inhibitors have not been assessed yet.

The aim of the study was to assess the relationship between the A1166C polymorphism of the AT_1 receptor gene and the hypotensive response and pulse pressure reduction during treatment with ACEI in patients with mild to moderate hypertension. Moreover, we sought to investigate the impact of insulin resistance and plasma renin activity on blood pressure reduction following treatment with perindopril depending on the A1166C polymorphism of the AT_1 receptor gene.

PATIENTS AND METHODS

The study involved 64 patients with mild and moderate hypertension who, at the same time, were assessed with respect to the impact of ACEI therapy on blood pressure reduction, depending on ACE I/D polymorphism, and the results of the study were published recently [3]. The mean age of the patients was 41 ± 16.2 years. Exclusion criteria were as follows: secondary hypertension, comorbidities (cardiomyopathies and heart valve disease, heart failure, hematologic diseases, malignancies, psychiatric diseases), a history of myocardial infarction or stroke, renal failure, liver dysfunction, pregnancy. All patients, prior to their enrollment in the study, were informed on the study and gave their written consent. Before the start of the study, its protocol was approved by an independent Bioethical Committee at the Poznań University of Medical Sciences. The study spanned 8–10 weeks and was divided into three stages:

- stage I – lasting 2 weeks, when the patients were not administered hypotensive medications (the wash-out period); it did not pertain to patients who had not been treated to date
- stage II – lasting 4 weeks, when the patients were administered perindopril 4 mg/24h
- stage III – lasting another 4 weeks, when the patients with unsatisfactory blood pressure control (i.e. when blood pressure values estimated by traditional method were exceeding 140/90 mmHg and/or mean arterial pressure in a daily activity period in ambulatory blood pressure monitoring [ABPM] was exceeding 135/85 mmHg) were receiving an increased perindopril dose (8 mg/24h); the others were administered the medication as before. For practical reasons, the length of individual treatment phases (± 3 days) was acceptable.

During the study, the patients did not receive any other medications and were asked to report for control every week.

At the beginning of the study, blood was taken for biochemical and genetic tests; the former tests were repeated at the end of the study.

Traditional blood pressure measurements, obligatory during each visit, was made with a mercury sphygmomanometer, in accordance with the 2007 European Society of Hypertension recommendations [15]. Blood pressure was measured twice with one minute interval, to an accuracy of 2 mmHg. Arithmetic means were calculated for all the data.

The SpaceLabs model 90207–30 by SpaceLabs Inc. was used for ABPM measurements. The measurement started between 8:00 AM and 10:00 AM. The instrument was put on the same arm as in traditional measurements. The time between 6:00 AM and 10:00 PM was assumed as the daily activity period, and between 10:00 PM and 6:00 AM, as a sleep period. Measurements were taken each 30 minutes throughout the whole day (24 h). In patients with excessive number of faulty readings, the study was repeated.

Blood for tests of the AT_1 receptor gene polymorphism (A1166C) was taken to test tubes with ethylenediaminetetraacetic acid. Genomic DNA was isolated from peripheral blood by means of a detergent, non-enzymatic, inorganic method [16].

The isolated, genomic DNA was subjected to polymerase chain reaction amplification according to the procedure proposed by Bonnardeaux [17] with a pair of synthetic oligonucleotides (primers P1: 5' CTT TTT TAT GUC TTT CTG GGG 3' and P2: 5' TGT GUC TTT GCT TTG TCT TG 3') in 35 cycles of the following temperature model: 94°C – 0.5 minutes; 60°C – 0.5 minutes, 72°C – 0.5 minutes. The obtained PCR product was subjected to digestion by restrictive enzyme Ddel (12 h in 37°C), and the obtained digestion products were separated by 4% agarose gel electrophoresis. Separated DNA fragments, visualized by ethidine bromide, were observed in UV light and compared to the DNA model of known length. For allele C, three 143, 126 and 115 bp

Table 1. Clinical characteristics of patients

	Entire group (n = 64)	AA (n = 35)	AC (n = 29)
Age (years)	40.5 ±16.4	40.9 ±16.7	40.1 ±18.7
Female/male)	23/41	11/23	12/18
BMI (kg/m ²)	27.4 ±4.1	27.8 ±6.2	27.0 ±6.4
Smokers/non-smokers	17/47	10/25	7/28
Duration of hypertension (years)	3.18 ±3.5	3.46 ±3.67	2.85 ±3.31
Glucose (mmol/l)	4.9 ±0.81	4.82 ±1.15	4.98 ±1.19
Insulin (mU/l)	15.2 ±9.7	15.4 ±9.9	15.0 ±10.0
Insulin resistance HOMA	3.31 ±2.24	3.28 ±2.04	3.35 ±2.36
PRA (ng/ml/h)	2.38 ±2.15	2.43 ±1.97	2.32 ±2.30
Creatinine (μmol/l)	74.4 ±12.9	75.5 ±13	73.1 ±13
Cholesterol (mmol/l)	5.81 ±1.43	6.05 ±1.37	5.5 ±1.46
Triglycerides (mmol/l)	1.49 ±1.03	1.53 ±1.12	1.45 ±0.89

AA – 1166AA genotype patients, AC – 1166AC genotype patients, BMI – body mass index, HOMA – homeostatic model assessment, PRA – plasma renin activity

long fragments were obtained, and for allele A, two 258 and 126 bp long fragments.

Plasma renin activity was assayed by means of radioimmunological method with Immunotech by Beckman Coulter Company [18].

Insulin levels were measured by a radioimmunoassay with POLATOM. Venous blood glucose levels were assayed with the ECA 2000 analyzer, using enzymatic-amperometric method; glucose levels were assayed using an enzymatic biosensor.

Insulin resistance was calculated according to the following formula: insulin (μU/ml) × glucose (mmol/l) / 22.5

The formula above was described by the homeostatic model assessment (HOMA) mathematical model proposed by Matthews et al. [19].

Parameter methods (Student's t test) for the observed blood pressure values and laboratory studies were used for statistical analysis. For insulin levels, plasma renin activity and insulin resistance, due to deviation from normal distribution, non-parameter methods (Wilcoxon test, Mann-Whitney test, χ^2 test and Spearman's rank correlation) were used.

RESULTS

The number of patients who completed the study was 64. AA genotype of the AT₁ receptor gene was found in 34 patients (53.1%), AC genotype in 28 (43.8%), and CC genotype in 2 patients (3.1%), respectively. Allele frequencies were in Hardy-Weinberg equilibrium. Similarly to other studies, two patients with CC genotype were added to the AC genotype subgroup [20].

Clinical characteristics of the studied population is shown in Table 1. No statistically significant differences between individual genotypes were observed. Mean values of blood pressure obtained in traditional measurements and ABPM prior to treatment and after 4 and 8 weeks of treatment are presented in Figure 1 and 2. Individual genotypes did not show a statistically significant difference in respect of systolic and diastolic blood pressure. In the AA genotype patients, after 4 weeks of therapy, perindopril dose was increased to an average of 7 mg daily and in the AC genotype patients to 6 mg daily. However, the difference was statistically insignificant. Lowering of both systolic and diastolic blood pressure in traditional measurements and ABPM after 8 weeks was significant, except for ABPM diastolic pressure in the AA group. The level of reduction in systolic and diastolic blood pressure did not show a statistically significant difference between individual genotypes (Tab. 2). Pulse pressure values in traditional measurements for AA genotype fell statistically significantly from 60.6 to 48 and in ABPM from 52.5 to 47.1 mmHg. For AC genotype, in traditional measurement from 58.9 to 47 mmHg, and in ABPM from 54.2 to 52.8 mmHg (statistically insignificant) (Tab. 3).

For the AA genotype patients, plasma renin activity was 2.43 ±1.97 ng/ml/h for the AC genotype patients, 2.32 ±2.30 ng/ml/h and in both subgroups the difference was statistically insignificant. Insulin resistance prior to therapy was 3.28 ±2.09 for the AA subgroup and 3.35 ±2.39 for the AC subgroup. Angiotensin convertase inhibitor therapy carried out for 8 weeks did not significantly change the insulin resistance value in any of the studied patient subgroup, and it was 3.35 ±1.92 and 3.75 ±2.5, respectively. In the AA genotype patients, the insulin resistance value correlated with body mass

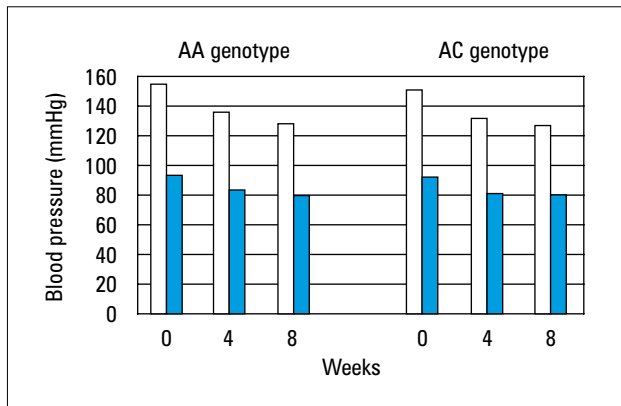


Fig. 1. Values of blood pressure measured by traditional method during perindopril therapy

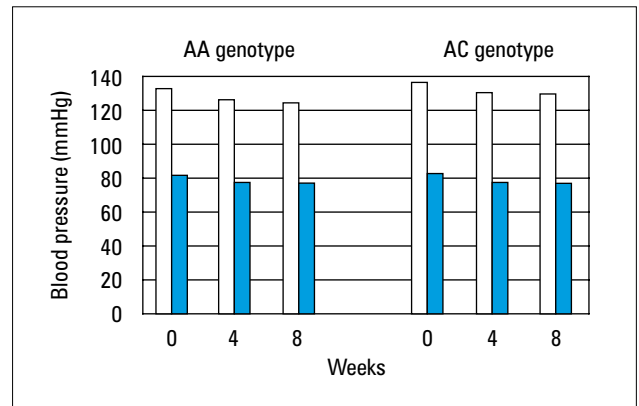


Fig. 2. Values of blood pressure measured by ambulatory blood pressure monitoring method during perindopril therapy

index (BMI) value ($r = 0.583$, $p = 0.00022$) and abdominal circumference ($r = 0.549$, $p = 0.00062$). There is no such significant relationship in the AC genotype patients. In the AA genotype patients, we observed high and statistically significant correlation ($r = 0.465$, $p = 0.006$) between the plasma renin activity and reduction in diastolic blood pressure measured by means of ABPM. Insulin resistance in this subgroup had no impact on reduction in systolic and diastolic blood pressure.

On the other hand, in the AC genotype group, reduction in systolic and diastolic blood pressure did not depend on plasma renin activity. Reduction of systolic pressure was inversely correlated with insulin resistance ($r = -0.365$, $p = 0.047$).

DISCUSSION

The impact of ACE polymorphism on hypertension incidence and on efficiency of hypotensive medications has been a subject of numerous studies [3,4,21]. There were relatively fewer papers assessing the impact of hypotensive medications on blood pressure reduction depending on the A1166C polymorphism of the AT_1 receptor gene [8-10]. In the current study, we failed to show that the genetic polymorphism had significant impact on therapeutical efficiency of a 8-week perindopril therapy in patients with mild and moderate hypertension. We also did not find differences in pulse pressure in the AA and AC genotype group. Kurland et al. observed higher reduction in left ventricular hypertrophy in the AC genotype hypertensive patients than in the AA genotype patients [22]. On the other hand, Benetos et al. [23] showed that irrespective of blood pressure values, the AC genotype patients have less compliant large blood vessels. Perindopril therapy caused a greater increase in vessel compliance measured with pulse wave propagation velocity in the AC genotype group than in the AA genotype group [23]. Patients with high vascular stiffness display substantial spread between systolic and

diastolic blood pressure, i.e. high pulse pressure. In the AC genotype patients involved in our study, we did not observe a significant reduction in pulse pressure (in ABPM) during perindopril therapy, while in the AA genotype patients reduction in pulse pressure was small, although statistically significant. Therefore, our indirect observations do not confirm those by Benetos et al. [23], which is probably a result of too short period of hypotensive therapy.

The relationship between insulin resistance and ACE insertion/deletion polymorphism has been evaluated in several studies [24,25]. However, there were only a few researchers who assessed the relationship between insulin resistance value and the A1166C polymorphism of the AT_1 receptor gene. Abdollahi et al. [11] observed lower serum glucose and insulin levels in glucose tolerance test in metabolic syndrome patients; however, they did not assess the insulin resistance value. On the other hand, Akasaka et al. [12] showed higher insulin resistance in the A allele carriers. That group, however, involved more hypertensive patients in comparison with the remaining study group, and it might have influenced the result. In our studies, we made insulin resistance value assay only in hypertension patients. At baseline and after perindopril therapy, it was quite similar in both subgroups in our study. We expected to demonstrate a close relationship between insulin resistance value and BMI values and abdominal circumference in all the studied hypertensive patients. However, we managed to show the relationship only in the AA genotype patients, while the AC genotype patients did not display such a relationship. However, in this subgroup we observed an inverse correlation between insulin resistance and the magnitude of diastolic pressure reduction (in ABPM). Therefore, in patients with high insulin resistance value, the reduction in diastolic pressure both after 4 and 8 weeks of perindopril administration was smaller than in patients with low insulin resistance value. In hypertensive patients with AC polymorphism we did not observe an association between insulin resistance and reduction in diastolic blood pressure. This may explain discrepant data in the literature where some au-

Table 2. Reduction in blood pressure following perindopril therapy in the studied groups

	Traditional measurement		ABPM	
	AA	AC	AA	AC
Reduction in systolic blood pressure after 8 weeks (mmHg)	26 ±9.6 ^a	23 ±9.3 ^a	9.4 ±16.04 ^b	6.9 ±9.77 ^c
Reduction in diastolic blood pressure after 8 weeks (mmHg)	14 ±8.05 ^a	12 ±7.9 ^c	3.94 ±8.26 ^d	5.5±8.16 ^c

^a $p < 0.001$, ^b $p < 0.05$, ^c $p < 0.01$, ^d not significant

Data are shown as mean ±standard deviation.

Abbreviations: ABPM – ambulatory blood pressure monitoring, other – see Table 1

Table 3. Pulse pressure (in mmHg) prior to and during perindopril therapy in patients with mild and moderate hypertension and AA and AC genotypes of AT₁ receptor gene

	Traditional measurement	ABPM
At baseline		
AA genotype patients	60.6 ±13.5	52.5 ±9.98
AC genotype patients	58.9 ±12.8	54.2 ±8.14
After 8 weeks		
AA genotype patients	48 ^a ±7.12	45.7 ^a ±9.72
AC genotype patients	47 ^a ±7.28	52.8 ^b ±7.59

^a $p < 0.01$, ^b not significant

Data are shown as mean ±standard deviation.

Abbreviations – see Table 1 and 2

thors demonstrated significantly lower efficiency of hypotensive therapy in overweight patients with high insulin resistance value, while other researchers did not observe such a relationship [26]. Among the patients resistant to the therapy, patients with high insulin resistance value and AC polymorphism likely are prevalent, whereas in the AA polymorphism patients, insulin resistance value has no impact on blood pressure reduction. During 8-week ACEI treatment, there was no reduction in insulin resistance value in any of the study subgroups. It can be speculated that too short period of therapy resulted in lack of the favorable impact of ACEI on the management of hyperglycemia [27-29].

Hypertensive patients with high plasma renin activity (e.g. in renal artery stenosis) have usually satisfactory response to ACEI therapy [30,31]. We decided to analyze this relationship in both study subgroups. It was only the AA subgroup where we observed a high ($r = 0.46$), significant correlation between diastolic blood pressure reduction (in ABPM) and plasma renin activity. We did not observe such a relationship either for systolic or diastolic blood pressure reduction in the AC subgroup.

The relationships demonstrated in our study have not been presented in the literature to date. Therefore, although allocation of patients to the AA or AC subgroup made no impact on blood pressure reduction (traditional measurement and ABPM) during perindopril therapy, more detailed analy-

sis showed that insulin resistance value affects blood pressure reduction only in the AC subgroup, and plasma renin activity value influences the reduction of diastolic hypertension only in the AA subgroup.

The study was limited by a relatively small number of patients and brief perindopril therapy. Cross-sectional studies usually assessed polymorphism distribution on a significantly higher number of patients; however, the analysis of impact of therapy on the studied parameters was limited in several studies to the number of patients comparable to our study. Despite only 8-week therapy, we achieved normalization of blood pressure in most patients. Insulin resistance was not assessed by means of hyperinsulinemic-euglycemic clamp (considered a “gold standard”) and only by HOMA. However, the latter method is frequently used in studies assessing insulin resistance and shows a close correlation with the hyperinsulinemic-euglycemic clamp method.

Conclusions from the presented study are as follow:

- 1) no significant differences were found between AA and AC genotypes of the AT₁ receptor gene (A1166C) in reduction of blood pressure following perindopril therapy, both in traditional method measurements and in ABPM. We also failed to demonstrate significant differences in pulse pressure values prior to and after perindopril therapy
- 2) insulin resistance value correlates with BMI value and waist circumference only in the AA genotype patients

- 3) moreover, in the AA genotype patients, we demonstrated a significant correlation between plasma renin activity and reduction in diastolic blood pressure measured by ABPM, whereas only in the AC genotype patients, we observed an inverse association between reduction in systolic blood pressure and insulin resistance value.

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