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Associations of the –344T>C polymorphism of CYP11B2 gene with 24-hour blood pressure profiles in middle-aged women with essential hypertension

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Summary

Background In this cross-sectional study, we assessed the impact of –344T>C polymorphism of the CYP11B2 gene which encodes aldosterone synthase on 24-hour blood pressure patterns.

Material and methods The study was performed in 137 females with essential hypertension aged 42–60 years. We measured plasma aldosterone level and renin activity (PRA), fasting glucose, lipid profiles and 24-hour urinary sodium and potassium excretion. Based on 24-hour blood pressure monitoring we identified cases with dipping and non-dipping patterns of blood pressure.

Results Mean PRA and aldosterone levels and aldosterone-to-renin ratio (ARR) were within normal range. Non-dipping hypertension was found in 54.3% of patients. Genotype frequencies of TT, CC and CT were 27%, 27% and 46%, respectively. Carriers of the C allele had significantly lower nocturnal blood pressure reduction (P = 0.004) and higher nocturnal systolic (P = 0.02) and diastolic blood pressure (P = 0.044), frequency of non-dipping profile (P = 0.001), and 24-hour urinary potassium excretion (P = 0.047). Urinary sodium excretion was positively correlated with a decrease in nocturnal blood pressure (R = 0.202; P = 0.037). In a multiple regression analysis, ARR and presence of the C allele adjusted for confounding variables were inversely associated with the nocturnal blood pressure decline (β = –0.348; P = 0.022 and β = –0.222; P = 0.018, respectively).

Conclusions In conclusion, in middle-aged females with essential hypertension carrying the C allele we found higher nocturnal blood pressure, lower nocturnal blood pressure reduction, and higher prevalence of non-dipping hypertension than in TT carriers.

key words: hypertension, aldosterone, 24-hour blood pressure, CYP11B2 gene

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Background

The prevalence of hypertension in the general population varies from approximately from 30% to 45% and is strongly associated with age, gender, race and genetic factors [1]. Among possible mechanisms underlying the development of hypertension, increased activity of the renin-angiotensin-aldosterone system (RAAS) seems to play a crucial role [2–9]. It has been suggested that the RAAS activity might be modified by some genetic factors. Earlier studies demonstrated that in women aged 40–70 years, but not in men; polymorphism of the renin gene was strongly associated with the risk of hypertension [10]. Other studies found the relationship

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between polymorphism of the aldosterone synthase gene and hypertension [11–13].

Aldosterone synthase (CYP11B2) is a cytochrome P450 enzyme, which catalyses the terminal steps of aldosterone synthesis in the adrenal glands. Common variations of the CYP11B2 gene include the –344T>C polymorphism (substitution of thymidine to citosine at position –344 in the promoter region) and the C-allele of this gene polymorphism [11–13]. Genetic variations of the CYP11B2 gene which affect its expression in target organs may predispose to the development of essential hypertension [14], low-renin hypertension [11], left ventricular hypertrophy [15], and myocardial infraction [16]. Mitsunobua *et al.* demonstrated in elderly or male subjects derived from general Japanese population that the CC genotype was associated with lower nocturnal blood pressure and lower prevalence of cardiovascular disease. They suggested a beneficial role of this genotype in maintaining the circadian rhythm of blood pressure [17]. Similarly, Casiglia *et al.* found in unselected elderly population that systolic blood pressure was significantly lower in subjects with the CC genotype, higher in the TT and intermediate in the CT [18]. On the other hand, other studies failed to demonstrate the differences in blood pressure between TT, CC and CT carriers [19]. Moreover, to our best knowledge, there have been no previous reports assessing the association of CYP11B2 polymorphisms with circadian variations in blood pressure. Therefore, in this study, we investigated possible associations of CYP11B2 genetic variations with RAAS activity and urinary sodium and potassium excretion rates. We were particularly interested in the assessment of potential impact of –344T>C polymorphism on blood pressure profiles evaluated by 24-hour monitoring.

Material and methods

Study population

The study included 137 women with primary hypertension aged 42–60 years who were hospitalized in the Department of Hypertension and Internal Medicine in Szczecin. We excluded cases with confirmed or suspicious diagnosis of secondary hypertension.

Measurements

We measured waist circumference, height, and weight and calculated body mass index (BMI). All patients had 24-hour blood pressure monitoring (ABPM) (Spacelabs Healthcare) and we analysed systolic, diastolic, and mean blood pressure during the whole monitoring period, daytime, and night time. Non-dipping blood pressure profile was defined as reduction of 0–10% in overnight blood pressure. PRA (normal range: 0.51–2.64 ng/ml/h) and plasma aldosterone (normal range: 10–160 pg/ml) were measured using commercially available assays. From these measurements we calculated the aldosterone-to-renin ratio (ARR). We also evaluated 24-hour urinary potassium (normal range: 25–125 mmol/24 h) and sodium (normal range: 40–220 mmol/24 h) excretion, lipid profiles, and fasting glucose.

CYP11B2 genotyping

Isolation of DNA extracted from whole blood was carried out by using MasterPure™ Complete DNA Purification kit (Epicentre Technologies; Madison, Wisconsin; USA), which provides the ability to obtain DNA concentration of about 80 μg/ml and purity of 85–90%. The –344T>C polymorphism of CYP11B2 gene was identified by polymerase chain reaction-restriction fragment length polymorphism, as described elsewhere [20].

Statistical analysis

Descriptive data are presented as mean ± SD or numbers and percentage. When comparing normally distributed variables between groups of patients with CC/TC and TT genotype, an independent *t* test was used for comparing means. For comparison of skewedly distributed variables between the study groups, median values were calculated and Mann-Whitney U test was used. Categorical variables were evaluated by Chi square test. Correlations between nocturnal blood pressure decline and the study variables were evaluated by Spearman's rank correlation. Multiple linear regressions including the presence of the C allele, ARR, BMI, age, and urine sodium and potassium levels predicted nocturnal blood pressure decline.

Results

Genotype frequencies of TT, CC and CT were 27%, 27% and 46%, respectively and they were consistent with Hardy-Weinberg equilibrium. Overall, frequencies of CC + CT genotypes were nearly three times higher than the TT genotype (Table I). Majority of subjects were overweight/obese and the mean value of waist circumference was above normal range. As many as 88% of patients had a positive family history of cardiovascular disease. Additionally,

Table I. Baseline characteristics of the study participants

Continuous variables	Mean	SD	Range
Age (years)	51.87	4.92	−42−60
Height [m]	1.61	18.44	−1.61−1.78
Weight [kg]	77.23	0.06	−48.6−148
Body mass index [kg/m^2]	29.76	5.77	−18.6−51.52
Waist circumference [cm]	96.17	13.78	−70−133
24-hour systolic blood pressure [mmHg]	121.7	16.56	−110−160
24-hour diastolic blood pressure [mmHg]	74.77	8.56	−53−98
24-hour mean arterial pressure [mmHg]	91.82	9.68	−70−118
Daytime systolic blood pressure [mmHg]	125.45	13.78	−97−162
Daytime diastolic blood pressure [mmHg]	77.65	8.99	−54−100
Daytime pulse pressure [mmHg]	47.78	8.9	−31−82
Daytime mean arterial pressure [mmHg]	94.74	10	−73−118
Nocturnal systolic blood pressure [mmHg]	117.1	15.24	−89−159
Nocturnal diastolic blood pressure [mmHg]	69.12	9.32	−50−98
Nocturnal pulse pressure [mmHg]	48.03	9.28	−31−89
Nocturnal mean arterial pressure [mmHg]	86.34	10.82	−65−121
Plasma renin activity [ng/ml/h]	1.88	1.75	−0.36−12.9
Aldosterone [ng/dl]	12.37	8.36	−2.14−58.6
Aldosterone-to-renin ratio [ng/dl per ng/ml/h]	10.61	10.72	−0.8−99.3
Glucose [mg/dl]	96.63	15.44	−75−189
Total cholesterol [mg/dl]	208.23	37.29	−107−326
Low density lipoproteins [mg/dl]	123.81	31.63	−46−218
High density lipoproteins [mg/dl]	55.09	17.8	−25−82
Triglycerides [mg/dl]	141.42	71.81	−44−467
Urinary sodium excretion [mmol/24 h]	140.05	63.10	−38−359
Urinary potassium excretion [mmol/24 h]	43.93	17.41	−11.1−92.07
Categorical variables	Number	Percent	
Family history of cardiovascular disease	120	87.6	
Smokers	38	27.7	
Diabetes	22	16.0	
Non-dippers	75	54.7	
TT genotype	37	27.0	
TC genotype	63	46.0	
CC genotype	37	27.0	

Data are mean ± SD or numbers (percentage)

16% had type 2 diabetes and 28% were smokers. In 24-hour ABPM more than half of the patients had a non-dipping pattern of blood pressure.

Comparisons in study parameters between CC/TC and TT (wild-type genotype) carriers are shown in Table II. Carriers of the C allele had significantly higher nocturnal blood pressure, lower blood pressure reduction at night time and higher 24-hour urinary potassium excretion. Overall, non-dipping blood pressure profile was much more frequent in patients with CC/TC than in those with TT genotype.

In all women combined, the nocturnal blood pressure decline was not correlated with BMI, waist circumference, aldosterone, PRA and urinary potassium excretion (Table III). There was only a weak positive correlation found between nocturnal blood pressure decline and 24-hour urine sodium

Table II. Comparison of groups with CYP11B2 polymorphism

Variable	CYP11B2 polymorphism		
	TC/CC (n = 100)	TT (n = 37)	P value
Age (years)	51.87 ± 4.73	51.25 ± 5.51	0.558
Height [m]	1.61 ± 0.06	1.6 ± 0.05	0.423
Weight [kg]	78.15 ± 16.5	73.51 ± 11.93	0.281
Body mass index [kg/m^2]	29.98 ± 5.99	28.43 ± 4.51	0.372
Waist circumference [cm]	95.49 ± 14.22	91.34 ± 10.38	0.184
24-hour systolic blood pressure [mmHg]	122.28 ± 17.47	119.42 ± 12.92	0.442
24-hour diastolic blood pressure [mmHg]	75.06 ± 8.46	74.14 ± 8.24	0.719
24-hour mean arterial pressure [mmHg]	92.33 ± 9.42	90.11 ± 9.38	0.479
Daytime systolic blood pressure [mmHg]	126.02 ± 13.56	123.51 ± 13.51	0.759
Daytime diastolic blood pressure [mmHg]	77.58 ± 8.8	78.11 ± 9.23	0.683
Daytime pulse pressure [mmHg]	48.36 ± 9.1	45.48 ± 8.07	0.314
Daytime mean arterial pressure [mmHg]	94.92 ± 9.7	94.0 ± 10.2	0.955
Nocturnal systolic blood pressure [mmHg]	119.1 ± 14.94	111.7 ± 13.41	0.022
Nocturnal diastolic blood pressure [mmHg]	70.06 ± 9.32	66.42 ± 7.95	0.044
Nocturnal pulse pressure [mmHg]	48.77 ± 9.51	45.22 ± 7.87	0.095
Nocturnal mean arterial pressure [mmHg]	87.50 ± 10.72	82.57 ± 9.29	0.034
Nocturnal blood pressure decline [mmHg]	7.4 ± 6.61	11.71 ± 6.49	0.004
Plasma renin activity [ng/ml/h]	1.83 ± 1.74	2.09 ± 1.85	0.755
Urinary sodium excretion [mmol/24 h]	140.76 ± 61.99	137.12 ± 70.02	0.796
Urinary potassium excretion [mmol/24 h]	45.37 ± 17.14	40.04 ± 84.24	0.047
Aldosterone [ng/dl]	12.84 ± 8.96	11.63 ±7.13	0.580
Aldosterone-to-renin ratio [ng/dl per ng/ml/h]	11.11 ± 11.82	9.01 ± 7.3	0.601
Glucose [mg/dl]	96.38 ± 14.4	93.34 ± 8.89	0.469
Total cholesterol [mg/dl]	209.47 ± 37.34	209.6 ± 36.1	0.661
Low density lipoproteins [mg/dl]	125.57 ± 30.86	122.37 ± 32.14	0.320
High density lipoproteins [mg/dl]	52.81 ± 15.15	62.77 ± 22.83	0.038
Triglycerides [mg/dl]	142.6 ± 72.8	131.3 ± 67.3	0.272
Dippers [n]	37 (37%)	25 (67.6%)	0.001
Non-dippers [n]	63 (63%)	12 (32.4%)	0.001

Data are mean ± SD or numbers (percentage)

Table III. Correlations of nocturnal blood pressure decline with measured variables

Variable	R	P value
Body mass index [kg/m^2]	−0.12	0.141
Waist circumference [cm]	−0.09	0.269
Urinary sodium excretion [mmol/24 h]	0.20	0.037
Urinary potassium excretion [mmol/24 h]	−0.12	0.198
Aldosterone [ng/dl]	−0.01	0.837
Plasma renin activity [ng/ml/h]	0.001	0.989
Aldosterone-to-renin ratio [ng/dl per ng/ml/h]	0.004	0.956

R refers to the Spearman rank correlation coefficient

(P = 0.037). In a multiple regression analysis, ARR and presence of the C allele adjusted for confounding variables (age, BMI and urinary sodium and potassium) were inversely associated with the nocturnal blood pressure decline (β = –0.348; P = 0.022 and β = –0.222; P = 0.018, respectively). In carriers of the C allele, a non-dipping blood pressure profile was positively associated with waist circumference (OR = 1.066; 95% CI: 1.0–1.13; P = 0.034).

Further we analysed all women in subgroups with high (> 120 mmol/24 h) and low (≤ 120 mmol/24 h) urine sodium (Table IV). We did not find significant

Table IV. Frequency distribution of blood pressure patterns and CYP11B2 polymorphisms in relation to low and high urinary sodium

	Urinary sodium ≤ 120 mmol/24 h	Urinary sodium > 120 mmol/24 h
Dippers	25 (23.5%)	27 (25.4%)
Non-dippers	23 (21.7%)	31 (29.2%)
TT genotype	13 (12.3%)	15 (14.2%)
TC genotype	22 (20.9%)	25 (23.8%)
CC genotype	12 (11.43%)	18 (28.5%)

Data are presented as numbers (percentage)

differences in frequencies of dipping and non-dipping patterns of blood pressure (χ^2 = 0.321; P = 0.57) nor frequencies of CC, CT, and TT genotypes (χ^2 = = 0.386; P = 0.82).

Discussion

In this study, we report for the first time that middle-aged women with essential hypertension who were carriers of the C allele had significantly higher nocturnal blood pressure, lower nocturnal blood pressure reduction, and higher prevalence of non-dipping hypertension than in TT carriers. Several earlier studies sought associations among genetic variations of the CYP11B2 gene and predisposition to essential hypertension but they yielded inconsistent results. Some authors found that T allele was frequent in patients with essential hypertension [18, 21, 22], whereas in other reports the CC genotype and C allele frequencies were also associated with hypertension [23–25], including results of a large-scale meta-analysis in Chinese [26]. Interestingly, the latter association may be significantly influenced by ethnicity even within the same country [26].

On the other hand, other studies demonstrated that the CC genotype was associated with lower nocturnal [17] and systemic [13, 18] blood pressure. Our results strongly suggest that CYP11B2 polymorphisms do not influence markedly the systemic blood pressure, but may have an impact on nocturnal blood pressure and the risk of non-dipping hypertension. These discrepancies in the literature, besides of the impact of ethnicity, may be associated with genetic variations in the CYP11B2 gene across gender [20], age [27, 28], and likely also comorbidities and antihypertensive treatments. In animal model, Chun and Siragy demonstrated that insulin-deficient diabetes increased, whilst lowering blood pressure with sartans and lowering blood glucose with insulin decreased renal cortical and total kidney CYP11B2 mRNA and protein [29]. Consistently with this observation, Bellili *et al.* found in the general French population that the –344T/C polymorphism was associated with increased risks for incident type 2 diabetes and metabolic syndrome [13]. Similar suggestions were from study of Ichikava *et al.* in which the CT/CC carriers had increased risk of type 2 diabetes by 40% in comparison to TT carriers [30]. Additionally, recent studies have emphasized that the aldosterone synthase CYP11B2 (–344T>C) gene polymorphism may be a useful predictor of the antihypertensive response to valsartan [25, 29]. Hence, because in our series we found a high prevalence of type 2 diabetes and we routinely use as first-line therapy for hypertension the angiotensin II receptor antagonists including valsartan, we cannot exclude that these factors might have an impact on our results.

It has been suggested that CYP11B2 polymorphism might be associated with salt sensitivity of hypertension [11, 31]. It has been estimated that in the general population this genetic variant is recognized in 36% of patients with salt-sensitive hypertension [32]. In the current study we did not assess salt-sensitivity on different dietary salt regimens but only measured 24-hour urine sodium level, which may reflect, among possible many other causes, individual preferences to high or low sodium intake in the diet [33]. We did not observe significant differences in 24-hour urinary sodium excretion between groups with CT/CC and TT genotypes. We only found a weak inverse correlation between nocturnal blood pressure decline and 24-hour urinary sodium excretion, which was not influenced by allelic variants of the CYP11B2 gene. However, in the multiple regression analysis, nocturnal blood pressure decline was inversely associated with ARR in the presence of the C allele, regardless of age, BMI, and urine sodium and potassium levels.

In conclusion, in middle-aged females with essential hypertension carrying the C allele we found higher nocturnal blood pressure, lower nocturnal blood pressure reduction, and higher prevalence of non-dipping hypertension than in TT carriers. These findings suggest genetic predisposition to the development of blunted nocturnal blood pressure dipping and clinical usefulness of –344T>C polymorphism of CYP11B2 gene in identification of patients at risk for cardiovascular outcomes associated with unfavourable profile of the blood pressure diurnal rhythm.

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