

Hypertension

Association between 894G>T Polymorphism in the Endothelial Nitric Oxide Synthase Gene and Circadian Variation of Blood Pressure in Patients with Essential Hypertension

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Background: Human essential hypertension has a genetic basis, and hypertension is associated with altered endothelial nitric oxide (NO) release. We hypothesized that functional alterations of the endothelium-derived NO pathway in the presence of the 894G>T polymorphism of the endothelial NO synthase (eNOS) gene may be related to circadian variation of blood pressure in patients with essential hypertension.

Methods: A total of 101 ambulatory patients (49 men, 52 women) with essential hypertension were recruited in this study. Noninvasive ambulatory blood pressure monitoring and genotyping by polymerase chain reaction amplification of all subjects were performed. The patients were then classified into four groups according to their dipping status: extreme dippers, dippers, non-dippers, and risers. Chi-square test was used for comparison of the allelic and genotypic frequencies among different groups.

Results: The frequencies of the genotypic and allelic frequencies in the study population were comparable to previous reports. There was a trend of increase of genotypic and allelic frequencies of the 894G>T polymorphism in the non-dipper group (non-dippers + risers; n = 52) as compared to the dipper group (dippers + extreme dippers; n = 49), although the difference was not statistically significant. However, a significant increase in the genotypic ($p = 0.021$) frequency and allelic frequency ($p = 0.028$) of the 894G>T variant in the risers (n = 8), compared to those of the dippers (n = 45) was noted. After adjustment for age, gender, body mass index, diabetes mellitus, hyperlipidemia, and smoking status, the presence of 894G>T variant remained a significant predictor of risers (odds ratio 7.95; 95% C.I. = 1.36-46.4; $p = 0.021$).

Conclusions: In this study, a significant association of the 894G>T variant with circadian variation of BP in patients with essential hypertension was demonstrated. These findings are clinically relevant and warrant further investigation in a larger study.

Key Words: eNOS gene polymorphism • Circadian variation of blood pressure • Essential hypertension

INTRODUCTION

The endothelium plays an important part in func-

tional changes in the vasculature by releasing physiologically active substances that locally modulate arterial tone. Nitric oxide (NO) synthesis by the vascular endothelium is important in the regulation of vasodilator tone and in the control of blood pressure (BP) in humans.¹ Human essential hypertension has a genetic basis,² and hypertension is associated with altered endothelial NO release.³ In humans, a variant of the endothelial NO synthase (eNOS) gene within exon 7 has been identified: G → T transversion at nucleotide position 894 of eNOS cDNA, resulting in a change of Glu298 (CAG) to Asp (GAT). A significant association between essential

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hypertension and the 894G>T (Glu298Asp) eNOS polymorphism has been found.² Therefore, functional alterations of the endothelium-derived NO pathway, especially those involved in the pathogenesis of hypertension, may be due to a lesser endothelial release of NO related to the presence of the 894G>T allelic form of the eNOS gene.

There is a marked diurnal variation in the onset of cardiovascular events, such as heart attack, stroke, and sudden death.⁴⁻⁷ The increased risk for these cardiovascular events is considered to be associated with circadian variation of BP in patients with essential hypertension.⁸⁻¹⁰ Individuals with a non-dipper circadian pattern of BP, in which the nocturnal decline in BP is diminished or absent, are at greater risk for cerebral and cardiovascular complications than are individuals with a dipper circadian rhythm.^{3,10} It is reported that endothelium-dependent vasodilation is blunted through a decrease in NO release in non-dippers compared with patients who have dipper hypertension.¹¹ However, little is known about the relationship between the presence of eNOS gene polymorphism and circadian variation of BP in hypertensive patients.

We therefore hypothesized that the 894G>T polymorphism of the eNOS gene may be related to circadian variation of BP in patients with essential hypertension, thus the aim of this study was to investigate such a possible association.

METHODS

Patient Selection

A total of 101 patients (49 men, 52 women) with essential hypertension were recruited from the outpatient clinics at Cheng-Hsin General Hospital according to the following criteria: (1) patient age > 20 years old; (2) onset of hypertension occurred < 60 years of age; (3) established essential hypertension defined either as long-term treatment of the disease, or, in those previously untreated, as average clinic systolic BP (SBP) > 140 mmHg and/or average clinic diastolic BP > 90 mmHg (average for each patient on 2 or more occasions on different days); (4) absence of secondary forms of hypertension as determined through extensive workup; and (5) successful 24-hour ambulatory BP monitoring

(ABPM).

Those with the following conditions were excluded: suspicion of secondary hypertension, insulin-treated diabetes mellitus, recent stroke including transient ischemic attacks (occurring within the previous three months), a past history of coronary artery disease, myocardial infarction or unstable angina pectoris, congestive heart failure, arrhythmia (including atrial fibrillation), or peripheral vascular disease, renal failure (serum creatinine level > 2.0 mg/dL); hepatic damage, chronic obstructive pulmonary disease, heart transplantation, pregnancy and refusal to undergo ABPM.

A complete clinical history, including cardiovascular risk factors such as smoking, hypertension and diabetes mellitus, was obtained. Clinic BP was measured after resting for at least 5 minutes in the sitting position. Serum glucose and lipids were measured after an overnight fast. Diabetes mellitus was defined by a fasting glucose level > 126 mg/dL or the use of an oral hypoglycemic agent or insulin. Hyperlipidemia was defined by a total cholesterol level \geq 200 mg/dL, LDL-cholesterol \geq 130 mg/dL, or triglyceride \geq 200 mg/dL, in combination with either a total cholesterol/HDL-cholesterol ratio > 5 or HDL-cholesterol < 45 mg/dL, or the use of an oral lipid-lowering agent. Smokers were defined as current smokers.

All of the subjects studied were ambulatory, and all gave informed consent for the study. The study protocol was approved by the institutional review board of Cheng-Hsin General Hospital.

24-hour ABPM

Antihypertensive medications were discontinued for at least 14 days before the ABPM study. Noninvasive ABPM was performed on a weekday with an automatic device (DynaPulse system, San Diego, CA, USA) that records BP and pulse rate every 30 minutes for 24 hours. The accuracy of this device had been validated previously,¹² and the ambulatory data used in the present study were those obtained by the oscillometric method. Those patients who obtained less than 80% of either awake or asleep valid BP readings were excluded. Patients who reported in our post-ABPM questionnaire that their sleep was severely disturbed by wearing the ABPM were also excluded from this study.

Sleep BP was defined as the average of BPs from the

time when the patient went to bed until the time he or she got out of bed, and awake BP was defined as the average of BPs recorded during the rest of the day. We classified the patients according to the percentage of nocturnal systolic BP (SBP) reduction [$100 \times (1 - \text{sleep SBP}/\text{awake SBP})$] as follows: extreme dipper if the nocturnal SBP reduction was $\geq 20\%$; dippers if the nocturnal SBP reduction was $\geq 10\%$ but $< 20\%$; non-dippers if the fall was $\geq 0\%$ but $< 10\%$; and risers if it was $< 0\%$.^{4,5}

Detection of the G-to-T Variation in the eNOS Gene

Genotyping of all subjects was performed by polymerase chain reaction amplification according to previously described procedures.^{2,12-15}

In brief, approximately 10 mL of blood was drawn into EDTA tubes, and white blood cells were separated by centrifugation. Genomic DNA was extracted from peripheral blood leukocytes by a commercial DNA extraction Kit (Gentra Systems, Minneapolis, MN, USA) according to manufacturer's instructions. Laboratory personnel performed genotyping without knowledge of the ABPM data. Detection of the G894→T transition in the eNOS gene was performed via polymerase chain reaction (PCR) amplification of exon 7 with the flanking intronic primers 5'-CATGAGGCTCAGCCCCAGAAC-3' (sense) and 5'-AGTCAATCCCTTTGGTGCTCAC-3' (antisense), followed by MboI restriction endonuclease digestion for 16 hours at 37 °C and resolution by electrophoresis on a 2.5% agarose gel.

Analysis of Differences in Clinical Parameters

Data are presented as mean \pm SD. Clinical parameters were analyzed in different groups. For categorical variables, the chi square or Fisher exact test was performed, as appropriate. For quantitative variables, one-way analysis of variance was used. *p* values of 0.05 or less were considered significant for single testing. Comparisons of clinical parameters in GG versus GT patients were also made by *t*-test.

Analysis of Genotype and Allele Frequencies for eNOS Variants

Chi-square test was used for comparison of the allelic and genotypic frequencies using the SPSS 12.0

program (SPSS Inc., Chicago, IL, USA). Allele frequencies were calculated by allele counting, and allele frequencies between groups and deviations of the observed genotype frequencies from Hardy-Weinberg equilibrium were identified by chi-square goodness-of-fit Test. Multiple logistic regression was performed to adjust for other confounding factors of circadian variation of BP. Odds ratio (OR) and 95% confidence intervals (CIs) were also calculated to assess the risk conferred by a particular factor.

A *p* value of 0.05 or less was considered significant for single testing.

RESULTS

Patient Characteristics

The clinical characteristics of the 101 study patients with essential hypertension are shown in Table 1. The extreme dippers were significantly younger than the risers, with dippers and non-dippers between them. No differences among the four groups were noted with respect to gender, height, weight, body mass index, fasting glucose levels, triglyceride levels, total cholesterol levels, LDL-cholesterol levels or HDL-cholesterol levels. The frequencies of diabetes mellitus and hyperlipidemia were similar among the four groups. However, the frequencies of smoking were significantly greater among dippers.

The awake SBPs were similar among the four groups. However, the sleep SBPs were significantly higher among non-dippers and risers, with significant differences between the extreme dippers, dippers, non-dippers, and risers ($p < 0.0001$, $p < 0.0001$, and $p = 0.020$, respectively), and between extreme dippers, dippers, and non-dippers ($p = 0.014$ and $p = 0.042$, respectively). In addition, the differences between sleep and awake SBPs, expressed as awake – sleep SBPs, were all significant between the extreme dippers, dippers, non-dippers, and risers ($p < 0.0001$, $p < 0.0001$, and $p < 0.0001$, respectively), between extreme dippers, dippers, and non-dippers ($p < 0.0001$ and $p < 0.0001$, respectively), and between extreme dippers and dippers ($p < 0.0001$).

As shown in Table 2, no differences between the GG and GT patients were found with respect to clinical parameters, including the diurnal blood pressures.

Table 1. Clinical parameters of the study population

	Extreme dippers (n = 4)	Dippers (n = 45)	Non-dippers (n = 44)	Risers (n = 8)	p value (ANOVA)
Age (yrs)	41 ± 6*	50 ± 11	54 ± 10	60 ± 14	0.024
Male gender, n (%)	2 (50%)	26 (58%)	18 (41%)	3 (38%)	NS
Height (cm)	158 ± 6	163 ± 9	162 ± 7	160 ± 7	NS
Weight (kg)	70 ± 15	70 ± 11	68 ± 12	61 ± 12	NS
Body mass index (kg/m ²)	28 ± 5	26 ± 3	26 ± 4	24 ± 3	NS
Glucose (mg/dL)	94 ± 18	99 ± 15	104 ± 28	96 ± 8	NS
Triglyceride (mg/dL)	154 ± 82	128 ± 60	110 ± 56	112 ± 55	NS
Cholesterol (mg/dL)	218 ± 22	201 ± 36	205 ± 37	201 ± 30	NS
LDL-C (mg/dL)	141 ± 4	130 ± 47	136 ± 30	117 ± 33	NS
HDL-C (mg/dL)	63 ± 28	57 ± 18	56 ± 18	61 ± 16	NS
Diabetes mellitus	0 (0%)	5 (11%)	5 (11%)	1 (13%)	NS
Hyperlipidemia	4 (100%)	28 (62%)	24 (55%)	4 (50%)	NS
Smoking	0 (0%)\$	13 (29%)	2 (5%)\$	0 (0%)\$	0.009
Awake SBP (mmHg)	148 ± 16	140 ± 13	138 ± 13	140 ± 15	NS
Sleep SBP (mmHg)	112 ± 11*#	120 ± 12*#	131 ± 11*	146 ± 15	< 0.0001
Awake – Sleep SBP (mmHg)	36 ± 6*#@	20 ± 5*#	7 ± 5*	-6 ± 3	< 0.0001

* $p < 0.05$, comparisons between extreme dippers, dippers, non-dippers, and risers;

$p < 0.05$, comparisons between extreme dippers, dippers, and non-dippers;

@ $p < 0.05$, comparisons between extreme dippers and dippers;

\$ $p < 0.05$, comparisons between extreme dippers, non-dippers, risers, and dippers.

Table 2. Comparisons of clinical parameters in GG versus GT patients

	GG Genotype (n = 83)	GT Genotype (n = 18)	p value (t test)
Age (yrs)	52 ± 12	53 ± 10	NS
Male gender, n (%)	40 (48%)	9 (50%)	NS
Height (cm)	162 ± 8	161 ± 7	NS
Weight (kg)	69 ± 12	64 ± 10	NS
Body mass index (kg/m ²)	26 ± 3	25 ± 3	NS
Glucose (mg/dL)	99 ± 15	105 ± 37	NS
Triglyceride (mg/dL)	125 ± 60	99 ± 55	NS
Cholesterol (mg/dL)	203 ± 34	207 ± 45	NS
LDL-C (mg/dL)	133 ± 36	124 ± 34	NS
HDL-C (mg/dL)	56 ± 15	63 ± 29	NS
Awake SBP (mmHg)	139 ± 14	143 ± 16	NS
Sleep SBP (mmHg)	126 ± 15	131 ± 16	NS
Awake – Sleep SBP (mmHg)	13 ± 10	11 ± 12	NS

Association between 894G>T Polymorphism of eNOS Gene and Circadian Variation of BP in Patients with Essential Hypertension

Because only four extreme dippers were identified in the present study, such a small number of cases in one group may not be appropriate for a genetic association study. Therefore, we divided the patients into two groups: the dipper group (extreme dippers and dippers; n = 49) and the non-dipper group (non-dippers and risers;

n = 52) for further analysis. The frequencies of the GG, GT and TT genotypes in exon 7 for the two study groups are shown in Table 3.

The frequencies of the GG, GT and TT genotypes in the study population were 82%, 18% and 0%, respectively. The frequency of the T allele was 9% in the study population. This polymorphism in our study population is in Hardy-Weinberg equilibrium. Our findings on the frequencies of the genotypes and allelic frequencies in the

Table 3. Comparison of genotype and allele frequencies for 894G > T polymorphism of eNOS gene in dipper and non-dipper groups

	Dipper Group (Extreme dippers + Dippers) n = 49	Non-dipper Group (Non-dippers + Risers) n = 52	Total n = 101	p value
Genotypes				0.245
GG, n (%)	43 (88%)	40 (77%)	83 (82%)	
GT, n (%)	6 (12%)	12 (23%)	18 (18%)	
TT, n (%)	0 (0%)	0 (0%)	0 (0%)	
Allele type				0.270
G, n (%)	92 (94%)	92 (88%)	184 (91%)	
T, n (%)	6 (6%)	12 (12%)	18 (9%)	

eNOS = endothelial nitric oxide synthase.

Table 4. Comparison of genotype and allele frequencies for 894G > T polymorphism of eNOS gene in different hypertensive subgroups

	Extreme dippers (n = 4)	Dippers (n = 45)	Non-dippers (n = 44)	Risers (n = 8)	Total (n = 101)
Genotypes*					
GG, n (%)	3 (75%)	40 (89%)	36 (82%)	4 (50%)	83 (82%)
GT, n (%)	1 (25%)	5 (11%)	8 (18%)	4 (50%)	18 (18%)
TT, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Allele type#					
G	7 (87%)	85 (94%)	80 (91%)	12 (75%)	184 (91%)
T	1 (13%)	5 (6%)	8 (9%)	4 (25%)	18 (9%)

eNOS = endothelial nitric oxide synthase.

* $p = 0.055$, comparisons between extreme dippers, non-dippers, risers, and dippers;

$p = 0.034$, comparisons between non-dippers, risers, and dippers;

$p = 0.021$, comparisons between risers, and dippers;

$p = 0.073$, comparisons between extreme dippers, non-dippers, risers, and dippers;

$p = 0.047$, comparisons between non-dippers, risers, and dippers;

$p = 0.028$, comparisons between risers, and dippers.

study population were comparable to previous reports, which demonstrated that the genotype distribution in the TT, GT, and GG groups were about 0-3.1%, 9-17.4% and 81.5-91%, respectively, in Taiwanese and Japanese populations, with a T allele frequency of 10% or so.^{2,13-16}

There was a trend of increase of genotypic ($p = 0.245$) and allelic ($p = 0.270$) frequencies of the 894G>T polymorphism in the non-dipper group as compared to the dipper group, although the difference was not statistically significant.

Analyses of Genotype and Allele Frequencies for 894G>T Polymorphism of eNOS Gene in Different Hypertensive Subgroups

The comparisons of frequencies of the GG, GT and TT genotypes in exon 7 for the four subgroups, i.e. the

extreme dippers, the dippers, the non-dippers, and the risers, are shown in Table 4. A borderline association of the 894G>T genotypic variant with circadian variation of BP was demonstrated ($p = 0.055$). Furthermore, a significant increase in the genotypic ($p = 0.021$) frequency and allelic frequency ($p = 0.028$) of the 894G>T variant in the risers ($n = 8$), compared to those of the dippers ($n = 45$) was noted.

To ensure that the effect of genotype was not due to confounding factors, a multivariate logistic-regression analysis was performed, taking into account genotype and main clinical variables (i.e., age, gender, body mass index, diabetes mellitus, hyperlipidemia, and smoking status). The result showed that the presence of the 894G>T variant appeared as the only significant predictor of risers (odds ratio 7.95; 95% C.I. = 1.36-46.4; $p = 0.021$) (Table 5).

Table 5. Predictors of risers: multivariate logistic-regression analysis

Variables	Odds ratio	95% C.I. for Odds ratio	<i>p</i> value
Age	1.075	0.994-1.163	0.069
Gender	0.678	0.111-4.147	0.674
Body mass index	0.781	0.577-1.058	0.110
Diabetes mellitus	1.381	0.077-24.75	0.826
Hyperlipidemia	0.391	0.065-2.364	0.306
Smoking	0.000	0.000	0.998
GT genotype	7.954	1.362-46.45	0.021

DISCUSSION

In the present study, we investigated whether 894G>T polymorphism of the eNOS gene, which is an important enzyme producing NO, is associated with circadian variation of BP in patients with essential hypertension. Our findings on the frequencies of the genotypes and allelic frequencies were comparable to those presented in previous reports.^{2,13-16} We demonstrated that there was a trend of increase of genotypic and allelic frequencies of the 894G>T polymorphism in the non-dipper group (non-dippers + risers) as compared to dipper group (dippers + extreme dippers), although the difference was not statistically significant. However, significant differences in genotype and allele frequencies of the 894G>T variant between risers and dippers were noted.

NO synthesis by the vascular endothelium is important in the regulation of vasodilator tone and the control of BP in humans.¹ Hypertension is associated with alterations in resistance artery endothelial function, and hypertensive patients with poor endothelial function had a worse prognosis compared to those who had mild endothelial dysfunction.^{1,3,11} Several different polymorphisms of the eNOS gene have been identified,^{2,17,18} and genetic contribution of the eNOS gene polymorphism to plasma NO levels has been previously demonstrated.^{19,20} The gene encoding eNOS is located on chromosome 7q35-36 and comprises 26 exons spanning 21 kb.²¹ The 894G>T variant of the endothelial NO synthase (eNOS) gene was identified within exon 7: G-to-T conversion at nucleotide position 894 of eNOS cDNA resulting in a replacement of glutamic acid by aspartic acid at codon 298 (Glu298Asp). Although the purported association of this polymorphism and CAD remains controversial,^{13,14,18,22,23} and it is suggested that this genetic variant of the eNOS

gene may not be an important risk factor for coronary artery disease or myocardial infarction among Taiwanese,^{13,14} this variant is consistently reported to affect vascular reactivity such as essential hypertension,² coronary spasm,¹⁵ and an enhanced vascular responsiveness to alpha-adrenergic stimulation.¹⁶ In the present study, we further demonstrate that the variant is associated with circadian variation of BP in patients with essential hypertension.

Twenty-four-hour ambulatory blood pressure monitoring (ABPM) demonstrated that blood pressure has a highly reproducible circadian profile.²⁴ However, there is considerable variation in the diurnal rhythm of BP in different patients.^{4-6,24-26} Previous studies have indicated that the degree to which BP falls or rises during the night, as measured by the difference or ratio of the average daytime and nighttime BPs, varies greatly from one patient to another, and that these different patterns (dipping, non-dipping, extreme dipping and rising) are associated with very different risks of strokes.⁴ For example, stroke risk was significantly associated with being classified as a riser.⁵ Individuals with a non-dipper circadian pattern of BP are at greater risk for cerebral and cardiovascular complications than are individuals with a dipper circadian rhythm.^{4,10} It is suggested that in non-dippers and risers, the higher "blood-pressure burden" may contribute to the increased cardiovascular risk.^{4,5,10,26}

Previous studies have shown that abnormalities in autonomic function, especially in the sympathetic nervous activity, inhibit the nocturnal decline in BP. It is suggested that the inappropriate reduction in nocturnal BP may contribute to impaired endothelium-dependent vasodilation in these patients.²⁷⁻²⁹ In non-dippers, the endothelium-dependent vasodilatation is blunted compared with patients who have dipper hypertension.¹⁰ The diminished nocturnal decline in BP in non-dippers may increase nocturnal plasma viscosity, resulting in decreased shear stress and NO production.¹¹ We hypothesize that functional alterations of the endothelium-derived NO pathway, such as the presence of the 894T allelic form of the eNOS gene, may further reduce the endothelial release of NO and therefore may exaggerate the vascular responsiveness to the abnormally activated sympathetic nervous system and result in increased sympathetic vasoconstriction in these patients. In the present study,

the significant increase in the genotypic and allelic frequencies of the 894G>T variant in the risers compared to the dippers and a trend of increase of the polymorphism in the non-dipper group compared with the dipper group are consistent with our hypothesis that the vascular responsiveness to vasoconstricting hormones may be modulated by the polymorphism of the eNOS gene.

Since increased risk for cerebral and cardiovascular events is considered to be associated with circadian variation of BP in patients with essential hypertension,⁴⁻¹⁰ the results of the present study may have important implications in antihypertensive therapy to ensure maximal cardiovascular protection. In a patient with hypertension, 24-hour BP monitoring has substantial appeal. It can identify dipping status and gives a far better representation of the "blood-pressure burden" than might be obtained in a few minutes at the doctor's office. The non-dippers and risers probably represent a worse course of hypertension with more endothelial dysfunction. Therefore, it is clinically important to individualize anti-hypertensive treatment to improve endothelial function and restore a normal circadian pattern of BP in patients with essential hypertension. Treatment of non-dippers and risers to render them dippers could partially normalize their endothelial function and partially improve their prognosis. In addition, the hypertensive patients of different genotypes may need different antihypertensive formulations that provide 24-hour or longer efficacy: for example, alpha-adrenergic blocking agents or the use of NO donor (such as nitrates) or supplementation of NO substrates (L-arginine)³⁰ may be given for this purpose in susceptible patients.

The current study is limited by its small sample size. The relationship of the 894G>T polymorphism of eNOS gene to circadian variation of BP in patients with essential hypertension on the basis of only 101 cases is relatively weak. Therefore, a large-scaled study maybe needed to confirm the results and further delineate the relationship between eNOS gene polymorphism and circadian BP changes in hypertensive patients. Furthermore, extreme-dippers have been reported to be at particularly high risk.⁴ It is suggested that a higher morning surge of BP that occurs on waking in these patients is associated with stroke risk independently of the nocturnal BP falls.⁵ The presence of the 894T allelic form of the eNOS gene may reduce the endothelial release of NO

and thus may contribute to the morning surge in BP in these patients.^{5-9,29} However, in our study population, only 4 extreme dippers were identified, and it is impossible to draw any conclusion from analysis of such a small number of cases. In addition, serum concentrations of L-arginine and NO and vascular reactivity were not checked in the present study.

CONCLUSIONS

In this study, an association of the 894G>T variant with circadian variation of BP in patients with essential hypertension was demonstrated. There was a significant difference in genotypic and allelic frequencies between risers and dippers and a tendency of increase of genotypic and allelic frequencies of the polymorphism in the non-dipper group (non-dippers and risers) compared to the dipper group (extreme dippers and dippers), although the latter difference was not statistically significant. These findings are clinically relevant and should be investigated in a larger study.

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內皮細胞一氧化氮合成酶之 894G>T 多型態與原發性 高血壓患者晝夜血壓變化之相關性

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背景 高血壓患者有遺傳傾向且其血管內皮細胞產生的一氧化氮 (nitric oxide; NO) 有減少的現象。吾人假設具有 894G>T 內皮一氧化氮合成酶 (endothelial NO synthase; eNOS) 基因多型態 (polymorphism) 的原發性高血壓患者會影響其血管內皮合成一氧化氮，因而和患者之晝夜血壓變化有關。

方法 本研究選取 101 位原發性高血壓患者，所有受試者均接受二十四小時血壓紀錄及 eNOS 之 894G>T 多型態檢驗。參與研究之高血壓患者依其二十四小時血壓紀錄分為四類型：夜間血壓下降極明顯者 (extreme dippers)、夜間血壓下降明顯者 (dippers)、夜間血壓下降不明顯者 (non-dippers) 和夜間血壓上升者 (risers)。再以統計方法分析各組間 894G>T 內皮一氧化氮合成酶多型態的發生率是否有差異。

結果 本研究選取之原發性高血壓患者其 eNOS 之 894G>T 多型態的發生率與過去研究報告結果相符。若將夜間血壓下降不明顯者和夜間血壓上升者合稱為夜間血壓未下降組 (non-dipper group, 計 52 人)；將夜間血壓下降極明顯者和夜間血壓下降明顯者合併起來稱為夜間血壓下降組 (dipper group, 計 49 人)；兩組比較發現：夜間血壓未下降組之 eNOS 894G>T 多型態的發生率較夜間血壓下降組有增加之趨勢，但未達到統計意義。然而若單獨將夜間血壓上升者 (計 8 人) 之 eNOS 894G>T 多型態發生率與夜間血壓下降明顯者 (計 45 人) 相比，則前者較後者明顯為高 (基因型發生率差異 p 值為 0.021；單套對偶基因型發生率差異 p 值為 0.028)。多變項分析發現，校正年齡、性別、體質指數、糖尿病、高血脂症和吸菸等變項後 eNOS 894G>T 多型態仍是預測夜間血壓上升者的獨立指標 (危險比為 7.95；95% 信賴區間為 1.36 至 46.4； p 值為 0.021)。

結論 eNOS 之 894G>T 多型態和原發性高血壓患者之晝夜血壓變化有關。此發現有臨床治療之意義，但仍需要大規模之研究加以確認。

關鍵詞：894G>T 內皮一氧化氮合成酶基因多型態、晝夜血壓變化、原發性高血壓。