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Cytochrome P450 *2J2*7* Single-nucleotide Polymorphism and Nocturnal Hypertension in an Elderly Turkish Population

Yaşlı Türk Popülasyonunda Sitokrom P450 *2J2*7* Tek Nükleotid Polimorfizmi ve Gece Hipertansiyonu

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ABSTRACT

Objective: Blood pressure shows a physiological diurnal rhythm. Altered blood pressure circadian rhythm is more common in the elderly. Nocturnal hypertension (NH) and/or impaired nocturnal dipping profile are associated with increased mortality risk. The *CYP2J2*7* polymorphism is associated with decreased arachidonic acid metabolite levels and increased cardiovascular mortality risk in different populations. The aim of this study was to investigate whether NH was associated with *the CYP2J2*7* polymorphism in an elderly Turkish population.

Methods: Ambulatory blood pressure data were obtained from 120 elderly (78 women and 42 men, aged 60-105 years) volunteers during 24 h. The *CYP2J2*7 (G/T)* polymorphism was evaluated using a Taqman® Drug Metabolism Genotyping Assay kit and a TAQMAN ABI7900 device.

Results: The *CYP2J2*7 T*-allele frequency was 6.7% in our study population. The 24 h, day, and night systolic blood pressures were found to be 2-5 mmHg higher in *CYP2J2*7 T*-carriers (n=15) than in individuals with *the GG* genotype (n=105), however, the differences between the genotype groups were not statistically significant. The systolic blood pressure morning increase slope values of *the CYP2J2*7* carriers and *GG* genotype group were 8.6±2.0 (mean ± standard error of mean) and 5.7±0.5, respectively, i.e., 50.7% higher in *T*-carriers (p=0.039). There was no statistically significant difference in the frequency of NH with the *CYP2J2*7* polymorphism.

Conclusion: Considering the existing literature with our findings, the *CYP2J2*7* carrier status may indicate an increased risk of cardiovascular events. However, further studies are required to verify the significance of this finding.

Keywords: Nocturnal hypertension, *CYP2J2*7*, cytochrome

ÖZ

Amaç: Kan basıncı fizyolojik günlük bir ritim gösterir. Kan basıncının sirkadiyen ritminin değişmesi yaşlılarda daha sık görülür. Gece hipertansiyonu ve/veya bozulmuş gece düşüş profili, artan ölüm riskiyle ilişkilidir. *CYP2J2*7* polimorfizmi, farklı popülasyonlarda araşidonik asit metabolit seviyelerinin azalması ve kardiyovasküler mortalite riskinin artmasıyla ilişkilidir. Bu çalışmanın amacı yaşlı Türk toplumunda gece hipertansiyonunun *CYP2J2*7* polimorfizmi ile ilişkili olup olmadığını araştırmaktır.

Yöntemler: Ambulatuvar kan basıncı verileri 120 yaşlı (78 kadın ve 42 erkek, 60-105 yaş arası) gönüllüden 24 saat boyunca elde edilmiştir. *CYP2J2*7* (*G/T*) polimorfizmi, Taqman® İlaç Metabolizması Genotipleme Test kiti ve TAQMAN ABI7900 cihazı kullanılarak değerlendirilmiştir.

Bulgular: Çalışma popülasyonumuzda *CYP2J2*7 T*-allel frekansı %6,7 idi. *CYP2J2*7 T*-alleli taşıyıcılarında (n=15), *GG* genotipli bireylere (n=105) göre 24 saatlik, gündüz ve gece sistolik kan basınçları 2-5 mmHg daha yüksek bulunmuştur, ancak genotip grupları arasındaki fark istatistiksel olarak anlamlı değildi. *CYP2J2*7* taşıyıcıları ve *GG* genotip grubunun sistolik kan basıncı sabah artış eğimi değerleri sırasıyla 8,6±2,0 (ortalama ± ortalama standart hatası) ve 5,7±0,5 idi, yani *T*-alleli taşıyıcılarda %50,7 daha yüksekti (p=0,039). *CYP2J2*7* polimorfizmi ile gece hipertansiyon sıklığı arasında istatistiksel olarak anlamlı bir fark yoktu.

Sonuç: Bulgularımız ile mevcut literatür göz önüne alındığında, CYP2J2*7 taşıyıcılığı artmış kardiyovasküler olay riskine işaret edebilir. Ancak bu bulgunun önemini doğrulamak için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Gece hipertansiyonu, *CYP2J2*7*, sitokrom

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INTRODUCTION

Hypertension is a multifactorial and complex disease. Environmental factors and many candidate genes have been investigated to explore the etiology of hypertension, including angiotensinogen, angiotensin-converting enzyme, angiotensin II receptor types I and II, renin, renin-binding protein, and aldosterone synthase, in various ethnic populations (1). The physiological blood pressure pattern is time dependent, with an increase in the morning (activity) time and a decrease in the sleeping (rest) time (2). For both normotensive and hypertensive individuals, sleep time average blood pressure values are generally lower than their daytime blood pressure, by approximately 10-20% (3). Circadian rhythm abnormalities are associated with several cardiac and renovascular diseases (2). Various studies have reported that clock gene mutations, including *Bmal1, Clock, Per1/2/3,* and *Cry1/2,* are frequently expressed in individuals with altered circadian blood pressure profiles and impaired vascular hemodynamics, leading to myocardial infarction and stroke (4). Nighttime blood pressure change patterns vary among individuals who can be defined as dippers, non-dippers, super dippers, or rising (reverse dippers) (3,5,6). The results of the Ohasama study have shown that the circadian patterns of blood pressure without reduction during the nighttime, reversing dipping and non-dipping, are associated with increased mortality risk (7). Nocturnal hypertension (NH) is defined as high blood pressure at night (5). It has been shown that nighttime blood pressure reduction decreases with age (8). As reviewed by Tadic et al. (9), the prevalence of NH is influenced by demographic, clinical, and ethnic factors. The prevalence of NH has been reported as 10-60%, varying in different studies (10-12). Several studies have shown a relationship between cardiovascular mortality or morbidity and NH (9).

Among several other factors, arachidonic acid metabolites and monooxygenase play an important role in the etiopathogenesis of hypertension (13). Several studies have shown that 20-hydroxyeicosatetraenoic acid and epoxyeicosatrienoic acid (EETs) metabolites have an impact on the regulation of vascular tone and pathogenesis of hypertension (13). Because cytochrome P450 (CYP) enzymes are involved in the metabolism of arachidonic acids, variations in the CYP2C*, 2J, 4A,* and *4F* gene families have been studied for their relationship with blood pressure regulation (14). Wu et al. (15) showed that the CYP2J2 enzyme, which metabolizes arachidonic acid into EET, is highly expressed in the human heart. Furthermore, CYP2J2 mRNA levels have been found to be higher than CYP2C8 and CYP2C9 in human heart, whereas CYP2C9 mRNA levels were higher than CYP2J2 mRNA levels in human aorta, coronary artery, and especially in ischemic heart (16). These data was supported by the fact that CYP2J2 mRNA levels were the most expressed CYP450 isoform in human left heart ventricular samples (17). The CYP2C8, CYP2C9, and CYP2C19 enzymes have been shown to play substantial roles in the epoxidation of arachidonic acid and production of EETs (18,19). Node et al. (20) reported that CYP2J2 also catalyzes the formation of EETs, which have an anti-inflammatory effect on the bovine aortic vascular wall. CYP2J2 overexpression also increases tissue plasminogen activator (t-PA) expression in addition to having a vasodilator effect on vascular endothelial cells (21).

Of the several genetic variants of CYP2J2, the *CYP2J2*7* polymorphism is located 76 nucleotides upstream of the first nucleotide of the translation start codon and 50 nucleotides upstream of the transcription start site (22). This G-50T mutation leads to decreased arachidonic acid metabolism and production of 14,15-dihydroxyeicosatrienoic acid (23).

In addition to essential hypertension, the *CYP 2J2*7* polymorphism (24,25) has also been reported to be associated with an increased risk of myocardial infarction in Taiwanese (26).

The frequency of the *CYP2J2*7 T*-allele has been reported to vary between 2.1% and 17% in different ethnicities (22) 14.1% in African Americans, 7.7% in Caucasians (24) and 2.6% in Chinese (27).

As mentioned before, many studies have investigated the risk of organ damage in the presence of NH or have attempted to find the predictive role of gene mutations in this disease across different ethnic groups (4,9).

Because aging is a risk factor for NH and the role of cytochrome P450 enzyme genetic mutations in the regulation of arachidonic acid metabolism, regulation of blood pressure, and organ damage risk, the aim of our study was to investigate whether the *CYP2J2*7* polymorphism is associated with NH in an elderly Turkish population.

MATERIALS AND METHODS

The study was conducted with the permission of the Local Ethics Committee of Gazi University Faculty of Medicine (approval number: 193, date: 14.06.2006; no: 413/26.11.2007). A total of 120 elderly subjects (78 women and 42 men, aged 60-105 years) from two different nursing homes in Ankara. participated in the study on a voluntary basis. Subjects diagnosed with secondary hypertension or terminal cancer and those who failed to cooperate with study requirements were excluded. All volunteers signed an informed consent form before their participation.

Ambulatory blood pressure monitors (ABPM) were applied throughout the 24 h (Spacelabs 90207 model, Spacelabs Limited, Redmond, Washington, USA). Monitors were attached to the upper arm of the inactive volunteers. All monitors were set to measure blood pressure every 20 min between 06:00 and 24:00 and every 30 min between 24:00 and 6:00. During monitoring, the volunteers continued their daily activities and sleeping habits. The measurement limits of the monitors were arranged in such a way that in cases where systolic blood pressure was ≤70 mmHg or ≥220 mmHg, and diastolic blood pressure ≤40 mmHg or ≥150 mmHg, the measured value was considered as an incorrect reading and was automatically excluded from examination by the program. The records were accepted if at least 75% of the monitor measurements were successful during the 24 h examination period and if there was at least one successful reading per hour.

Monitoring records were analyzed using the ABPM-FIT (University of Heidelberg, Germany, version 2.2) and CV-SORT programs. Nocturnal and daytime blood pressures were calculated considering each volunteer's bedtime (resting period) and wake-up time.

Genetic Analysis

A 5 mL whole blood sample was collected and maintained at -20 °C until isolation of DNA. Genomic DNA was isolated from peripheric leucocytes using a QIAMP DNA Kit (Qiagen, Hilden, Germany) according to manufacturer's guidance and analyzed for

the *CYP2J2*7* (-76G>T) *(rs890293)* single nucleotide polymorphism (SNP) using a Taqman® Drug Metabolism Genotyping Assay kit (C_9581699_80) (Applied Biosystems, Foster City, CA, USA) and a TAQMAN ABI7900 (Applied Biosystems, Foster City, CA, USA) device. Taqman universal mixture, allelic discrimination mix, bovine serum albumin, and autoclaved distilled water were used to prepare a final reaction volume to 9 µl Master mix for each sample according to kit guidelines. Thermal Cycling conditions were applied as 50 °C, 2 min; 95 °C, 10 min and 45 cycles; 92 °C, 15 sec. and 60 °C, 1 min for the PCR reaction.

Data Analysis

Based on the analysis of the ABPM records, subjects were classified as NH or nocturnal normotensive (NN) based on the systolic blood pressure average ≥125 mmHg or below 125 mmHg, respectively, during resting period, according to the ABPM records. The subjects were also classified as dippers, non-dippers, or reverse dippers. Subjects with a nocturnal mean systolic blood pressure decrease of 10-20% compared with daytime levels were classified as Dippers, those with a decrease of less than 10% as non-dippers, and those with a mean systolic blood pressure increase during the night period compared with the daytime period were classified as reverse dippers.

Systolic and diastolic blood pressure morning increase slopes and night decrease slopes were also calculated on the basis of the ABPM data using mean blood pressure readings of each subject 3 h before and after wake-up time and 3 h before and after bedtime, respectively.

On the basis of the ABPM records, each subject's blood pressure load was also recorded with ABPM monitors. The load value is the percentage of the number of measurements over the limits in each period (28). The accepted limits were 140 mmHg (24 h period), 140 mmHg (daytime), and 125 mmHg (night time for systolic blood pressure).

Statistical Analysis

Statistical analysis was performed using Sigma Stat 3.1. Results are presented as mean ± standard error of mean. Student's t-test/Mann-Whitney U test were used for comparisons of the characteristics between the NH and normotensive subjects. The genotype frequencies of the groups were evaluated using Fisher's exact/chi-square test. Fisher's exact chi-square test was also used for categorical features. Statistical significance was set with p-value <0.05.

RESULTS

Of the 120 subjects included in the study, 47% (n=56) had NH (≥125/80 mmHg). The main characteristics of the volunteers are shown in Table 1. A total of 12% of the participants had diabetes mellitus. The majority of the participants, 37.5% (n=45) were on prescription for antihypertensive medication/medications. In addition, 19.6% (n=11) of NH and 14% (n=9) of NNs used more than one antihypertensive medication. Antihypertensive medications included beta blockers, calcium channel blockers, angiotensin II receptor antagonists, angiotensin receptor antagonist and diuretic combinations, angiotensin converting enzyme inhibitors (ACEI) and

Table 1. Main characteristics (n=120)

	Nocturnal hypertensive SBP ≥125 mmHg, (n=56)	Nocturnal normotensive SBP <125 mmHg, (n=64)	p
Age	82.3±1.0	79.7±1.3	**p>0.05**
Women/men	38/18	40/24	**p>0.05***
Body mass index	26.27	26.71	**p>0.05**
Systolic blood pressure (mmHg)			
24 h	137.1±1.4	118.3±1.3	**p<0.001**
Day	136.2±1.5	121.8±11.4	**p<0.001**
Night	137.8±1.5	111.1±1.9	**p<0.001**
Night load (%)	74.2±3.3	12.5±1.8	**p<0.001**
Morning blood pressure increases slope	4.9±0.6	7.1±0.7	**p<0.05**
Night blood pressure decrease slope	-5.7±0.8	-7.0±0.6	**p<0.05****
Diastolic blood pressure (mmHg)			
24 h	72.8±1.1	67.3±0.9	**p<0.001**
Day	73.5±1.2	69.8±1.0	**p<0.05**
Night	70.8±1.3	61.4±0.9	**p<0.001**
Night load (%)	22.7±3.6	4.6±1.0	**p<0.001**
Heart rate			
24 h	70.8±1.4	72.3±1.2	**p>0.05**
Day	72.9±1.5	75.0±1.3	**p>0.05**
Night	67.6±1.5	67.6±1.1	**p>0.05**

*Chi-square test, **Mann-Whitney U test, Student's t-test was used for other parameters, all results presented as mean ± standard error of mean. SNP: Single nucleotide polymorphism.

diuretics combinations, and ACEIs and alpha blockers in order of frequency.

*CYP2J2*7* SNP Allele and Genotype Frequency

Only one of the 120 participants was homozygous for the *CYP2J2*7 T*-allele, whereas 14 participants were heterozygous (G/T) and the rest (n=105) had the wild-type *GG* genotype. Homozygous and heterozygous T variant carriers were combined for statistical evaluation. The *T*-allele frequency was 6.7% [confidence interval (CI) 95%=0.4-0.8].

Allele frequencies and genotype distributions in the NH participants and those without NH groups are shown in Table 2.

24 h Blood Pressure Data in *CYP2J2*7* Genotype Groups

In this study, neither *CYP2J2*7* genotypes nor *T*-allele frequencies differed between the NH and NN groups as evaluated with Fisher's exact chi-square test [odds ratio (OR)=0.7; CI 95%=0.2-2.2, (p=0.8); (OR=0.7; CI %95=0.2-1.9), respectively].

The 24 h, day, and night systolic blood pressures were numerically 2-5 mmHg higher in *CYP2J2*7 T* carriers than in the *GG* genotype group (n=105) (Figure 1); however, the differences were not statistically significant (p>0.05).

Table 2. *CYP2J2*7* SNP allele and genotype frequency

	Nocturnal		**Nocturnal normotensive**		**p-value**
Genotype	**n**	**%**	**n**	**%**	
GG	50	89.3	55	85.9	**0.8**
GT	6	10.7	8	12.5	
TT	0	0	1	1.6	
	Nocturnal hypertensive group		**Without nocturnal hypertensive group**		
Allele	**n (%)**		**n (%)**		**Total n (%)**
G	106 (44)		118 (49)		224 (93.3)
T	6 (2.5)		10 (4.1)		16 (6.6)
			Total		240

*Percentages are presented as column percentages, SNP: Single nucleotide polymorphism.

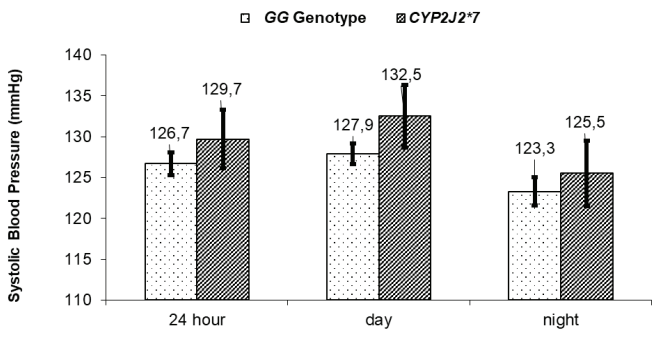

Figure 1. 24 h, day, and night systolic blood pressure of *CYP2J2*7* SNP carriers (n=15) and *GG* genotype (n=105) groups in the overall study population.

SNP: Single nucleotide polymorphism.

The systolic blood pressure morning increase slope values of *CYP2J2*7* carriers and the *GG* genotype were 8.6±2.0 and 5.7±0.5, respectively, i.e., 50.7% higher in *T*-carriers p=0.039 (Figure 2). However, the difference in systolic blood pressure night decrease slopes was not statistically significant between the groups (p>0.05).

Although the mean systolic blood pressure of NH *CYP2J2*7* carriers was 4-5 mmHg higher than that of NH *GG* genotype volunteers (Figure 3), this result was not statistically significant (p>0.05).

The systolic blood pressure load values of *CYP2J2*7* carriers tended to be higher than those in the *GG* group for 24 h, day and night, but again the difference did not reach statistical significance (p>0.05) (Figure 4).

No differences in diastolic blood pressure evaluations were found between *CYP2J2*7* carriers and the *GG* genotype group concerning morning increase, nighttime decrease, or heart rate (Table 3).

Dipping Patterns and *CYP2J2*7* Genotype

Of all participants, 27.5% were dippers, 52.5% were non-dippers, and 20 % were reverse dippers. No difference was observed between

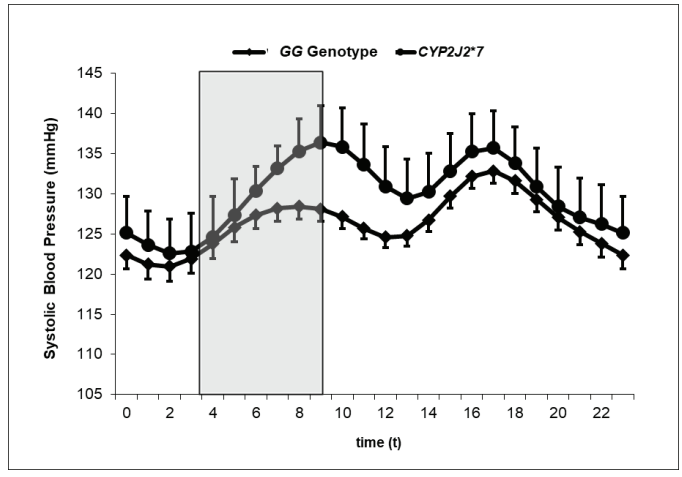

Figure 2. 24 h profile of systolic blood pressure of *CYP2J2*7* SNP carriers (n=15) and *GG* Genotype (n=105) subjects in the overall study population.

**Shaded area covers the 3 h before and after wake-up time of volunteers, SNP: Single nucleotide polymorphism.*

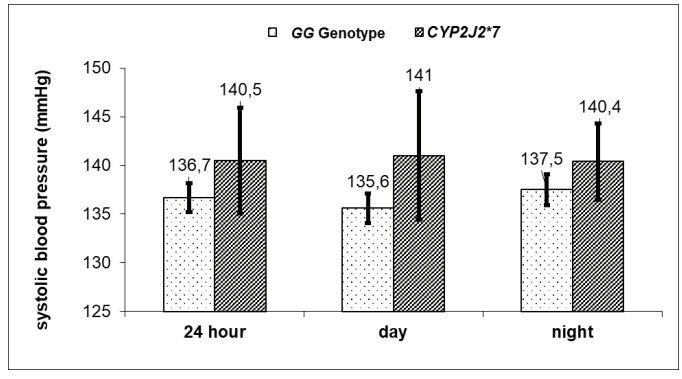

Figure 3. 24 h, day, and night systolic blood pressure values of "nocturnal hypertensive" *CYP2J2*7* SNP carriers (n=6) and *GG* genotype (n=50) groups.

SNP: Single nucleotide polymorphism.

the groups in terms of the frequency of those with and without polymorphism according to night-time blood pressure fall patterns (p>0.05). Although only the *CYP2J2*7* homozygote participant had a non-dipping profile, the distribution of the dipping patterns did not show a statistically significant difference between *CYP2J2*7* carriers and the *GG* genotype (Table 4).

DISCUSSION

In this study, there was a statistically significant association between morning slope and *CYP2J2*7* mutation carrier status. Several earlier studies have shown that sudden death and ventricular arrhythmias tend to occur in the morning time (29) and this has been explained by the impaired vascular endothelial function and increased prothrombotic activity observed in the morning hours, leading to an increased risk of cardiovascular events (30). In our study population, the morning systolic blood pressure increase slope of *CYP2J2*7 T*-carriers (n=15) was significantly higher than that in the group of *GG* subjects (p-value=0.039). Morning blood pressure surge is a substantial risk factor for target organ damage and a known trigger for cardiovascular events (31). Previously, the *CYP2J2*7* polymorphism was reported to be associated with premature myocardial infarction in Taiwanese patients in addition to smoking-related risk factors (26). It has been stated that more studies are needed regarding the clinical significance of morning blood pressure surge and even the clinical effectiveness of divided or timed doses of long-acting drugs in blood pressure control (32). Based on our findings, the carrier status for *CYP2J2*7* can be a predictor of increased morning systolic blood pressure slope and related risk of cardiovascular events. However, this aspect needs to be supported with long-term follow-up studies evaluating cardiovascular disease risk in association with the *CYP2J2* genotype.

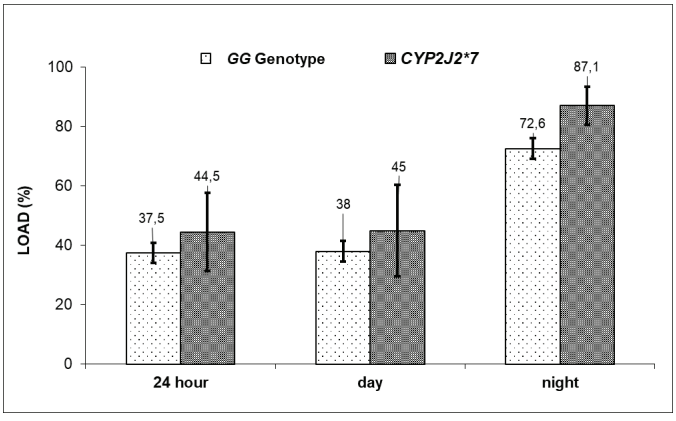

Figure 4. 24 h, day, and night systolic load values of *CYP2J2*7* SNP carriers (n=15) and *GG* genotype (n=105).

SNP: Single nucleotide polymorphism.

Table 3. Diastolic blood pressure values in relation to *CYP2J2*7* genotypes in the study population (n=120)

	***GG*, (n=105)**	***GT* or *TT*, (n=15)**	**p-value**
24 h	69.6±0.8	71.6±2.2	>0.05
Day	71.2±0.8	73.7±2.5	>0.05
Night	65.6±1.0	66.8±2.0	>0.05
Morning blood pressure increases slope	4.5±0.3	6.0±1.7	>0.05
Night blood pressure decrease slope	-4.9±0.4	-4.4±0.8	>0.05

The results of the Ohasama study in a population of Japanese subjects aged 40 years or older with approximately 10 years of follow-up of ambulatory blood pressure have shown that lower night-time mean blood pressure values predicted lower cerebrovascular and cardiovascular mortality rates (33). Moreover, the Dublin outcome study further supported that high values of nighttime blood pressure measurements affect mortality risk (34). Previously, a statistically significant association between *CYP2J2*7* polymorphism and hypertension has been reported in African-Americans, Caucasians, and Arabic people, respectively (24,35). Additionally, the association of *CYP2J2* polymorphism and essential hypertension has been reported in the Chinese Han population (36).

Based on the evidence in the literature concerning the association between hypertension and the *CYP2J2* genotype, we investigated ambulatory blood pressure data and the distribution of *CYP2J2*7* in a group of elderly subjects in two residential institutes in Ankara, Türkiye. We found no significant association between NH and either the *CYP2J2*7* genotype or *T*-allele frequency (Table 2). Although the 24 h, day, and night systolic blood pressure average were 2-5 mmHg higher in *CYP2J2*7* carriers (one homozygote and 14 heterozygote) than in *GG* genotype subjects (n=105) (Figure 1), the difference was not statistically significant (p>0.05). Similarly, no difference in diastolic blood pressure or heart rate was observed between *CYP2J7* genotype groups. This is most probably due to the major limitation of our study, namely, the size of the study population.

The CYP2J2 protein is highly expressed in vascular tissue and the heart and is involved in fatty acid metabolism, regulating vascular tone, inflammation, and cellular proliferation and angiogenesis (37). Spiecker et al. (23) reported that reduced basal CYP2J2 enzyme activity in turn might be related to coronary artery disease risk. In their study in healthy Caucasians, the allele frequency of *CYP2J2*7* was 10.6%. While King et al. (24) reported a higher frequency in African-American hypertensives (14.1%) than in Caucasians (7.7%), in a healthy Chinese volunteer population, an allele frequency

Table 4. Frequency of the *CYP 2J2*7* carrier status and dipping profile

	Frequency of dippers % (n)	**Frequency of non-dippers % (n)**	**Frequency of reverse dippers % (n)**
G/G	28 (29)	51 (54)	21 (22)
T carriers (*G/T* and *T/T*)	27 (4)	60 (9)	13 (2)
Total	28 (33)	53 (63)	20 (24)

Frequencies are defined as line percentages.

of 2.6% was reported (27). Li et al. (38) reported that the Chinese Uyghur healthy population *CYP2J2*7* allele frequencies are 3.45%. In our study population, the *CYP2J2*7* allele frequency was 6.7%, which was slightly higher than that reported in Chinese and similar to that reported in Western Caucasians.

White et al. (39) previously reported that over the 40% of load (percentage of high levels of blood pressure) were related to increased left ventricular mass and cardiac risk. On the other hand, it has been shown that systolic blood pressure load (>130 mmHg) is associated with a 14% increase in cardiac events (40). High blood pressure at night and impaired dipping profile, particularly riser pattern, were associated with overall cardiovascular diseases (41).

NH *CYP2J2*7* carriers' night systolic load (percentage of measurements >125 mmHg) was 87%, whereas the corresponding figure in *GG* carriers was 73%.

Study Limitations

Important limitations of our study are the small population size and the cross-sectional study design, leading to low power and lack of long-term observation data concerning cardiovascular disease risk. Moreover, there was only one subject homozygous for the *CYP2J2*7 T*-allele; therefore, we could not evaluate the impact of this genotype.

CONCLUSION

We have observed that *CYP2J2*7* polymorphism carrier status is related to an increased morning surge, which was reported to be one of the risk factors for cardiovascular diseases in earlier studies in the field. Considering the existing literature with our findings, it is further shown that the *CYP2J2*7* carrier status might indicate an increased risk of cardiovascular events. Evaluation of the *CYP2J2*7* genotype together with ambulatory blood pressure to identify the morning slope of individuals would be helpful to assess the risk of cardiovascular diseases and plan their blood pressure treatment accordingly.

Ethics

Ethics Committee Approval: The study was conducted with the permission of the Local Ethics Committee of Gazi University Faculty of Medicine (approval number: 193, date: 14.06.2006; no: 413/26.11.2007).

Informed Consent: All volunteers signed an informed consent form before their participation.

Author Contributions

Concept: E.H.V., A.Ç., H.Z., Design: E.H.V., A.Ç., H.Z., Data Collection or Processing: E.H.V., Analysis or Interpretation: E.H.V., Literature Search: A.G.G., M.L.D., Writing: E.H.V., A.G.

Conflict of Interest: No conflict of interest is declared by the authors.

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