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β2 adrenergic receptor polymorphisms and nocturnal blood pressure dipping status in the Wisconsin Sleep Cohort Study

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Abstract

Non-dipping nocturnal blood pressure (BP) is associated with target organ damage and cardiovascular disease. We hypothesized that β1- and β2-AR-associated SNPs would associate with non-dipping BP patterns. Participants (N=497, age range 30–74 years, 40% female) of the Wisconsin Sleep Cohort Study with at least one ambulatory BP monitoring test were included. Non-dipping was defined as less than a 10% dip in sleep BP compared to wake BP. Dipping ratios were calculated as sleep/wake BP. Single nucleotide polymorphisms in the β1-AR (rs7076938, tagging for Gly389Arg) and β2-AR (rs17778257 and rs2400707, tagging for Arg16Gly and Gln27Glu) were selected. β2-AR SNP rs2400707 A-positive subjects (tagging for Glu27) had higher systolic and diastolic dipping ratios in a dose-response fashion. Systolic dipping ratios were: GG=0.846; AG=0.854; AA=0.861 (p-trend=0.015). Diastolic dip ratios were: GG=0.807; AG=0.815; AA=0.824 (p-trend=0.026). The β2-AR rs17778257/rs2400707 A/A haplotype was associated with dipping ratios and systolic non-dipping status (non-dipping OR 2.0 [1.0, 3.8] for A/A versus A/G). Results were similar when models included participants on antihypertensive medications. Higher dipping ratios indicating a lack of nocturnal BP dipping are associated with β2-AR polymorphisms. Nocturnal dipping patterns may be modulated by β2-AR polymorphisms.

Keywords

single nucleotide polymorphisms; sympathetic nervous system; ambulatory blood pressure

INTRODUCTION

Ambulatory blood pressure monitoring (ABPM) provides useful information that is not captured from conventional office-based blood pressure (BP) measurement, such as mean BP over 24 hours and night-day patterns. In most healthy individuals, nocturnal BP dips by 10–20% compared to daytime values[1]. Persons that lack a normal decline in BP are referred

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to as “nondippers”, while individuals with a normal diurnal BP variation are termed “dippers”[2]. Studies of both hypertensive and normotensive individuals found ambulatory BP, and specifically nighttime BP, to better predict cardiovascular morbidity compared to clinic and daytime BP[3–5]. Non-dipping has been associated with target organ damage, including development and progression of renal disease, cerebrovascular disease, and cardiovascular morbidity and mortality.[5–8]

The mechanisms accounting for individual differences in dipping patterns are incompletely understood. Autonomic imbalance is a feature of many cardiovascular risk factors such as diabetes and chronic heart failure, and is likely an important mechanism underlying impaired diurnal BP variation. The sympathetic nervous system (SNS) plays a major role in BP regulation and is considered to be a potential factor in the magnitude of nocturnal BP variation.[9] Norepinephrine and epinephrine levels show a diurnal variation, with reduced levels during nighttime sleep.[10] One study showed attenuated urinary norepinephrine and epinephrine reduction in non-dippers compared to dippers, lending weight to the hypothesis that adrenergic stimulation is a factor in night time BP regulation. Given the importance of the SNS in BP regulation, including diurnal variation, genetic variations underlying adrenergic receptor structure and function may be associated nocturnal BP dipping.

Beta-adrenergic receptor (β-AR) single nucleotide polymorphisms (SNPs) have been associated with hypertension and responses to antihypertensive medications[11,12] —as well as survival following acute coronary syndrome,[13] and metabolic outcomes in cardiac patients[14] —but their relation with 24-hour BP variation has not been explored. The beta-1 and beta-2 adrenergic receptors (β1-AR and β2-AR, respectively) are G-protein-coupled receptors that specifically bind and are activated by endogenous catecholamines including epinephrine. Single nucleotide polymorphisms are known to map within the 2.89 kb *ADRB1* and 2kb *ADRB2* genes, including those that change amino acid encoding and several with documented functional relevance.[15,16,17] In this study, we hypothesized that β1- and β2-AR-associated SNPs would be related to non-dipping BP patterns. We chose to examine the beta-adrenergic system as these polymorphisms are frequent in the general population, data are available regarding their functional significance on post-receptor activities, and previous research supports their association with blood pressure and response to antihypertensive medications. The alpha adrenergic receptor mediates vasoconstriction and catecholamine release, but data are limited as to its role in blood pressure regulation. To explore associations of β-AR genetic variants with non-dipping patterns, we used a population-based large sample of men and women participating in the ongoing Wisconsin Sleep Cohort Study who had both 24-hour ambulatory blood pressure measurements (to assess BP dipping) and have been genotyped on high density genotyping arrays.[18]

METHODS

The study sample consisted of a subset of 497 individuals enrolled in the Wisconsin Sleep Cohort Study from 1991–2003. The protocols and design for Wisconsin Sleep Cohort Study protocols and informed consent documents were approved by the Health Sciences Institutional Review Board at the University of Wisconsin, and have been previously described.[19]. Briefly, the sample consisted of a probability sample of employees of 4 Wisconsin state agencies, aged 30–60 years, invited to undergo an overnight sleep study protocol at baseline and follow up studies at 4-year intervals. Exclusion criteria for the main study were pregnancy, unstable cardiopulmonary disease, airway cancers, and recent surgery involving the upper airway. For this specific analysis, participants with at least one ABPM measurement and who provided blood for genetic typing were included; for most analyses, individuals taking antihypertensive medications—which may affect diurnal BP patterns—were excluded (n=258), leaving 497 subjects and 802 ABPM events for analysis.

Data collection

Ambulatory-wake blood pressure measurement—ABPM studies were performed with the Accutracker II (SuntechMedical Instruments/Eutectics Electronics, Raleigh, NC), a 24-hour BP monitoring device that uses a modified auscultatory method. Details of the study protocol and ABPM quality data have been previously published.[20] ABPM readings were obtained at random intervals averaging every 15 to 20 minutes during wakefulness and every 30 minutes during sleep. All daily activities could be performed while wearing the monitor except showering or bathing, although vigorous exercise during the protocol was discouraged. Activity, posture, bedtime, and time on awakening from sleep were recorded by participants on diaries. Individual mean sleep and wake BPs were computed by averaging ABPM measurements during sleep and wake defined by participants' recorded sleep and wake times. The wake BP readings were averaged to obtain one measure for an ambulatory-wake systolic BP reading and one measure for an ambulatory-wake diastolic BP reading. Similar calculations were made to obtain average readings for sleep systolic and diastolic BP. Non-dipping was defined as less than a 10% dip in mean sleep BP compared to mean wake BP. Dipping ratios were calculated as mean sleep BP divided by mean wake BP.

Genotyping—Genotyping of members of the Wisconsin Cohort on the Affymetrix 500K arrays set , and 6.0 chips has been previously described.[18] Genotype calling was performed using the Birdseed-dev algorithm for Affy 6.0 and BRLMM for Affy 500K arrays set chips, and data was stored in our Progeny Lab 7 database. Proxy SNPs were identified by analyzing HAPMAP linkage disequilibrium (LD) data for the CEU population (www.Hapmap.org), and selecting SNPs with the highest r^2 values that were present on the Affymetrix chips. It is important to note that although we used Affymetrix data, in this analysis we tested a specific hypothesis related to nondipping and β-AR variants; it was not our goal to perform a genome wide association study of nondipping due to our limited sample size. In the *ADRB1* receptor two frequent SNPs have been extensively studied: rs1801252 encoding Ser49Gly, located in the extracellular N terminus, and rs1801253 encoding Gly389Arg within the proximal C terminal region, crucial for G-protein coupling.[21] No suitable Affymetrix platform SNP proxies could be identified for rs1801252, however SNP rs7076938 on the Affymetrix 6.0 chip had an r^2 value of 0.91 with rs1801253 Gly389Arg, and was selected as a proxy for analysis (Table 1). In the *ADRB2* gene, two common SNPs have undergone extensive functional study: rs1042713 encoding Arg16Gly, and rs1042714 encoding Gln27Glu. Located only 33 base pairs apart, the two SNPs occur in three common diplotypes. Two SNPs were chosen as proxies that were located on both the Affymetrix 500K and 6.0 chip platforms: rs17778257 had an r2 value of 0.94 with rs1042713, and rs2400707 had an r2 value of 0.96 with rs1042714. Genotypes for 5 markers rs11168066, rs11959615, rs17778257, rs2400707, and rs2116715) in the region were extracted. Haplotypes were examined in Haploview, and phasing was performed in Plink. Phasing results for the two marker haplotype were unambiguous in all cases with a posterior probability of 1 in all samples.

Statistical Analyses—SAS software, version 9.1.3 (SAS Institute, Cary, NC) was used for all statistical analysis. Approximately half (42%) of the participants in this study underwent more than one ABPM at 4-year intervals, thus specialized techniques were used to account for the intrasubject correlation. Mixed models for continuous outcomes and generalized estimating equation (GEE) techniques for binary outcomes, PROC MIXED (SAS Institute Inc. SAS/STAT Software Release 9.1. Cary, NC: SAS Institute, 2002–2003.) and PROC GENMOD (The GENMOD Procedure. SAS/STAT Software: Changes and Enhancements through Release 6.11. Cary, N.C.: SAS Institute Inc., 1996.) computed robust standard errors for hypothesis testing. Unadjusted models with the genotype group as a categorical predictor variable were first used to identify potential differences between the

baseline demographics of the groups. Then, multiple mixed regression models were used to asses relationships between each SNP and haplotype and systolic and diastolic dipping ratios and multiple GEE regression models were used to asses relationships between each SNP and haplotype and presence of systolic and diastolic non-dipping. Model covariates, chosen *a priori*, included age, sex, body mass index (BMI), and self-reported "heritage" (countries of recent ancestral origin). Other covariates such as apnea-hypopnea index (AHI) – a measure of sleep disordered breathing - and cardiovascular disease were not included as they did not improve the models' ability to detect genotype associations. Presence/absence of allelic variants (C/T for rs7076938 [tagging Gly389Arg]; G/A for rs2400707 [tagging Gln27Glu], and A/T for rs17778257 [tagging Arg16Gly]) and haplotypes were examined as the predictor variables in all models. In addition, trend tests for number of each allelic variants and haplotypes (0, 1 or 2) predicting BP dipping ratios and non-dipping was performed. P-values of less than 0.05 for all tests (Chi-square and t-tests) were used to indicate statistical significance.

RESULTS

Subjects

Baseline characteristics of all the analyzed subjects, and broken down by genotype groups, are shown in Tables 2 and 3. We included 497 individuals and a total of 802 ABPM tests as follows: 290 participants contributed one test, 135 participants contributed 2 tests (with 4 years between tests), and 72 contributed 3 tests (4 years apart). Of 497 participants not taking antihypertensives, mean age was 51 ± 8 (range 30–74 years), and 199 (40%) were female. Mean BMI was 30 ± 5 (range 17–52). Participants homozygous for AA of rs2400707 were of similar ages and BMI compared to those homozygous for GG. Likewise for rs17778257 and rs7076938, individuals from the different genotypes were similar in characteristics. Participants grouped into three major haplotypes: T/G (64.6%, tagging for Arg16Gln27), A/G (34.2%, tagging for Gly16Gln27), and A/A (65.1%, tagging for Gly16Glu27), and two participants carried the rare T/A haplotype, tagging for Arg16Glu27.

Dipping, non-dipping, and dipping ratios

Using JNC VII criteria for hypertension classification,[22] 65 (13%) were considered to have hypertension based on wake BP readings. Mean wake BP for the group was 126/77 mmHg, and mean sleep BP was 107/62 mmHg. Mean systolic dipping ratio in the study sample was 0.85 ± 0.06, and mean diastolic dipping ratio was 0.81 ± 0.07. Of 802 ABPM tests, 143 (18%) and 87 (11%) exhibited systolic and diastolic dipping ratios > 0.9, indicative of a non-dipping status. Of note, out of 207 individuals that had multiple ABPM tests, 52 had a discordant dipper/non-dipper status between tests. However, in 36 (69%) out of 52 of the discordant tests a participant who was first classified as a dipper was later found to have a non-dipping status on a subsequent test.

Association of β-AR SNP with non-dipping status and dipping ratios

Participants with the β2-AR rs2400707 AA and AG genotypes (tagging for Glu27Glu and Gln27Glu) had 68% and 19% higher risks for non-dipping compared to those with the GG genotype (Table 4). Of individuals with a systolic BP non-dipping status, 109 (41%) had at least one A allele of the β2-AR rs2400707 variant. For diastolic non-dipping status, 64 (27%) had AA or AG genotypes of the β2-AR rs2400707 variant. Similarly, individuals with an AA genotype exhibited higher systolic dipping ratios compared to those with AG and GG genotypes (0.861 versus 0.854 and 0.846, p-trend=0.015) (Table 5), and AA positive individuals also had higher diastolic dipping ratios compared to those with AG and GG genotypes (0.824 versus 0.815 and 0.807, p-trend=0.026). In contrast, the β1-AR rs7076938 and β2-AR rs17778257 polymorphisms were not associated with non-dipping status or

systolic and diastolic dipping ratios. Of note, results were similar when models were repeated including patients on antihypertensive medications.

When examining dipping status and dipping ratios by β2-AR haplotypes, the A/A haplotype (tagging for Gly16Glu27) had a two-fold higher risk for systolic non-dipping. The A/G haplotype was associated with a reduced risk for diastolic, but not systolic, non-dipping (p-trend=0.04), and the T/G haplotype not associated with non-dipping status. For dipping ratios, individuals carrying 2 copies of the A/A haplotype had significantly higher systolic (0.86 versus 0.855 and 0.847, p-trend=0.03) and diastolic (0.823 versus 0.816 and 0.807, p-trend=0.04) dipping ratios compared with those who had one or no copies of the A/A haplotype. There was a trend toward higher systolic and diastolic dipping ratios among participants with the A/A haplotype compared to those with the A/G haplotype (systolic dipping ratio 0.860 versus 0.834, p=0.07, diastolic dipping ratio 0.823 versus 0.792, p=0.06). As in single SNP analyses, results did not differ when models included those on antihypertensive medications.

DISCUSSION

We found that in mostly non-hypertensive individuals, the β2-AR rs2400707 polymorphism was associated with non-dipping status and dipping ratios, such that A allele (tagging for Glu27) positive individuals had higher systolic and diastolic dipping ratios and greater risk for a non-dipping status. Moreover, we noted that the β2-AR rs17778257/rs2400707 A/A haplotype (tagging for Gly16Glu27) was also associated with systolic non-dipping and systolic and diastolic dipping ratios. Finally, we did not detect significant associations between the β1-AR variant and non-dipping status and dipping ratios. These data suggest that the beta-adrenergic system, and specifically β2-AR activities, may influence BP dipping, and as such that genetic polymorphisms affecting β2-AR function may be associated with nocturnal BP variations.

The timing of onset of CV events strongly parallels the circadian rhythm of BP.[23, 24] The absence of a normal drop in blood pressure from day to night is predictive of heart failure, myocardial infarction, stroke, as well as sudden cardiac death.[25] Non-dipping has also been associated with increased left ventricular mass and wall thickness in hypertensive adults.[26] Mechanisms for blunted nocturnal BP dipping are poorly understood, but are thought to involve the SNS.[27] It is therefore of interest to examine factors which may modify SNS activity, such as genetic variations of the beta adrenergic receptors.

In our study, participants with the β2-AR rs2400707 (proxying Gln27Glu) AG or AA genotype had higher dipping ratios compared to those with the GG genotype, and were more likely to exhibit a non-dipping nocturnal BP pattern. Since the rs2400707 is in tight LD with the Gln27Glu β2-AR variant (r2=0.96, with rs2400707A tagging the Glu27 variant), our data is consistent with previous findings suggesting that the β2-AR Glu27 genotype is associated with systolic and diastolic blood pressure.[28–30] Bray et al reported significantly higher blood pressures in participants with *ADRB2* genotypes Gly16/Gly16 or Gly16/Arg16, proxied in our analysis by rs17778257, and higher frequencies of the Glu27 genotype among hypertensive individuals..[28] However, opposite results have also been suggested; in another study of 522 hypertensive adults, the *ADRB2* Gln27/Gln27 genotype was associated with higher systolic BP compared to Gln27/Glu27 genotype.[31] It is also important to note, however, that several other studies did not find an association with the Arg16Gly and Gln27Glu polymorphisms and hypertension phenotypes.[32,33] One potential explanation for these disparate findings is the lack of haplotype analyses, an especially relevant consideration as the Arg16Gly and Gln27Glu polymorphisms are tightly linked.

A number of potential mechanisms could explain how the β2-AR A/A haplotype (proxying for Gly16Glu27) may be associated with non-dipping BP patterns. The Gly16 genotype portends attenuated vasodilatory responses to catecholamines.[34] This may be a contributing genetic component in the regulation of systemic arterial pressure, such that individuals homozygous for Gly16 may have impaired nocturnal vasodilatory responses, leading to a non-dipping pattern of blood pressure. The functional β2-AR polymorphism rs1042714 (Gln27Glu, or C79G) is in tight LD with our genotyped β2-AR rs2400707 variant. Functional studies of this polymorphism suggest that the Glu27 allele is subject to less pronounced agonist-stimulated receptor downregulation compared to the Gln27 allele,[35] but implications for nocturnal blood pressure responses remain unclear.

We did not detect a significant association of the β1-AR rs7076938 polymorphism with dipping ratios and non-dipping status. This variant is also in tight LD with another known β1-AR variant with functional effects, rs1801253 (Arg389Gly, r2=0.91). This variant has been shown to alter post-receptor signaling, with the Arg389 receptor (tagged by rs7076938T) coupling more efficiently with its corresponding G protein (Gs).[36] Although a few studies found the Arg389 receptor to correlate with blood pressure,[37,38] other studies failed to find allelic differences between hypertensive and normotensive subjects with either the Ser49Gly (encoded by rs1801252) or the Arg389Gly variants.[39,40] In our study, it is possible that with reduced catecholamine stimulation of β1 receptors at night, these genetic variants may not be as influential on 24-hour blood pressure patterns. We were unable to perform haplotype studies, as rs1801252 has not been typed on the HapMap, and we were unable to identify an Affymetrix SNP proxy. Moreover, in the context of greater importance of β-2 adrenergic responses on vasodilation, the β-1 adrenergic receptor polymorphisms may not play major roles as risk factors for human hypertension, and our study is likely underpowered to detect subtle associations associated with β-1 polymorphisms.

Several limitations to our study should be noted. First, we did not directly genotype the SNPs encoding the commonly studied β1 and β2-AR genetic variants as part of the chip used for genetic analyses in the Wisconsin Sleep Cohort Study. Nonetheless, the genetic variants we chose to examine are in tight LD with the polymorphisms of interest, and we are confident that these variants can be used as proxy polymorphisms with sound results. Second, we cannot link genetic data with catecholamine activity since we did not measure catecholamine concentrations in this study. As such we cannot discount the possibility that catecholamine levels, and not activity at the β-adrenergic receptor, drive the non-dipping phenomenon. Future studies will need to address the potential interaction of β-AR genotype with catecholamine levels on night time blood pressure dipping more specifically. Since systolic blood pressure is especially subject to effects of the SNS, we expected stronger genetic associations with systolic non-dipping status, but observed somewhat stronger associations with diastolic non-dipping status. It is possible that mean daytime systolic blood pressures observed in this study were lower than in other studies examining blood pressure due to the younger mean age of our cohort or the exclusion of treated hypertensives in a population with relatively high health insurance coverage. Our study subjects were mostly normotensive and only 13% were classified as (untreated) hypertensive. Therefore, our results cannot be extrapolated to hypertensive individuals and it is possible that patients with elevated blood pressure may exhibit differing nocturnal blood pressure phenotypes in relation to β-AR genotypes. We did, however, repeat our analyses including those on antihypertensive agents, and results did not differ significantly. Due to the small percentage of non-dippers in this mostly normotensive cohort, we also cannot exclude the possibility that genetic associations found are due to chance alone. There are few studies examining genetic associations with 24-hour blood pressure variations. Our study provides new information regarding a potential link between SNS activity and nocturnal dipping status

and dipping ratios, however, due to limited information in this area our results require further verification.

PERSPECTIVES

Our study may elucidate potential mechanisms of abnormal dipping patterns and their possible link to genetic variation within the β2-AR. Future studies should examine whether therapies specifically targeting the SNS could be beneficial in patients with certain genetic profiles and nocturnal non-dipping blood pressure patterns. Moreover, further elucidation of optimal timing of antihypertensive medications in the setting of patients with genetic predisposition to non-dipping blood pressure patterns may be warranted.

CONCLUSION

In conclusion, we found that the β2-AR rs2400707/rs17778257 A/A haplotype and rs2400707 polymorphism are associated with nocturnal blood pressure dipping status and dipping ratios among mostly normotensive adults. These results suggest that genetic predisposition involving the sympathetic nervous system may play a role in abnormal blood pressure dipping patterns.

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Table 1

Adrenergic receptor	Functional SNP	Major/Minor alleles	Amino acids	Proxy SNP	r2 linkage with functional SNP	Major/Minor alleles
β1-AR	rs1801253	C/G	Arg/Gly	rs7072938	0.91	C/T
β2-AR	rs1042713	G/A	Gly/Arg	rs17778257	0.94	A/T
β2-AR	rs1042714	C/G	Gln/Glu	rs2400707	0.96	G/A

Table 2

Participant characteristics

Characteristic	Value
# of Participants	497 (802 studies)
Gender, n (%)	
Male	470 (59)
Female	332 (41)
Age (yrs), mean (sd) [range]	51 (8) [30–74]
Body Mass Index (kg/m^2), mean (sd) [range]	30 (5) [17–52]
Blood Pressure Medication Use, n (%)	NA
Measured Hypertension using Wake Blood pressure, n (%)	108 (13)
Mean Wake Systolic Blood Pressure, mmHg, (sd)	126 (12)
Mean Sleep Systolic Blood Pressure, mmHg, (sd)	107 (12)
Mean Wake Diastolic Blood Pressure, mmHg, (sd)	77 (7)
Mean Sleep Diastolic Blood Pressure, mmHg, (sd)	62 (7)
Mean Sleep/Wake Ratio for Systolic Blood Pressure (sd)	0.85 (0.06)
Mean Sleep/Wake Ratio for Diastolic Blood Pressure (sd)	0.81 (0.07)
Non-Dipping Systolic Blood Pressure	143 (18)
(Wake/Sleep Ratio >0.90), n (%)	
Non-Dipping Diastolic Blood Pressure	87 (11)
(Wake/Sleep Ratio >0.90), n (%)	
rs2400707	
AA	166 (21)
AG	342 (43)
GG	294 (37)
rs17778257	
TT	155 (19)
AT	353 (44)
AA	292 (37)
rs7072938	
CC	30 (4)
CT	333 (47)
TT	350 (49)

Table 3

Table 3 a– Participant characteristics by β2-AR rs2400707 genotype (N=802 studies)

Characteristic	rs2400707 AA	rs2400707 AG	rs2400707 GG	p-value
Male Gender, M n (%)	97 (58)	201 (59)	172 (59)	0.89
Age	53 (8)	51 (8)	51 (9)	0.29
BMI, kg/m^2 (SD)	29 (6)	29 (6)	30 (5)	0.93
Mean wake SBP, mmHg (SD)	126 (11)	127 (13)	126 (11)	0.5
Mean wake DBP, mmHg (SD)	77 (7)	77 (8)	76 (7)	0.68
Mean sleep SBP, mmHg (SD)	109 (12)	107 (12)	106 (11)	0.21
Mean sleep DBP, mmHg (SD)	63 (8)	62 (8)	61 (7)	0.15
Mean sleep/wake systolic dipping ratio (SD)	0.86 (0.06)	0.85 (0.06)	0.84 (0.05)	0.04
Mean sleep/wake diastolic dipping ratio (SD)	0.83 (0.08)	0.81 (0.07)	0.80 (0.07)	0.050
Non-dipping systolic BP, n (%)	40 (24)	59 (17)	44 (15)	0.19
Non-dipping diastolic BP, n (%)	27 (16)	37 (11)	23 (8)	0.08

Table 3 b– Participant characteristics by β2-AR rs17778257 genotype (N=800 studies)

Characteristic	rs17778257 TT	rs17778257 AT	rs17778257 AA	p-value
Male Gender, M n (%)	95 (61%)	208 (59%)	167 (57%)	0.84
Age	51 (9)	50 (8)	52 (8)	0.33
BMI, kg/m^2 (SD)	29.1 (5)	29.7 (6)	29.6 (6)	0.3
Mean wake SBP, mmHg (SD)	125 (11)	126 (13)	127 (11)	0.59
Mean wake DBP, mmHg (SD)	76 (7)	77 (8)	77 (7)	0.43
Mean sleep SBP, mmHg (SD)	106 (12)	107 (12)	108 (12)	0.64
Mean sleep DBP, mmHg (SD)	62 (7)	61.9 (7)	63 (8)	0.31
Mean sleep/wake systolic dipping ratio (SD)	0.85 (0.06)	0.85 (0.05)	0.85 (0.06)	0.85
Mean sleep/wake diastolic dipping ratio (SD)	0.81 (0.07)	0.81 (0.07)	0.82 (0.08)	0.47
Non-dipping systolic BP, n (%)	26 (17%)	57 (16%)	60 (21%)	0.53

Table 3 b– Participant characteristics by β2-AR rs17778257 genotype (N=800 studies)

Characteristic	rs17778257 TT	rs17778257 AT	rs17778257 AA	p-value
Non-dipping diastolic BP, n (%)	17 (11%)	31 (9%)	39 (13%)	0.33

Table 3 c– Participant characteristics by β1-AR genotype (N=802 studies)

Characteristic	rs7072938 CC	rs7072938 CT	rs7072938 TT	p-value
Gender, M n (%)	11 (37)	187 (56)	220 (63)	0.20
Age	50 (7)	51 (8)	52 (9)	0.91
BMI, kg/m^2 (SD)	29 (6)	30 (6)	29 (5)	0.20
Mean wake SBP, mmHg (SD)	120 (11)	126 (12)	127 (12)	0.17
Mean wake DBP, mmHg (SD)	73 (6)	77 (8)	77 (7)	0.09
Mean sleep SBP, mmHg (SD)	103 (10)	107 (12)	107 (12)	0.38
Mean sleep DBP, mmHg (SD)	59 (6)	62 (8)	62 (7)	0.20
Mean sleep/wake systolic dipping ratio (SD)	0.86 (0.05)	0.85 (0.06)	0.85 (0.06)	0.77
Mean sleep/wake diastolic dipping ratio (SD)	0.82 (0.06)	0.81 (0.08)	0.81 (0.07)	0.99
Non-dipping systolic BP, n (%)	7 (23)	58 (17)	59 (17)	0.76
Non-dipping diastolic BP, n (%)	3 (10)	40 (12)	32 (9)	0.61

Table 4

Association of β1-AR and β2-AR variants with non-dipping status

	Systolic Non-Dipping OR (95% Confidence Interval)	Diastolic Non Dipping OR (95% Confidence Interval)
rs2400707		
GG	REF	REF
AG	1.19 (0.77, 1.84)	1.52 (0.87, 2.66)
AA	1.68 (0.96, 2.94)	2.14 (1.10, 4.16)
	p-trend=0.077	p-trend=0.023
rs17778257		
TT	REF	REF
AT	1.1 (0.6, 1.8)	0.9 (0.4, 1.6)
AA	1.2 (0.7, 2.1)	1.2 (0.6, 2.2)
	p-trend=0.44	p-trend=0.51
rs7076938		
TT	REF	REF
CT	1.0 (0.7, 1.6)	1.3 (0.8, 2.2)
CC	1.4 (0.5, 3.9)	1.0 (0.3, 3.0)
	p-trend=0.59	p-trend=0.43
Haplotype Analyses		
T/G*		
0	REF	REF
1	0.8 (0.5, 1.3)	0.7 (0.4, 1.2)
2	0.8 (0.5, 1.3)	0.8 (0.4, 1.5)
	p-trend=0.35	p-trend=0.39
A/G		
0	REF	REF
1	0.9 (0.6, 1.4)	0.7 (0.4, 1.1)
2	0.3 (0.1, 1.5)	0.2 (0.0, 2.0)
	p-trend=0.2	p-trend= 0.04
A/A		
0	REF	REF
1	1.2 (0.8, 1.9)	1.6 (0.9, 2.8)
2	1.6 (0.9, 2.8)	2.0 (1.0, 3.8)
	p-trend=0.11	p-trend= 0.04

*T/G tags for Arg16Gln27; A/G tags for Gly16Gln27, and A/A tags for Gly16Glu27

Table 5

Association of β2-AR and β1-AR SNPS and β2-AR haplotype with Systolic and Diastolic Dipping Ratio[+]

	Mean Systolic Dip Ratio[*]	Mean Diastolic Dip Ratio[*]
rs2400707		
GG	0.846 (0.004)	0.807 (0.01)
AG	0.854 (0.004)	0.815 (0.01)
AA	0.861 (0.005)	0.824 (0.01)
	p-trend=0.015	p-trend=0.026
rs17778257		
TT	0.8511 (0.01)	0.811 (0.01)
AT	0.8531 (0.004)	0.8134 (0.01)
AA	0.8534 (0.004)	0.8180 (0.01)
	p-trend=0.74	p-trend=0.36
rs7076938		
TT	0.851 (0.004)	0.814 (0.01)
CT	0.852 (0.004)	0.815 (0.01)
CC	0.856 (0.01)	0.815 (0.02)
	p-trend=0.69	p-trend=0.83
Haplotype Analyses		
T/G		
0	0.854 (0.004)	0.819 (0.01)
1	0.852 (0.004)	0.813 (0.01)
2	0.851 (0.01)	0.811 (0.01)
	p-trend=0.61	p-trend=0.29
A/G		
0	0.856 (0.003)	0.817 (0.004)
1	0.846 (0.01)	0.812 (0.01)
2	0.834 (0.012)	0.792 (0.015)
	p-trend= 0.01	p-trend=0.14
A/A		
0	0.847 (0.004)	0.807 (0.01)
1	0.855 (0.004)	0.816 (0.01)
2	0.860 (0.01)	0.823 (0.01)
	p-trend= 0.03	p-trend=0.04

[*] Least Square Means adjusted for age, sex, body mass index, heritage T/G tags for Arg16Gln27; A/G tags for Gly16Gln27, and A/A tags for Gly16Glu27