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The Effect of Sleep Duration on Systolic Pressure and Nitric Oxide Concentration in Hypertensive Patients

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A b s t r a c t

Background: *Poor blood pressure control of hypertensive patients is caused partially by bad lifestyle management, which increases the risk of a cardiovascular event by stimulating the defective endothelial function.* ***Objective****: This study aimed to investigate the effect of night sleep duration on systolic blood pressure and Nitric Oxide concentration in hypertensive patients.* ***Methods****: 60 hypertensive patients age >40 years based on the medical record participated in this study. The sleep duration and sleep quality were performed using the PSQI questionnaire. The 40 participants thus selected randomly for the NO concentration assay using NO Salivary Elisa Kit ab65238.* ***Results****: 53 participants experienced night sleep duration ≤ 6 hours, and 44 (73.7%) participants had poor sleep quality. Night sleep duration was associated significantly with hypertensive patients' systolic blood pressure (p = 0,000 <0.05; Odds ratio=0.008).* ***Conclusion:*** *The longer duration of sleep at night among hypertension patients, the lower systolic pressure were found. There was no correlation between night sleep duration on NO concentration (p> 0.05). These findings provide evidence that night sleep duration is associated strongly with the increased systolic blood pressure but not directly caused by the alteration of endothelial function.*

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INTRODUCTION

The prevalence of hypertension is increasing globally, and it is estimated that in 2025 29% of adults worldwide become hypertension.[1] Only 27% of Americans and 22,6% until 34.0% of Asian hypertensive patients are well controlled by achieving blood systolic pressure target under 140 mmHg and diastolic pressure less than 90 mm Hg.[2,3] Blood pressure can be controlled by improving risk factors.[2,4,5] Many articles reported the effect of sleep deprivation on the risk of hypertension.[6] Several studies conducted by sleep study centers with cardiovascular function reported participants who slept less than 5 hours/night have a greater risk of suffering from hypertension.[4,7,8] Night workers experiencing a change in their sleep pattern and short sleep duration also have a greater risk of hypertension.[9]

One complication of uncontrolled hypertension is the increased risk of a cardiovascular event such as coronary heart disease and cerebrovascular disease preceded by endothelial dysfunction.[10,11] Endothelial dysfunction causes peripheral resistance and progression of atherosclerotic plaque formation.[12–14] The research used Sprague-Dawley mice deprived of sleep for five days to lose weight, increase blood pressure, and decrease NO, cGMP, and related phosphorylation of e-NOS in the aortic endothelial cells of experimental animals.[15] Alteration in night sleep time,

which always accompanies inadequate night sleep, will disrupt the circadian rhythm. The results of several research publications using samples of experimental animals (*in vivo*), explants of the heart and blood vessels (*ex vivo*), and heart myocyte cells, vascular smooth muscle cells, endothelial cells, fibroblasts (*in vitro*) concluded that circadian clock components B-mal1 regulate the e-NOS vascular function by activating Akt-intracellular signal transduction.[16]

Considering the growing evidence suggesting a strong link between inadequate sleep and endothelial dysfunction as the pathological process in vascular function which makes blood pressure remains high and contributes to hypertension complication, this study examined the associations between sleep duration with systolic blood pressure and NO concentration as endothelial dysfunction marker which has never been investigated before.

METHODS

Study Population and Design

The study design was an analytic observational cross-sectional study. Participants were patients at RST Tk. II Soepraoen Hospital Malang Indonesia. All participants got a brief explanation and were signed informed consent before participating in this research. This study was approved by The UIN Institutional Review Board No.052/EC/KEPK-FKIK/2019. This study's inclusion criteria were as follows: (1) age 40-80 years old, (2) hypertension by the medical record. Exclusion criteria were: (1) had a genetic sleep disorder, (2) in psychological treatment.

Assessment of Night Sleep Duration and Sleep Quality

Sleep duration and sleep quality were performed using the validated Pittsburgh Sleep Quality Index (PSQI) questionnaire with a global sum≥5 indicates poor sleep and <5 indicate good sleep quality. The PSQI indicators were also reported individually (subjective sleep quality, sleep latency, sleep efficiency, sleep disturbances, sleep medication, daily dysfunction).[17]

Assessment of Physical Activity

The participants answered Global Physical Activity Questionnaire (GPAQ). GPAQ comprises three categorical behavioral domains: work, travel and recreational activities, and sedentary activities with total 19 questions. Questions for the domain work, travel and recreational activities assess the frequency and duration of 2 different categories of activity defined by the energy requirement or intensity (vigorous or moderate intensity). Results were reported as a continuous variable (MET/Metabolic Equivalent of Task, minutes a week). MET minutes represent the amount of energy expended carrying out physical activity.[18]

Body mass Index (BMI)

The tools used to measure BMI are scales and stature meters. The BMI were defined as weight in kilograms divided by the square of height in meters. Based on the official Asia Pacific cut off points, participants were recognized as underweight if BMI < 18.5, of normal weight if 18.5≤ BMI<24, overweight if 24≤BMI<27, and obese if 27≤ BMI.[19]

Assessment of NO concentration

Nitric oxide concentration was assessed with ELISA using Quantichrome TM Nitric Oxide Kit (D2NO-100) Bioassay System. Saliva samples were taken at 8 am. Participants were suggested neither to eat nor to drink within two hours before saliva collection. If the volunteers had eaten any food the morning of the sampling, they were told to avoid any high NO_3^- foods (ex. spinach, beets, lettuce, and other green leafy vegetables). In addition, volunteers were not allowed to use mouthwash but were permitted to brush their teeth preparation. Prior to assay, saliva was centrifuged at 14.000 rpm at 4°C. Supernatant were used as sample for the assay. Sample and

standard was mixed with the working reagent, thus incubate for 10 minutes at 60°C. After the incubation process, centrifuge once again to collect the pellet. The pellet was transferred to 96 well plate and read Optical Density at 540 nm.[20]

Assessment of Systolic Blood Pressure

Hypertension diagnosis was checked in the medical records. Hypertension control state (well or poor controlled) was rated by measuring blood pressure and compared with the use of medication. Suitable subjects underwent blood pressure measurement by a sphygmomanometer (Riester- Novaecoline Germany) and stethoscope (Littman classic 3rd series). Before the assessment, the proper cuff was matched with the size of the subject's arm. The bottom cuff was placed two-three cm just above the cubital fossa as high as the heart. The ear tip of the stethoscope was put right into the examiner's ear, while the diaphragm was lightly pressed over the brachial artery just below the cuff's edge. Rubber bulb was pumped until the brachial artery pulse was heard. The first sound that was listened to was systolic blood pressure. Rubber bulb was pumped again up to 20-30 mm Hg. The control valve was loosened so that mercury drops at a speed of 2 - 3 millimeters of Hg per second. The last pulse was called diastolic blood pressure.

Statistical Analysis

All data were presented as means ± SD or as prevalence. For the socio-demographic profile we conducted multivariate statistic using linier regression test in terms of the following criteria: age, gender, BMI, and physical activity compared with night sleep duration. The ordinal logistic regression was performed to get information about the association between night sleep duration compared with other sleep component in PSQI: subjective sleep quality, sleep latency, sleep efficiency, sleep disturbances, sleep medication, daily dysfunction. Moreover, the correlation between sleep duration and NO, the association between NO and systolic blood pressure were analyzed using Pearson Product Moment test. If the data showed normal distribution test. Thus, Spearman Rank test was used to replace pearson product moment if the distribution of the data was not normal. The p value < 0.05 were considered significant. Data processing was executed using SPSS 18.0 software.

RESULTS

The baseline characteristics of the participants were shown in Table 1. Participants in this study dominated by 61-70 years old (45%). The data demonstrated that the lower the level of education, the higher the incidence of hypertension. Women are more likely to develop hypertension than men. As many as 96.6% participants with hypertension were non-smokers. This study also reported that the number of comorbid accompanying hypertensive patients was high and dominated by type 2 diabetes mellitus (53.3%).

Table 1. Sociodemographic Profile of Study Population

Variables	Mean ±SD	Frequency, percentage (%)
Age, y	62.60±12.6225	
31-40		2 (3.35)
41-50		6 (10)
51-60		10 (16.7)
61-70		27 (45)
>70		15 (25)
		N= 60
Gender		
Male		21(27.6)
Female		39 (51.3)
		N= 60
Education profile		
Elementary		20 (33.3)
Junior high school		14 (23.3)
Senior high school		19 (31.7)
Vocational		3 (5)
Bachelor		4 (6.7)
		N= 60
Employment		
Housewife		28 (46.7)
Businessman		11 (18.3)
Ex-civil attendant		16 (26.7)
Students		1 (1.7)
Farmer		4 (6.7)
		N= 60
Smoking Habituation		
Smoker		2 (3.3)
Non-Smoker		58 (96.6)
		N= 60
BMI. kg/m2		
Underweight		4 (6.7)
Normal		26 (43.3)
Overweight		20 (33.3)
Obese		10 (16.7)
		N=60
History of chronic disease/comorbid		
Diabetes mellitus		32 (53.3)
Chronic kidney disease		5 (8.3)
Asthma		1 (1.7)
Heart failure		1 (1.7)
Cerebrovascular disease		4 (6.7)
Coronary heart disease		1 (1.7)
		N=60

The hypertension control based on this study was still relatively low (15%), even though two or three therapeutic regimens have been prescribed to the patients. Majority of participants (57.9%) experienced poor sleep quality. Fifty-three (53) participants experienced night sleep duration ≤ 6 hours. The detail information about sleep and blood pressure profile could be seen in Table 2.

Table 2. Profile of Sleep and Blood Pressure of Study Population

Variables	Mean ±SD	Freq table (%)
Blood pressure (mmHg)		
Systolic	150.4667±17.5696	
Diastolic	81.30±14.6175	
Blood pressure control		
Well controlled		9 (15)
Poor controlled		51(85)
		N= 60
PSQI score		
Poor Sleep Quality		44(57.9)
Good Sleep Quality		16 (21.1)
		N= 60
Sleep Duration		
≥7 hours		7 (9.2)
6 hours		28 (36.8)
5 hours		9 (32.8)
< 5 hours		16 (21.1)
		N= 60
Medication		
Telmisartan		8 (8.8)
Candesartan		10 (11)
Irbesartan		12 (13.2)
Bisoprolol		10 (11)
Amlodipin		26 (28.6)
Captopril		3 (3.3)
Ramipril		1 (1.1)
Furosemide		6 (6.6)
HCT		3 (3.3)
Spironolakton		2 (2.2)
Nifedipine		10 (11)
		N= 60
Pharmacological therapy single/combination		
Single therapy		20 (33.3)
Dual therapy		23 (38.3)
Triple therapy		17 (28.3)
		N= 60

Correlation between Night Sleep Duration and Systolic Blood Pressure

The data show normal distribution for sleep duration (0,063), systolic blood pressure (0,054) but not for other variable. Therefore subsequent analysis used for linear regression test was limited to see the effect of sleep duration toward systolic blood pressure on hypertensive patients.

Linear regression analysis demonstrated a significant correlation between night sleep duration and systolic blood pressure. The correlation and significance can be seen in Figure 1.

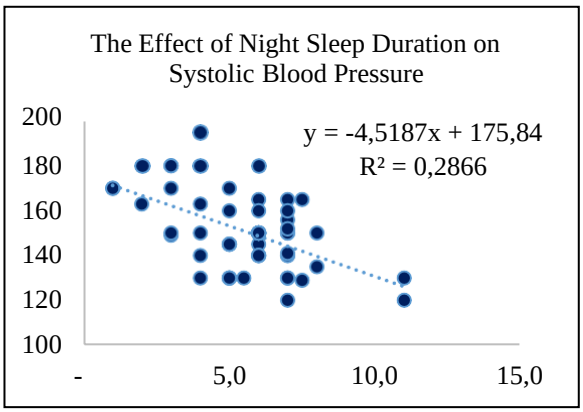

Figure 1. The Effect of Night Sleep Duration on Systolic Blood Pressure among Hypertensive Patients

Logistic ordinal regression analysis showed significant correlation between night sleep duration and sleep efficiency with systolic blood pressure but not with other sleep component which can be seen in table 3.

Table 3. Association between each indicator of PSQI with systolic blood pressure.

Criteria	P-Value	Odds Ratio
Subjective sleep quality		
Very good	0.311	0.212
Good enough	0.185	0.170
Bad	0.426	0.335
Very bad	.	0
Sleep latency (minute)		
< 15	0.837	1.157
16-30	0.374	0.530
31-60	0.419	0.595
> 60	.	0
Sleep Duration (hour)		
>7	0.001	0.046
6-7	0.055	0.321
5-6	0.038	0.193
<5	.	0
Sleep efficiency (%)		
>85	0.018	0.220
75-84	0.109	0.145
65-74	0.030	0.014
<65	.	0
Sleep disturbances		
0	.	0
1-9	0.875	0.884
10-18	0.134	0.313
19-27	.	0
Sleep medication (in a day)		
never	0.281	3.212
1 x	0.150	6.172
1-2 x	.	0.000
>3 x	.	0
Daily activity dysfunction		
0	0.766	1.275
1-2	0.346	2.128
3-4	0.910	1.096
5-6	.	0

Correlation between Sleep Duration and Nitric Oxide

The impairment of endothelial function was suggested as possible mechanism which could explain how alteration in night sleep duration would cause the increase of systolic blood pressure in hypertensive patients. Endothelial function was assessed by measuring NO concentration. The data was tested using linier regression with two equations.

Table 4. Correlation Between Sleep Nitric Oxide and Systolic Pressure in Study Participants

Variable	Mean±SD	P-Value
NO concentration (pg/ml)	5.2521±2.064	
Sleep duration and NO		0.313
NO and systolic pressure		0.768

There was no correlation between either sleep duration-NO and NO-systolic pressure. Based on Spearman Rank result due to the distribution of the data was not normal. The data shown did not support the hypothesis. There was no correlation between NO dan sleep duration. In addition, there was also no correlation between NO and systolic blood pressure. Consequently, the alteration in NO production was not the explanation how sleep duration affecting the systolic blood pressure in hypertensive patients (Table 4).

DISCUSSION

Poor blood pressure control in participants may be related to other comorbid factors (65% of respondents have other diseases that may precede hypertension or complications). Hypertensive patients with Diabetes mellitus type 2, which is more seen in this study, can cause difficulty in controlling blood pressure due to changes in the Renin-Angiotensin-Aldosterone system, changes in chymase, the excess volume of body fluids, pseudo-resistance, continuous sympathetic activation, and the appearance of depression in patients.[21-23]

Another factor that affects the high blood pressure in hypertensive patients was the poor lifestyle that is not controlled, such as diet, sleep pattern, physical activity level, smoking habits, and stress levels.

Interestingly, this study found that physical activity, age, sex, BMI did not significantly affect hypertensive patients' blood pressure. Our works showed that duration of sleep 5-6 hour and >7 hours had a positive effect on systolic blood pressure. Even though the 6-7 hours' sleep did not show significant value based on ordinal logistic regression test, but the previous linier regression showed the significant value between sleep duration and systolic blood pressure. Therefore, we assume the range of sleep duration which could maintain the systolic normal pressure was >5 hours a day. Although, several reports stated that the duration of sleep at night at the range of 6-8 hour is the best condition for maintain body homeostasis, but many studies also reported that the lower range is in 5 hours sleep. Our findings support Motomura study which stated that the chronic restricted less than 5 hours have deteriorate effect to human health as an important risk factor for hypertension and metabolic disease. Despite of total sleep time, REM sleep is the item critical in determining of sleep quality. This stage of sleep occurs during the second half of the nights. Alteration of rem sleep contributing to decreased of sleep efficiency. There is limitation of the study. We did not specify the maximum sleep time that interfere with systolic pressure. On the other hand, long sleep duration has also been associated with health issues and an increased risk of mortality. Using meta-regression analyses a linear association between increased mortality incident cardiovascular disease

and longer sleep duration more than 9 hours a day was also found.[24] These results reinforce previous research reported that sleep duration affects systolic pressure, where if it occurs at a young age can increase risk factors for hypertension, while if it occurs in hypertensive patients, it increases the occurrence of complications. A study conducted by a sleep study center with cardiovascular function stated that respondents who slept less than 5 hours/night had a higher risk of suffering from hypertension.[4,7,8,25] Studies of poor sleep efficiency have been shown to correlate with an increase in systolic blood pressure of 4 mmHg. Several studies using night worker models with short sleep duration have also succeeded in proving changes in sleep patterns, increasing hypertension incidence [9]. Getting the right amount of sleep can help prevent or treat hypertension. Proper sleep duration can help reduce cardiovascular-related mortality and complications due to hypertension.[26]

Although this study's results have proven that the shorter the duration of night sleep, the higher the blood pressure (systolic), but NO does not mediate this condition. This study's results support previous studies that found no correlation between sleep duration and flow-mediated dilatation (FMD). Fitness study HUNT 3 (Nord-Trøndelag Health Study) also produced negative results characterized by the absence association between endothelial dysfunction and insomnia.[27,28] Different results were obtained from Kim's study in 2010 using night worker respondents who reported a significant decrease in FMD and NOx after three measurements.[29] Sauvet, in his study, evaluated microvascular reactivity and biological markers of endothelial activation for 40 hours of continuous total sleep deprivation (TSD) in 12 healthy men (29 ± 3 years) with the conclusion that acute exposure to 40 hours of TSD appears to cause vascular dysfunction before an increase in sympathetic activity and systolic blood pressure.[30] This result was supported by Aggarwal's research in 2018, which found a significant correlation between poor sleep quality and activation of the kappa B nuclear endothelial factor (b = 30.6; P = 0.03) and also proved the correlation between insomnia and more latency of sleep onset a long time with activation of the kappa B endothelial nuclear factor (b = 27.6; P = 0.002 and b = 8.26; P = 0.02).[31]

Initially, the hypothesis of this study wanted to prove the mechanism of short sleep duration in increasing systolic pressure through NO, where if the hypothesis is accepted, then NO can be used as a predictive marker for assessing the success of accurate control of hypertension in addition to just measuring blood pressure. The lack of correlation between sleep duration with NO and systolic pressure in this study might be due to sampling time because circadian rhythms influence NO secretion. The second possible factor is due to aging's physiological condition, where the production and activity of e-NOS have already decreased, and consequently, NO production will also reduce.[32,33] The decrease in night sleep duration no longer affects e-NOS, which is already low, because most of the study respondents were above 60 years old. This conjecture is reinforced in experimental studies using rat animals made sleep deprived in the REM (Rapid Eye Movement) phase, where the impaired aortic endothelial function occurs in middle-aged rats but not in young rats.[15] Therefore, to find a predictive marker of the success of hypertension therapy is not enough just with NO but in the future carried out a broader investigation of the possibility of other molecular compounds that more accurately describe its effect on systolic pressure.

We recognize that the present study has several limitations. The design used for this study was cross-sectional, so for future research, it should use prospective cohort design. Variables should be confirmed more accurately, not just by questionnaire. The endothelial function should be assessed by Flow Mediated Dilation (FMD), e-NOS activity beside NO. Different sleep patterns

and sleep measurement techniques like EEG (Electroencephalography) to detect sleep waves should be involved. The time chosen for measuring parameters is also essential since it is affected by circadian rhythm.

CONCLUSION

In conclusion, our study provides direct evidence that short night sleep duration increases systolic blood pressure in hypertensive patients. NO does not mediate alteration of systolic pressure in hypertensive patients caused by sleep duration.

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