Effect of the Circadian Rhythm on Blood Pressure

Undergraduate Project

An Undergraduate Project Submitted in Partial Fulfillment of the Requirements for the Degree of Bachelor in Medicine at University of Diyala/College of Medicine

By

Zahraa Hamodi Hussien

Supervisor

Dr. Asmaa Abbas Ajwad

2022-2023

ABSTRACT OF PROJECT

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Circadian rhythms are 24-hour cycles that are a part of the body's biological clock and work to carry out vital processes and functions. Circadian rhythms, which are coordinated with a master clock in the brain, are used by several systems of the body. Circadian rhythms are linked to the cycle of day and night because this master clock is directly influenced by environmental stimuli, particularly light. Thus, over the course of a 24-hour day, the majority of body functions change. Body temperature, sleep-wake cycles, metabolism, and blood pressure (BP) are a few examples of circadian rhythms. The superchiasmatic nucleus (SCN) of the hypothalamus contains the body's primary clock, which coordinates with peripheral clocks to regulate these circadian rhythms. With or without hypertension, the disruption of this circadian pattern of BP is linked to a higher risk of cardiovascular disease. There is significant interest in determining the mechanism underlying this dysregulation.

In this study, we examined the impact of the circadian rhythm on both systolic blood pressure. Our findings revealed that, other from a minor increase in systolic blood pressure that may have been caused by age or weight considerations, all blood pressure levels were within the normal range (120/80). Then, after comparing the systolic blood pressure readings taken during the day and night, we found that there was a definite drop in the reading taken at night compared to the reading taken during the day. This is in line with what the literature has shown to be true. Regarding the age factor and its impact on blood pressure, our data revealed a steady rise in blood pressure with age up until the age of 50; after this age, however, there was still an increase, but with some variation that may have been caused by the effect of the number of subjects in each age group, some outliers in our data, and menopause in women. Our research shows that men had greater systolic blood pressure than women both throughout the day and at night (the same trend as in 24-hour). Males and females appear to have the same diastolic blood pressure during the day, although it somewhat decreased in females throughout the night. Our data also verified the inverse relationship between height and blood pressure. The effect of circadian rhythm seems more during the days than the night.

In conclusion, circadian rhythm has an impact on systolic and diastolic blood pressure along with the effect of age, gender, and height. More analysis is required to combine all these factors in one analysis along with weight factor.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Introduction

The circadian clock evolved so that organisms could adjust to the 24 h light/dark cycles that take place on our planet. From cyanobacteria to humans, circadian rhythms in physiological function have been discovered in a variety of organisms. In higher eukaryotes and mammals, a central clock that is directly entrained by light is found in the suprachiasmatic nucleus (SCN) of the brain. Other parts of the brain, as well as the majority of other cell types and tissues throughout the body, all contain peripheral clocks. These clocks communicate via hormonal and neural impulses and synchronize in response to food and light stimuli. Chronic jet lag and shift work, which can desynchronize the circadian clock, are linked to an elevated risk for a range of conditions [1], [2].

Circadian rhythms are driven by an internal circadian "clock" that is responsible for regulating daily functioning of all major organs. These rhythms are critical for maintaining a variety of beneficial health effects in humans. The circadian clock can be categorized into two distinct components: the central clock and the peripheral clocks. The central clock, located in the suprachiasmatic nucleus (SCN) found within the hypothalamus, serves as the fundamental factor for creating and maintaining circadian rhythmicity in mammal, see figure 1 [3], [4]

The systematization of physiological and behavioral functioning from day to day, as seen in all mammals, is made possible by the intricate 24-hour day/night cycle initiated by the circadian clock and is exhibited in both the central and peripheral clocks. External photic and nonphotic environmental cues, also called zeitgebers, including light stimuli, time of feeding, ambient temperature, and exercise have the ability to influence and synchronize circadian rhythmicity. Typical circadian rhythmicity occurring over a 24-hour period can be altered by non-photic cues; understanding these non-photic cues could lead to treatment strategies for the entrainment of the circadian clock. Strategies may include adjusting sleep schedules – such as in the case of shift work – as well as altering feeding patterns. For instance, when shift workers sleep through the day, hypertension is often observed due at least in part to misalignment of circadian rhythmicity [3].

Daily circadian synchronization of physiological functioning is critical for the functioning of peripheral organs, including the heart. Several studies have reported that the circadian clock influences important CVD risk factors such as heart rate and blood pressure. Circadian misalignment, even when short-term, can increase 24-hour blood pressure and decrease parasympathetic activity. If circadian misalignment becomes

chronic, ongoing elevation of blood pressure poses a risk factor for the development of CVD [3] . Among the physiological variables that present a circadian variation, blood pressure is one of the most studied due to its impact on chronic cardiovascular diseases and complex events such as strokes and heart failure.
This circadian variation profile is mainly related to the activity/rest cycle and presents a morning increase, a small postprandial valley, and a deeper descent during night-time rest [5].

Both systolic and diastolic blood pressure (SBP and DBP) have a circadian rhythm that repeats every 24 h in healthy humans. Healthy individuals experience a 10–20% decrease in BP at night. People who do not exhibit this "dip" of at least a 10% change in resting BP are termed "non-dippers." Non-dipping hypertension is associated with activation of the renin-angiotensin-aldosterone system (RAAS), increased risk of chronic kidney disease and adverse cardiovascular events [4].

Various studies have shown that ambulatory blood pressure (BP) is superior to clinic BP in predicting cardiovascular risk in hypertensive patients. Noninvasive ambulatory BP monitoring gives the opportunity to detect daytime, nighttime, and 24-hour BP, circadian BP changes, BP variability, and ambulatory BP phenotypes [6]. Ambulatory healthy adults exhibit a 24-hour rhythm in blood pressure (BP), with levels being highest during the daytime and lowest at nighttime. Impaired BP reduction at night (i.e., "nondipping") is clinically relevant and is predictive of nonfatal and fatal cardiovascular events. Consequently, it is important to understand its origin. Day/night changes in behaviors such as posture, physical and mental activity, arousal (i.e., wake and sleep), and the internal circadian timing system may contribute to the 24-hour rhythm in BP. Daily changes in posture and physical activity are thought to be 2 major contributors to 24-hour BP variability [7]. The premise that daily changes in posture and physical activity are major contributors to 24-hour BP variability is based on the knowledge that BP is affected by dynamic exercise and transitions between postures (supine, sitting, and upright).

Clinical and epidemiological studies in humans demonstrate the importance of the 24 hr BP rhythm and shed light on contributing mechanisms which likely include BP-regulatory systems such as the SNS, the CNS, kidney, the vasculature, and the heart [4].

Daytime and nighttime BP and their relationship may change with aging. Indeed, in adult subject's daytime BP may be influenced by physical activity and job stress, generally no longer present to the same extent in the elderly, whereas old patients generally have reduced nighttime BP dip and higher nighttime BP [6]. An increase in blood pressure (BP) has always been taken as an inevitable consequence of ageing in

industrialized societies, leading to hypertension in a high proportion of elderly subjects. However, the characterization and definition of what constitutes hypertension in the elderly has changed over the years [8], [9].

In recent years the interest in studying the impact of sex steroids and gender on the regulation of blood pressure and cardiovascular disease has been growing. Women are protected from most cardiovascular events compared to men, until after menopause, and postmenopausal women are at increased risk of cardiovascular complications compared to premenopausal women [10], [11].

In this project, we evaluated the effect of circadian rhythm on different variables related to blood pressure. Additionally, the effect of age, gender, weight, and height were all included in this project to see how they may change the blood pressure.

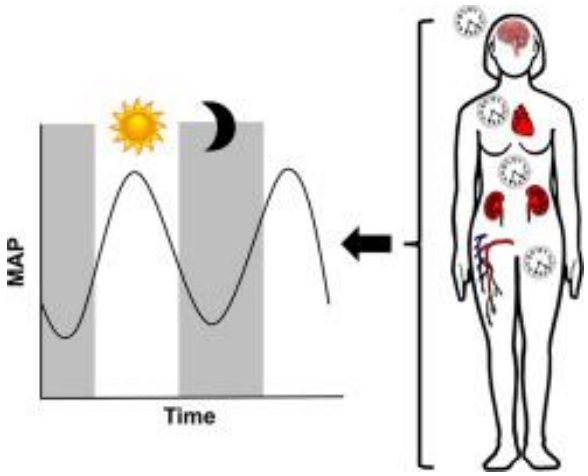

Figure 1: Blood Pressure Changes with Circadian Rhythm. BP dips at night during rest, undergoes a steep increase in the morning (known as the "morning surge"), and peaks typically in the late afternoon. This circadian rhythm of BP is present in the mouse and rat models that are commonly used to model human cardiovascular physiology.

Methods

Subjects and Data Collection

The purpose of this study was to investigate the effect of circadian rhythm on blood pressure variables. Data from 30 subjects was collected and compiled in a private medical cardiac facility in Diyala province in Iraq from September 2021 to September 2022. Medical history, physical examination, blood pressure, weight, height, and drug history were all included in the clinical evaluation of each subject. The ethical criteria developed by the scientific committee of the institute of medicine faculty/ university of Diyala/Iraq were

followed throughout the investigation. Age, gender, weight, and height factors were included in the analysis to see their effect on blood pressure, figure (2) shows the data distribution according to those four factors.

Statistical Analysis

Different blood pressure parameters of the subjects were compared using Wilcoxon signed-rank test. Wilcoxon rank-sum test (Mann–Whitney test) was used to assess the effect of circadian rhythm on the average blood pressure during days and nights, systolic and diastolic blood pressure during days and nights, and the overall blood pressure during days and nights. Age, gender, weight, and height factors effect on blood pressure were statistically assessed. Statistical significance was defined as a *p*-value of less than 0.05. All data analysis was done using MATLAB package (2015a).

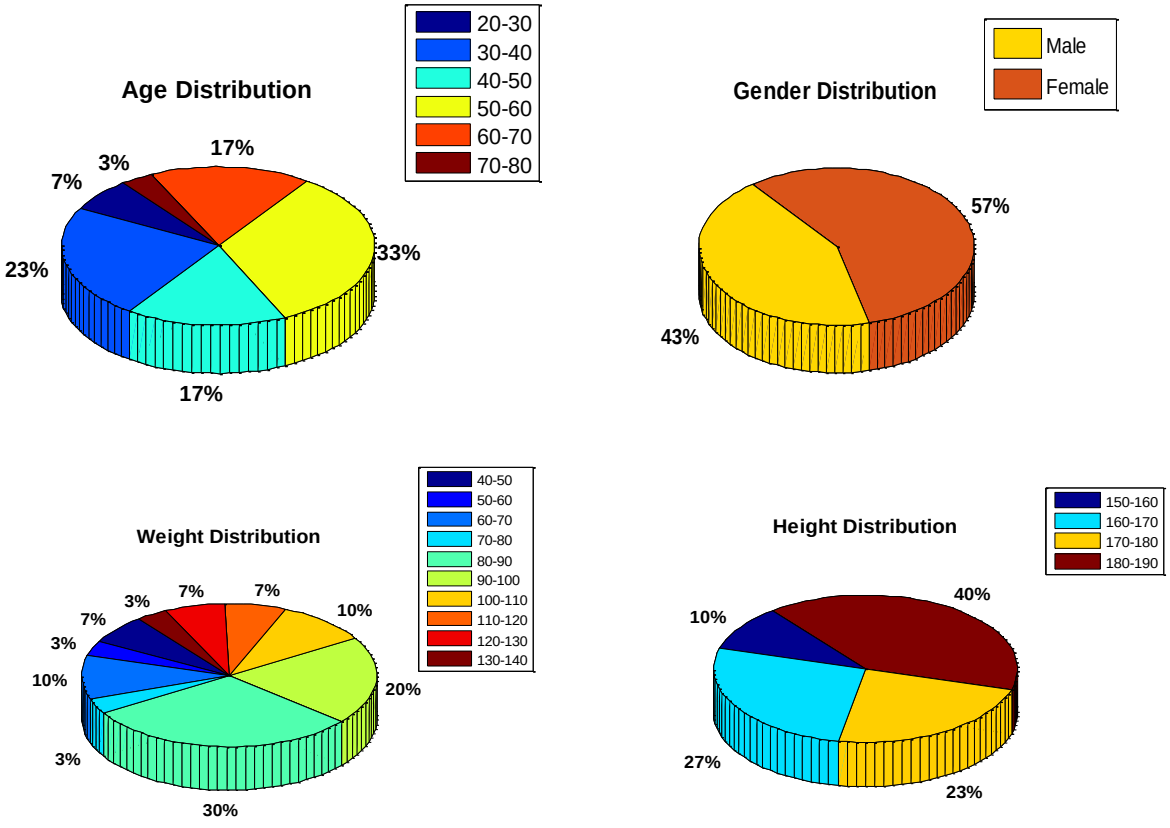

Figure 2: Distribution of Age, gender, weight, and height. Figure (2. A) shows that most patients had age range between 30 to 40 years old while the least age range was for patients with age of 70 to 70 years old. Figure (2.B) shows the gender distribution which looks fair to make a comparison between males and females. Figure (2.C) shows a wide range of the patient's weights. Figure (2.D) shows the height distribution ranges.

Results

Changes in Blood Pressure during Day and Night

Several publications have been documented and verified that blood pressure (systolic or diastolic) goes up during the day times and down during the night. As a first step toward our goal and analysis of this project, we assessed the overall blood pressure (systolic and diastolic) over 24 hours as a mean of our data from 30 subjects and we found that all blood pressure values were within the normal range (120/80) with a slight increase in systolic blood pressure which could be due the effect of age or weight factors. Then, we have looked at the systolic blood pressure during the day and night and found that there was a clear decrease in its value during the night compared to its value during the day. This is consistent with what has been documented in the literature as we will discuss in discussion section. While average systolic blood pressure during the day was 126.17 mmHg, it was 121.94 mmHg during the night as shown in figure (3). Diastolic blood pressure dropped during the night compared to its value during the day and as shown in figure (3) which is also consistent with what has been reported in the literature. Diastolic blood pressure was 77.5 mmHg during the day and 74.8 mmHg during the night.

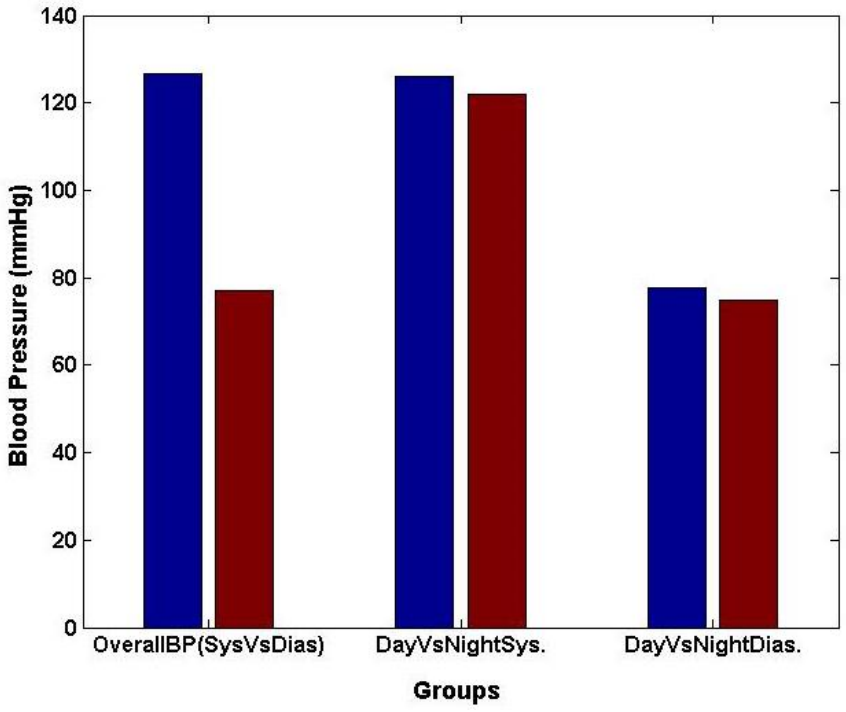

Figure 3: Changes in average blood pressure, systolic blood pressure, and diastolic blood pressure during day and night

Both systolic and diastolic blood pressure are affected by the changes occur during day and night (circadian rhythm) and its associated factors. Thus, we have looked at the percentage of systolic blood pressure that exceeded 140 mmHg (Normal upper limit) during the day and that exceeded 120 mmHg during the night assuming that the systolic blood pressure is higher during the day than the night. The, we looked at the diastolic blood pressure that is greater than 90 mmHg during the day and that is greater than 80 mmHg during the night going with the fact that diastolic blood pressure is higher during the day than its value during the night. As you can see in figure 4, the percentage of systolic blood pressure that exceeded 140 mmHg during the day is much less than the systolic blood pressure that exceeded 120 mmHg during the night. The percentage of diastolic blood pressure that crossed 90 mmHg during the day is also much less than its value during the night that crossed 80 mmHg.

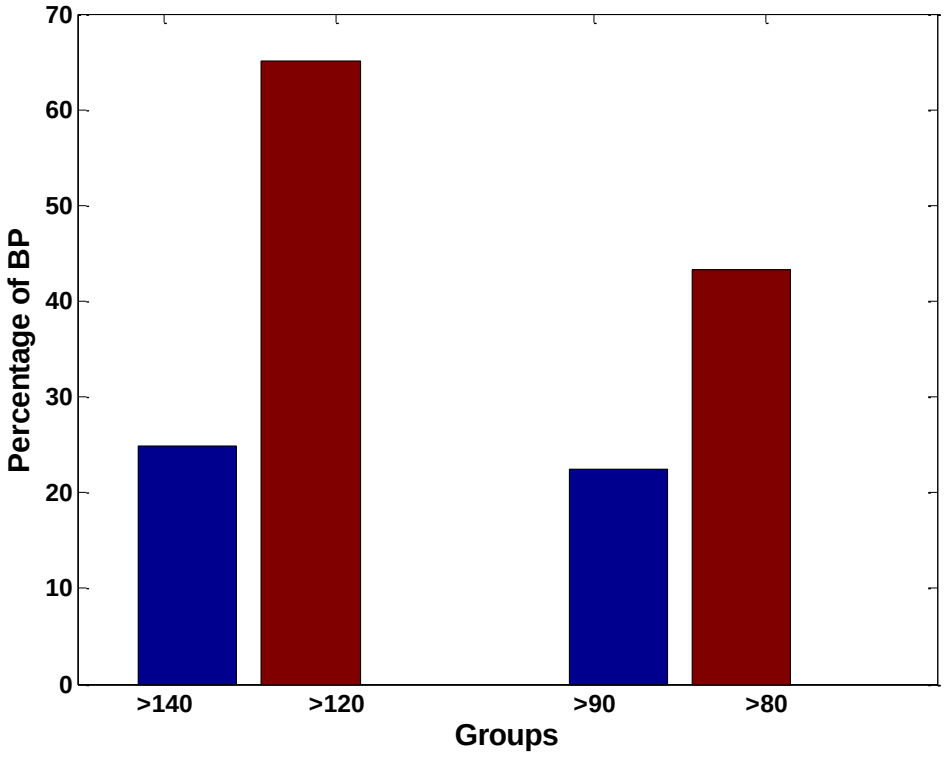

Figure 4: Percentage of systolic blood pressure that exceeds 140 mmHg and 120 mmHg during the day and night respectively (left bars). The right bars show the percentages of diastolic blood pressure that exceeded 90 mmHg and 80 mmHg during the day and night respectively.

Effect of Age Factor on Blood Pressure during the Day and Night

An increase in blood pressure (BP) has traditionally been viewed as an inevitable side effect of aging, which causes hypertension and some other cardiovascular problems in a significant share of senior patients. Based on the data we have collected, we divided our data into five subgroups based on the age of the subjects. While the first group included subjects with age range between 20-30 years old, the second group was within the range of 30-40 years old. Age ranges between 40-50, 50-60, 60-70, and 70 to 80 represented the third, fourth, fifth, and sixth groups respectively. Table (1) shows the results of the average systolic and diastolic blood pressure over 24 hours, the average systolic blood pressure during the day and night, and the diastolic blood pressure during the times of day and night for the six subgroups we already explained. The table shows a consistent increase in blood pressure with the age till age 50, after this age there still an increase but with some variation which could be due to the effect of the number of the subjects in each age group, some outliers of our data points, and menopause in women.

Table 1: Effect of Age and Circadian Rhythm on systolic and Diastolic blood pressure.

Age Group	Systolic BP over 24 hour	Diastolic BP over 24 hour	Systolic BP during the day	Systolic BP during the night	Diastolic BP during the day	Diastolic BP during the night
20-30	**115**	**69**	**116**	**107**	**69**	**65**
30-40	**124**	**78**	**124**	**121**	**79**	**74**
40-50	**128**	**82**	**130**	**117**	**83**	**72**
50-60	**130**	**78**	**126**	**133**	**76**	**80**
60-70	**128**	**76**	**131**	**115**	**78**	**76**
70-80	**126**	**64**	**126**	**106**	**64**	**51**

Effect of Gender Factor on Blood Pressure during the Day and Night

It has been reported that early in adulthood, women's systolic blood pressure (SBP) is lower than men's, but after the sixth decade of life, the converse is true. Regardless of age, women generally have somewhat lower diastolic blood pressure (DBP) than males [12]. Thus, to see if our data is consistent what we found in the literature, we statistically evaluated the difference in overall systolic and diastolic blood pressure, systolic blood pressure during days and nights, and diastolic blood pressure during days and nights all between male and female. Rank sum test was used in performing the statistical analysis. Table (2) shows the results of blood pressure differences and you can see that female systolic and diastolic blood pressure over 24 hours is lower in females than in males which is consistent with Barrios results [12]. To get an idea about how the circadian rhythm can affect blood pressure along with the gender factor, we statistically assessed the systolic and diastolic blood pressure during days and nights between males and females. Interestingly, we have found that both systolic blood pressure during days and nights are higher in male than in female (the same trend as in 24-hour). While diastolic blood pressure during days seems the same in males and females, it slightly dropped in females during the night. The difference in all values did not reach the level of significance (p-value was set to be 0.05).

Table 2: Effect of Gender and Circadian Rhythm on systolic and Diastolic Blood Pressure.

Measure	Male	Female	P-Value
Average Systolic BP	**130**	**124**	**0.24**
Average Diastolic BP	**78**	**76**	**0.53**
Systolic BP/Day	**128**	**125**	**0.61**
Systolic BP/Night	**124**	**120**	**>0.05**
Diastolic BP/Day	**76**	**77**	**>0.05**
Diastolic BP/Night	**77**	**73**	**>0.05**

Effect of Height on Blood Pressure during the Day and Night

Many authors independently conducted a systematic review to examine the data on height and blood pressure. Evidence was discovered to support the inverse relationship between height and blood pressure across numerous significant studies with a variety of patient demographics [13], [14]. According to our data and based on height of the subjects, we had four subgroups. While the first group included subjects with height range (150-160) cm, the second group included those with height range between 160-170 cm. Height ranges of 170-180 cm and 180-190 cm were the third and fourth groups. Table (3) shows the results of systolic and diastolic blood pressure over 24-hour, systolic and diastolic blood pressure during the days and nights. The first two columns of the table verified what we found in the literature. The effect of circadian rhythm seems more during the days than the night.

Table 3: Effect of Height and Circadian Rhythm on systolic and Diastolic Blood Pressure.

Height Group (cm)	Systolic BP over 24 hour	Diastolic BP over 24 hour	Systolic BP during the day	Systolic BP during the night	Diastolic BP during the day	Diastolic BP during the night
150-160	**121**	**69**	**118**	**112**	**69**	**63**
160-170	**124**	**76**	**127**	**122**	**79**	**73**
170-180	**130**	**78**	**124**	**129**	**75**	**84**
180-190	**128**	**79**	**120**	**120**	**81**	**74**

Discussion

Studies have shown that blood pressure (BP) has a circadian pattern; it increases in the morning and decreases at night. Although the underlying molecular mechanisms are still unclear, it has been found that disturbance of the circadian BP rhythm is associated with deteriorating of the cardiovascular outcomes. In this project, we examined how blood pressure changed throughout the day and night. Our findings verified that blood pressure in people has a circadian fluctuation profile, with an increase during the day and a deeper decline at night. Both systolic and diastolic blood pressures were examined during the day and at night, and it was found that there was a definite drop in their values at nights compared to days.

Regarding the age factor, our results revealed that blood pressure rose steadily with age until the age of 50. After this age, blood pressure increased again, although there was some variance, which may have been caused by the effect of the number of participants in each age group, certain outliers in our data, and menopause in women. This alteration results from the stiffening of the major arteries and the lack of elastic recoil due to the collagen fibers that have replaced the elastic fibers. This aging process has the effect of increasing the pulse wave velocity and expanding the pulse pressure. An increasing prevalence of strokes and cardiovascular diseases (CVDs) is linked to these hemodynamic alterations. Recently, it was discovered that in people older than 60, the risk of stroke decreased when the DBP was below 71 mm Hg. As a result, care should be taken while treating SBP in the elderly to avoid lowering the DBP below this level in order to reduce the risk for CVD and stoke [7]. Our findings, which took into account the gender element, revealed that women have lower systolic and diastolic blood pressure over the course of a 24-hour period than men, which is consistent with what has been reported in the literature. Our data has also shown that men experience higher systolic blood pressure during the day and at night than women do (the same trend as in 24-hour).

Conclusions and Future Work

A growing body of research shows that maintaining circadian rhythm in blood pressure is closely related to maintaining cardiovascular homeostasis. Numerous anti-hypertensive drugs also showed clear circadian time-dependent efficacy, and many studies have taken into account chronotherapeutic evaluation when managing hypertension and related cardiovascular diseases. In conclusion, this project shows that the value of daytime and nighttime systolic/diastolic BP is different and the age, gender, and height are three factors that have an impact on blood pressure. As a future work, we are collecting more data and expanding our

analysis to include other factors such as weight and combining age, gender, weight, and height all in one analysis.

References

[1] C. J. Morris *et al.*, "Day/night variability in blood pressure: Influence of posture and physical activity," *Am. J. Hypertens.*, vol. 26, no. 6, pp. 822–828, 2013.

[2] Y. Kawano, "Diurnal blood pressure variation and related behavioral factors," *Hypertens. Res.*, vol. 34, no. 3, pp. 281–285, 2011.

[3] I. M. Hower, S. A. Harper, and T. W. Buford, "Circadian rhythms, exercise, and cardiovascular health," *J. Circadian Rhythms*, vol. 16, no. 1, pp. 1–8, 2018.

[4] L. G. Douma and M. L. Gumz, "Circadian clock-mediated regulation of blood pressure," *Free Radic. Biol. Med.*, vol. 119, pp. 108–114, 2018.

[5] J. Cortés-Ríos and M. Rodriguez-Fernandez, "Circadian Rhythm of Blood Pressure of Dipper and Non-dipper Patients With Essential Hypertension: A Mathematical Modeling Approach," *Front. Physiol.*, vol. 11, no. January, 2021.

[6] F. Coccina *et al.*, "Prognostic value of daytime and nighttime blood pressure in treated hypertensive patients according to age and sex," *J. Clin. Hypertens.*, vol. 22, no. 11, pp. 2014–2021, 2020.

[7] S. G. Chrysant and G. S. Chrysant, "The Age-Related Hemodynamic Changes of Blood Pressure and Their Impact on the Incidence of Cardiovascular Disease and Stroke: New Evidence," *J. Clin. Hypertens.*, vol. 16, no. 2, pp. 87–90, 2014.

[8] E. Pinto, "Blood pressure and ageing," *Postgrad. Med. J.*, vol. 83, no. 976, pp. 109–114, 2007.

[9] M. Gurven, A. D. Blackwell, D. E. Rodríguez, J. Stieglitz, and H. Kaplan, "Does blood pressure inevitably rise with age?: Longitudinal evidence among forager-horticulturalists," *Hypertension*, vol. 60, no. 1, pp. 25–33, 2012.

[10] Cr. Maranon and J. F. Reckelhoff, "Sex and Gender Differences in Control of Blood Pressure," *NIH Public Access*, vol. 7, no. 125, pp. 311–318, 2013.

[11] H. H. Alhawari *et al.*, "Blood Pressure and Its Association with Gender, Body Mass Index, Smoking, and Family History among University Students," *Int. J. Hypertens.*, vol. 2018, 2018.

[12] V. Barrios, C. Escobar, R. Echarri, and A. Matalí, "Gender and blood pressure control," *Hypertension*, vol. 51, no. 6, 2008.

[13] J. M. Cochran *et al.*, "The Relationship between Adult Height and Blood Pressure," *Cardiol.*, vol. 146, no. 3, pp. 345–350, 2021.

[14] Y. Shimizu, H. Hayakawa, N. Sasaki, M. Takada, T. Okada, and M. Kiyama, "Association between Height and Hypertension: A Retrospective Study," *BioMed*, vol. 2, no. 3, pp. 303–309, 2022.