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Circadian Rhythm and Blood Pressure: research of the latest circadian rhythm in the treatment of hypertension

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Abstract. The goal of this review was to synthesize present knowledge on the effect of circadian rhythms on blood pressure (BP), circadian misalignment mechanisms that contribute to hypertension, circadian rhythm, and hypertension relationship, the latest research of circadian rhythm diet and pharmacological intervention and assess the possibility of chronotherapy in treatment. BP by modulating biological function is determined by the circadian rhythm process mainly under endogenous control, including the central clock in the suprachiasmatic nucleus (SCN) and peripheral clock. Hypertension has been associated with disruption of this rhythm which is a major cardiovascular disease risk factor. A high risk for adverse cardiovascular outcomes is circadian misalignment, which is reflected mostly by nocturnal non-dipping. Shift work, hormone release, dietary habits, and others that affect circadian rhythms seem implicated, according to studies. Bedtime dosing of antihypertensive medications and other forms of chronotherapy have the potential to improve BP control. Time-dependent feeding and lifestyle interventions consistent with circadian rhythms offer benefits for hypertension management, as well. Increasingly, it is recognized that circadian rhythm disruption contributes to hypertension. Because interventions that realign circadian rhythms, including chronotherapy or circadian-aligned lifestyle changes, may decrease cardiovascular risk in hypertensives, they are worthy of further study.

Keywords: circadian rhythm, hypertension, chronotherapy, suprachiasmatic nucleus, blood pressure.

1. Introduction

At least one-third of adults globally (approximately 1.28 billion) have hypertension (high blood pressure), and the vast majority of these (1.18 billion) live in low and middle-income countries[1]. A silent condition, with few obvious symptoms until it's very advanced, when it can result in coronary disease, stroke, and kidney failure. Extensive research continues in hypertension but much more of this effort has been devoted to the complex interplay between hypertensive status and circadian rhythms, an internal time-dependent process that follows a 24-hour cycle and serves as the body' s key controlling device for many of its normal functions. Treatment of hypertension is usually accompanied by lifestyle modifications as well as pharmacological interventions. Antihypertensive drugs are typical ways of treatment which may be accompanied by side effects, e.g. dizziness, fatigue, and changes in the function of the kidneys. In many cases, lifestyle changes (less sodium in the diet, more physical activity, and weight loss) are as effective as drug therapy. Hypertension is a growing area of study related to circadian

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rhythms. Routine interference with these rhythms being common disruptions from shift work or irregular sleep patterns has been linked to an increased risk of hypertension. Treatment of hypertension might be more optimal if treatments were coordinated with the body's natural circadian rhythms. Examples include that BP medications are taken at specific times of the day by the circadian rhythm and are considered more effective[2]. The dietary intervention of time-restricted eating (a form of intermittent fasting) has also been examined with regard to blood pressure. According to some studies, limiting food intake to a specified daily window may even help control hypertension. But other studies have found that extended periods without eating increased the risk of death from cardiovascular causes, whereas very short eating windows — of below 8 hours a day — may do likewise. While it is clearly feasible, it is not yet proven to be long-term, and more data is needed before definitive guidelines can be recommended.

As a result, hypertension is a common condition that affects a great majority of the world, and the treatment of it is complex and includes medication as well as changes to an individual's lifestyle. Circadian rhythms play an emerging role in hypertension and insights into their role may lead to improved treatment of the disorder. The results for time-restricted eating are promising and warrant further research to explore the long-term effects of its practice as well as establish best practices.

2. The relationship between circadian rhythm and hypertension

Methods to estimate the human circadian phase have been established but disruption of circadian rhythm has been associated with an increased risk of contraction of a range of illnesses, including sleep disorders, metabolic syndrome, and cancer[3]. Circadian rhythm is regulated by the central clock in the suprachiasmatic nucleus (SCN) of the hypothalamus, and the peripheral clock everywhere else in the body simultaneously.

The BP pattern in the main follows an approximately circadian pattern, with an increase in BP after waking and a decrease in BP during overnight sleep. Historically, the human phenotype of nocturnal BP fall in the published literature has included normal 'dipping' as a≥ 10% fall in BP during sleep, and 'non-dipping' as a < 10% fall in BP at sleep[4]. It is not that only the movement rhythms cause rhythmic changes in BP. Indeed, peripheral circadian action may also directly direct rhythmic BP. The relationship between locomotor capacity and the BP rhythm varied during the day (and not in a circadian fashion) when examined over the whole 24 hours[5]. Consequently, it also has significant effects on BP rhythm regulation. In fact, ablation of the SCN causes the disappearance of circadian variation of BP[6]. We then find that circadian misalignment affects BP 24h significantly to the same degree and direction as shown to be achieved in a Dietary Approaches to Stop Hypertension (DASH) study and by some individual antihypertensive drugs. Because an increased risk of cardiovascular disease is associated with such a gradual increase in BP from normal resting values, the circadian disorder-mediated increases in BP may have clinical implications. Circadian dysregulation has mainly adverse effects on 24-hour BP, mostly by increasing BP during sleep, not while awake. Awake BP is better predicted by sleeping BP on adverse cardiovascular events and all-cause mortality. In addition, circadian misalignment attenuated the decrease in systolic blood pressure during sleep. BP reduction during sleep was also an independent predictor of adverse cardiovascular events and all-cause mortality.

Circadian misalignment is one of the disorders characterized by the induction of clinical symptoms, including hypertension. As an example, for both black and white women, take shift workers: For black women who had been employed for more than 12 months during the two previous years and had worked more than 12 months on night shifts, the multivariable hazard ratio was 1.81 for developing hypertension compared with none[7]. One Nurses' Health Study found rotating night shift workers had a higher risk for cardiovascular disease than nurses who never worked night shifts[8]. A Danish cohort study also showed a significantly increased relative risk for developing cardiovascular disease (CVD) in nonday workers compared with day workers[9]. In addition, a study has confirmed that circadian rhythmicity is imperative to the general cardiovascular system in that shift-work male workers have higher stroke and cardiovascular mortality than day workers in Swedish paper mills, but not higher all-cause mortality[10].

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Hypertension and cardiovascular damage due to circadian disturbances, and some clinical studies have demonstrated that bedtime chronotherapy resulted in lower BP[11,12].

3. Other type of circadian rhythm influence BP

Many articles currently suggest that circadian rhythms lead to hypertension but the current diagnostic and therapeutic strategies have paid little attention to the circadian rhythm of BP. Circadian rhythms are not only slept circadian rhythm that regulates the circadian rhythm of BP, circadian rhythm can also be seen in body temperature, hormone release, dietary habits, digestive function, renal and cardiovascular functions, and other functions in the host that have a significant impact on the circadian rhythm of BP[13, 14].

Doi M also performed another interesting piece of work showing that global double Cry1/2 KO mice have an adrenal disease associated with Hsd3b6-dependent aldosterone overproduction and altered aldosterone rhythm mimicking salt sensitivity hypertension in Cry1/2 KO mice [15]. Tanaka S's was also demonstrating the role played by the adrenal circadian clock in a spontaneously hypertensive population. In comparison with normotensive individuals, several adrenal circadian clock genes (Bmal 1, Per 2, Per 3, and Cry 1) are late phase. The main role that the adrenal gland plays in the steroidogenesis of glucocorticoids, mineralocorticoids, and androgens. Star, the rate-limiting enzyme for steroidogenesis, was identified late in the circadian expression profile, as were blood levels of corticosterone and aldosterone[16]. These steroids of course are both associated with the BP rhythm. Since this is an observational study, it would also be of interest to pursue further investigation of the direct effects of adrenal circadian rhythms on BP rhythms.

Renal and cardiovascular function is most dependent on arterial stiffness. Arterial stiffness is used in part to predict vascular aging, which in turn is an independent predictor of cardiovascular events. Structural and functional changes in large elastic arteries are correlated with increased arterial stiffness, and vascular calcification involving the reverse conversion of vascular smooth muscle cells (VSMC) into bone-like cells strengthens arterial ossification. Stiffness results from endothelial structure alterations resulting in the chronicity of such phenomena may be behavioral dysfunction due to irregular diets and sleep patterns. The signaling pathways linking the circadian clock with vascular stiffening will continue to be the subject of compelling future research. Given the poor understanding of the circadian regulation of vascular smooth muscle cells (VSMC), the current work is motivated by the need to understand how VSMC work in tandem with other resident vascular cells and circulating cells to determine vascular calcification, stiffness, blood pressure, and vascular aging

4. Diet therapy and chronotherapy

Approximately 1.28 billion persons aged 30 to 79 globally suffer from hypertension, predominantly residing in low- and middle-income nations[17]. Hypertension can cause damage to organs. It can cause many heart conditions such as coronary artery disease, enlarged left heart, and heart failure. Also, it will increase the risk of stroke or transient ischemic attacks. Finally, it may result in damage to the blood vessels in the retina[18]. To sum up, hypertension is a major cause of premature death worldwide[19]. Here we divide the meal time and chronotherapy respectively, to substitute the conventional treatment of hypertension for example by using medicines to control the BP.

Another promising area for science about circadian blood pressure rhythm concerns further elucidation of the impact of the time of food intake on blood pressure, namely nocturnal hypertension and nondipper blood pressure. Current data suggest that night eating is associated with increased blood pressure and shiftwork distorted rest wake cycle[20]. A large number of articles associated time-restricted meals with potential cardiometabolic benefits in humans[21]. A new concept introduced states that lower urine sodium in a day leads to high blood pressure in the evening[22]. A small population study indicates that elevated nocturnal blood pressure correlates with an increased percentage of salt excretion during the night[23]. Del Giorno's research in older adults indicated that reduced daytime sodium excretion correlated with elevated overnight blood pressure[24]. In this context, it is essential to comprehend the influence of particular dietary elements (e.g., sodium, lipids, etc.) on nocturnal blood pressure. For instance, the reduction of sodium intake restorative of the dipping pattern in salt-sensitive and hypertensive individuals was equally achieved[25]. Finally, since circadian disturbance is common with many populations including shift workers, understanding these blood pressure and renal regulation systems will help reduce the high disease risk in such persons. Clinical and epidemiological studies suggest that using antihypertensive medication at sleep may enhance nightly blood pressure lowering and mitigate early morning blood pressure rising. The research about antihypertensives administered at bedtime rather than in the morning, indicating an improvement in clinical results, has been inconsistent. In placebo-controlled including HOPE (Heart Outcomes Prevention and Evaluation), Syst-Eur (Systolic Hypertension in the Elderly), and Syst-China (Systolic Hypertension in China), the antihypertensive medication started with use in the evening to reduce cardiovascular outcomes, although morning medications were later added for BP control in most patients. Moreover, lifestyle modifications, including a nutritious diet, weight reduction, consistent physical activity, cessation of smoking, and moderation of alcohol use, are crucial components in the management of hypertension.

5. Conclusion

This paper is a discussion of the important research that has been done to demonstrate the role of circadian rhythms in the pathophysiology of hypertension as well as the principle that the drug discovery process in this area requires efforts in the following three areas: Of relevance, disruption of these endogenous rhythms regulated by the SCN and other peripheral oscillators necessarily leads to dysregulation of BP with potential clinical consequences. A review of the literature has shown that nocturnal non-dipping, a circadian misalignment phenotype, predicts cardiovascular events and mortality. Our findings suggest circadian misalignment can significantly impact BP in a manner similar to DASH studies; and to the effects of antihypertensive drugs. The effect of this misalignment is mostly manifest during sleep and underscores the value of sleep BP as a primary indicator of cardiovascular health. The review also reveals the opportunities of chronotherapy in treating hypertension by matching the intervention timing with the body's circadian rhythm. Thus, this approach may be in a position to provide more optimal management of hypertension, especially for populations with a high prevalence of disruption of circadian rhythm, for example, shift workers. Additionally, the paper references the control of BP by other circadian rhythms, such as the release of hormones, bodily temperature, and digestion. One of the specific discussed areas offers promising further investigations: the adrenal circadian clock and steroidogenesis together with the influence on the regulation of BP. In dietary therapy, the evidence supports potential BP control benefits from time-restricted eating. With concerns to dietary therapy, the findings highlighted the possibility of time-restricted eating lowering BP among patients. This approach, combined with lifestyle modifications such as reduced sodium intake and the DASH diet, could provide an alternative or adjunct to pharmacological treatments.

To conclude, consideration of circadian rhythm in hypertension management is a field to investigate. Aligning treatments to the body’s natural rhythms could improve BP control and reduce the global toll of cardiovascular disease caused by hypertension. These are important pathways, and greater understanding is required to explain them and to bring the results into clinical practice.

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