Chronobiology in Dysautonomia and Cerebrovascular Disease

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Abstract: The study of chronobiology is based on the concept that homeostasis in the milieux interieur fluctuates within specific time cycles. Time-series data collected with a specific time frame are required to evaluate the characteristics of biological rhythms. Although no completely adequate method for the analysis of time-series measurements has been established, the new MemCalc system may be highly valuable. This system is very helpful to study biological rhythms that are difficult to elucidate using conventional analytical methods. It is ideal to perform infinite time-series analyses over continuing time, but current technology has its limitations. In this study, we reviewed disrupted biological rhythms in patients with dysautonomia or cerebrovascular disease within specific time frames of milliseconds, seconds, hours, days or still longer periods, focusing on time-series analyses of heart rate/blood pressure rhythm variations using the MemCalc system. We also introduced current chronological research findings relevant to this study. A chronobiological approach to heart rate/blood pressure rhythm variations using time-series analysis will enable clinicians to predict the occurrence and prognosis of cerebrovascular events or brain attack.

Key words: Heart rate/blood pressure variability; Time series analysis; Cerebrovascular disease; Neurodegenerative disease

Introduction

The concept of biological rhythms is based on temporal ordering. In this paper, we reviewed disrupted biological rhythms in neurologic disease within several specific time frames, focusing on a time-series analysis of heart rate/blood pressure variability, which has been widely employed in the clinical setting.

Blood Pressure Rhythm in Milliseconds

Various biological rhythms are noted in the living body in a continuous time cycle. In the case of the biological rhythm of blood pressure, a biological signal, the arterial pressure pulse wave is the smallest time rhythm that can be analyzed. Aterial pressure pulse wave analysis has been demonstrated to reveal the
basic characteristics innate in biological rhythms, in contrast to the other time-frame analyses described below. Ohtomo et al. reported exponential spectral characteristics in the Lorenz/ Rouverse/ Daffing model, known as the chaos dynamic system. Ohtomo's study revealed for the first time in the world that chaos exists in biological time series, by proving that arterial pressure pulse waves have exponential spectral characteristics. The coefficient of the exponential characteristics, however, has been reported to be affected by mental stress.

Figure 1 shows the exponential characteristics of an arterial pressure pulse wave in a healthy subject. Unlike those of the 1/f spectrum described later, these exponential spectral characteristics do not vary between healthy people and patients with cerebrovascular disease or neurodegenerative disease associated with dysautonomia. Thus, these exponential spectral characteristics may be essential to biological activities. The beat-to-beat variation shows a 1/f rhythm.

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**Note 1** Maximum entropy method (MEM): MEM is a spectral analysis method proposed by Jaynes, based on the concept of informational entropy. MEM analysis, which has been widely used, applies an algorithm suggested by Burg. MEM rapidly estimates the spectrum of the observation data with high resolution.

**Note 2** MemCalc system: MEM analysis has the problem of lag dependency in power spectral density (PSD). Ohtomo, Tanaka and coworkers resolved this problem in determining the optimal lag in such a way as not to be in conflict with the MEM theory, based on the analysis of the sunspot. This has been proposed as the MemCalc system. The system is a time-series analytical method, which combines the MEM spectral analysis method and the nonlinear least squares method (LSM). Since least squares fitting calculated by the LSM reproduces the original time-series data, the validity of the MEM spectrum can be confirmed.
Fig. 2 Relationship between 0.1 Hz-cerebrovascular blood flow rhythm and baroreceptor sensitivity

In this plot, the y axis describes the oscillation of the 0.1 Hz-cerebrovascular blood flow rhythm, obtained by spectral analysis using the MemCalc system for the blood flow velocity at the middle cerebral artery, which was measured by transcranial Doppler ultrasound; the x axis illustrates baroreceptor sensitivity based on the ratio of heart rate and blood pressure rhythms of around 0.1 Hz. The lower the BRS, the smaller the oscillation of the 0.1 Hz-cerebrovascular blood flow rhythm. The two parameters are lower in healthy elderly subjects ($n=7$) than in healthy young subjects ($n=12$). Both parameters are the lowest in patients with multiple lacunar infarcts associated with leukoaraiosis ($n=4$), indicating that the 0.1 Hz-cerebrovascular blood flow rhythm is related to the risk of cerebrovascular infarction and the BRS.

Heart Rate/Blood Pressure Rhythms in Seconds

Heart rate/blood pressure rhythms on a time cycle of seconds are directly related to autonomic activity and are measured in many clinical situations for evaluating autonomic function via the baroreceptor reflex. Blood pressure rhythms of around 0.1 Hz (10-second cycles) and heart rate rhythms of around 0.25 Hz (4-second cycles) are known to reflect vasomotor sympathetic activity and vagal activity, respectively, while the ratio of the heart rate and blood pressure rhythms, each around 0.1 Hz, is known to reflect the vasopressor reflex function. These biological rhythms are disturbed in patients with neurodegenerative disorders associated with dysautonomia, such as in Parkinson’s disease, multiple system atrophy, pure progressive autonomic failure, and cerebrovascular disease. The severity of autonomic dysfunction can be assessed according to variations in these heart rate/blood pressure rhythms.

Furthermore, biological rhythms in seconds have been detected not only in the heart rate and blood pressure, but also in respiration, muscle nerve sympathetic activity, electroencephalographic activity and cerebral blood flow. In time, a possible correlation between these various biological rhythms in our body may be elucidated as shown in Fig. 2. A rhythm of around 0.1 Hz has been recognized in blood flow to the brain as in the blood pressure, but this rhythm is considered to be under a different regulatory mechanism to that of the blood pressure rhythm. The rhythm in cerebral blood flow is attenuated in patients with multiple lacunar infarcts associated with leukoaraiosis. Such attenuation is closely related to blunted baroreceptor reflex function, suggesting that cerebral arteriolosclerosis may affect the mechanism regulating the rhythm.

On the other hand, Kobayashi and Musha have demonstrated that the arterial pulse pressure wave and beat-to-beat blood pressure rhythm variations exhibit a $1/f$ spectrum, as shown in Fig. 1. The $1/f^\beta$ spectrum has been identified as an intermittent chaotic phenomenon, which also indicates that the regulatory mechanism of these heart rate/blood pressure rhythms is closely related to autonomic function. Ohtsuka et al. have clarified that the slope of $1/f$, or the elevation of $\beta$, is affected by atropine loading, aging, and Parkinson’s disease.

Blood Pressure Rhythms in Hours (Mainly Circadian Rhythms)

Twenty-four hour time-series data of heart rate/blood pressure can be readily collected by Holter recording and ambulatory blood pressure monitoring. Abnormal circadian rhythms have been observed in many disease conditions. Recognition of impaired circadian
many researchers’ attention. For the prevention of cerebrovascular attacks, control of such impaired circadian patterns of blood pressure, especially such as the morning surge or non-dipping patterns of blood pressure in hypertensive patients, has therefore been emphasized, and \( \alpha_1 \) blockers have been successfully used in the management of excessive blood pressure surges in the early morning.\(^{10}\)

The circadian rhythm of blood pressure could be influenced by exogenous factors. The two strongest modifiers are believed to be physical activity during sleep and wakeful stages, and mental stress. Neurologic disease is generally associated with motor dysfunction. Reduced physical activity associated with motor dysfunction has also been considered to contribute to the disrupted circadian rhythm of blood pressure in patients with cerebrovascular diseases or Parkinson’s disease.

Figure 3 shows the circadian rhythms of blood pressure obtained from a 120-day 6° head-down bed rest study (unpublished data). Twenty-four hour blood pressure rhythm variations can be measured in basic cycles of 8, 12 and 24 hours. Blood pressure measurements in such cycles were performed to compare the values obtained at baseline, after 60 days of bed rest, after 120 days of bed rest, and at the end of the experimental period, and were analyzed using the MemCalc system. The bed rest study allowed the subjects to be physically inactive and under microgravity. However, no changes were observed in the structure of the systolic blood pressure rhythms in these basic cycles.

Blood pressure during sleep is usually 15 to 20% lower as compared with that during physical activity. Subjects showing such physiological nocturnal decline are referred to as dippers. Patients with hypertensive or cerebrovascular disease often do not show the physiological nocturnal decline in blood pressure and are referred to as non-dippers. However, some hypertensive patients are extreme-dippers, and show a nocturnal blood pressure decline of more than 20% as compared to the daytime blood pressure.\(^{10}\) Non-dipper or extreme-dipper patterns of nocturnal blood pressure decline in patients with hypertension are more likely to be associated with target organ damage. The incidence of cerebral infarction has been reported to be significantly high in association with these patterns.\(^{10}\)

Since it has been suggested that the chance of occurrence of cerebral infarction is at its highest in the early morning, the finding of the morning surge in blood pressure in association with a disrupted circadian rhythm has drawn many researchers’ attention. For the prevention of cerebrovascular attacks, control of such impaired circadian patterns of blood pressure, especially such as the morning surge or non-dipping patterns of blood pressure in hypertensive patients, has therefore been emphasized, and \( \alpha_1 \) blockers have been successfully used in the management of excessive blood pressure surges in the early morning.\(^{10}\)

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Figure 3 shows the circadian rhythms of blood pressure obtained from a 6° head-down bed rest study. Bed rest study is an approach used in space medicine, in which subjects are immobilized at bed rest in a supine position in microgravity for 24 hours. The protocol of a 120-day bed rest study was accepted by the ethical committee of the State Scientific Center Institute of Biomedical Problems in Russia, and all the 6 healthy male volunteers gave informed consent.

In this study, the circadian rhythm of blood pressure was measured in basic 8-, 12- and 24-hour cycles to compare the values obtained at baseline, after 60 days of bed rest, after 120 days of bed rest, and at the end of the study. No significant changes were observed in these basic cycles of circadian rhythms were observed at these time points. These findings indicated that physical inactivity during sleep or wakefulness has no effect on the circadian rhythms of blood pressure. Therefore, disrupted circadian rhythms of blood pressure in patients with neurologic disease may result from the disease itself.
Blood Pressure Rhythms in Periodic Cycles of Days or Longer

Brain attacks, including cerebral infarction, have been reported to be more common on Mondays and during winter. These findings suggest that weekly or yearly circadian patterns may influence the risk of cerebrovascular events. Blood pressure rhythms in 7-day cycles have been reported.

Few studies on blood pressure rhythms in cycles of 7 days or longer have been reported. We conducted blood pressure measurements over 2 years in patients with cerebral infarction or Parkinson’s disease, using a home sphygmomanometer. The collected data were analyzed by the maximum entropy method (M E M). The results showed that the incidence of cerebral infarction shows a yearly cycle, with a peak during the winter season. The M E M spectrum showed a 1/ f2 rhythm in 6 out of 10 patients with cerebral infarction and a 1/ f0 rhythm in 2 out of 3 patients with Parkinson’s disease, while a 1/ f rhythm was observed in 7 out of 10 healthy controls. The 1/ f2 rhythm, known as brown noise, is strongly confined to past time series and is less flexible to the body. 1/ f0, or white noise, is characterized by random fluctuation.

Figure 4 shows the results of M E M spectral analysis of daily blood pressure data measured over a period of 6 years in a patient with cerebral infarction associated with complete occlusion of the right internal carotid artery.

Blood pressure was measured daily with a home sphygmomanometer at a prescribed waking time in the morning. The data for every 2 years were analyzed using the MemCalc system. The upper panel shows trend analysis of the SBP and the bottom panels represent the corresponding MEM spectrum illustrated in a log-log scale. The MEM spectrum showed a 1/ f2 rhythm from 1989 to 1991, interposed by two cerebral infarction events and one transient ischemic attack (TIA). A 1/ f rhythm was observed from 1991 to 1993, and the 1/ f2 rhythm was again noted from 1993 to 1995.

Conclusion

More and more genetic research for understanding biological rhythms has been per-
formed since the clock genes were identified in humans. The role of the nervous system network is practically important for understanding the biological rhythms of the body. On the other hand, analysis of biological rhythms, such as that of the heart rate or blood pressure, both of which are target parameters in the study of the control or maintenance of physiological function, provides an overall approach in terms of the self-organized systematization of these parameters. Further studies taking these two viewpoints into consideration are warranted to understand biological rhythms in greater detail.

REFERENCES