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Circadian Rhythm in the Cardiovascular System: Considerations in Non-Invasive Electrophysiology

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Abstract. **Most cardiovascular activities show a circadian rhythm, as do electrophysiological phenomenon. Under the influence of both external stimuli and endogenous homoeostatic mechanisms, cardiac electrophysiological properties change diurnally and enable the cardiovascular system adapt to rest-exercise cycles. According to recent reports, almost all non-invasive electrophysiological phenomena, such as electrocardiographic indices, cardiac refractoriness and conduction, pacing and defibrillation threshold, heart rate variability indices, and even Q-T dispersion and T-wave alternans, show diurnal variability. Furthermore, many of these changes are clinically significant and may affect results of some diagnostic studies. These characteristics of the cardiovascular system require us keep in mind the "time" factor any time we analyze electrophysiological results and make clinical decisions.**

Key Words. **circadian rhythm, cardiovascular system, electrophysiology, chronobiology**

Biological rhythms are a universal phenomenon in living organisms and enable adaptation to the environment. Biological rhythms can be divided into three types based on their cycle lengths: Circadian (or diurnal) rhythms, with a period of about 24 hours; Ultradian rhythms, with a period significantly shorter than 24 hours (hours, minutes or even seconds); and infradian rhythms, with a period longer than 24 hours (days, months or longer). Circadian rhythms, for example the rhythm associated with many cardiovascular parameters, are the most common and best studied among these rhythms.

To describe circadian data, Halberg and co-workers [1] developed a mathematical technique—cosinor fitting by least squares. Three indices were used to illustrate the characteristic of a particular diurnal rhythm: the midline estimating statistic of rhythm (MESOR), the value midway between the highest and the lowest values of the (cosine) function which best fits the data; the amplitude, the measure of one half of the magnitude of the rhythmic change estimated by the mathematical model (i.e., the cosine curve) best fitting the data; and the acrophase, a measure of the time of the maximum value of the cosinor function (see Figure 1). These indices permit comparison of circadian rhythms between patient groups. Continuously measured parameters, e.g., heart rate, are usually averaged, e.g., hourly, before undertaking cosinor analysis.

In the cardiovascular system, most physiological phenomenon (such as heart rate, blood pressure, atrioventricular conduction, etc.) and pathological events (cardiac ischemia and/or infarction, sudden cardiac death, etc.) have circadian rhythms [2]. Circadian rhythms have also been described in non-invasive cardiac electrophysiological (EP) phenomenon. In the following section, we will discuss the diurnal changes in some non-invasive cardiac EP indices.

Heart Rate

Circadian rhythm of heart rate has been extensively studied [2]. It has been shown that there is a surge in heart rate in the period around awakening, or soon after waking and commencing activity, which reaches its peak value (acrophase) between 10 and 12 o'clock in the morning. After that, heart rate gradually begins to slow (although some studies have found a second weaker peak in the afternoon) and maintains a lower level during the whole night. The trough value has been reported to occur between 3 and 5 AM, or 1 to 2 hours before awakening in the morning in different studies. The circadian change of heart rate ensures that the heart adapts to the needs of different activity levels during the day and night by increasing or decreasing cardiac output, although a circadian rhythm in heart rate continues to be seen in experimental subjects on total bedrest [3].

Electrocardiographic Indices

ECG measurements also display diurnal changes. P wave duration and its area, P-R interval, QRS duration, Q-T interval, all have been found to show diurnal changes [4–6]. During the daytime, when

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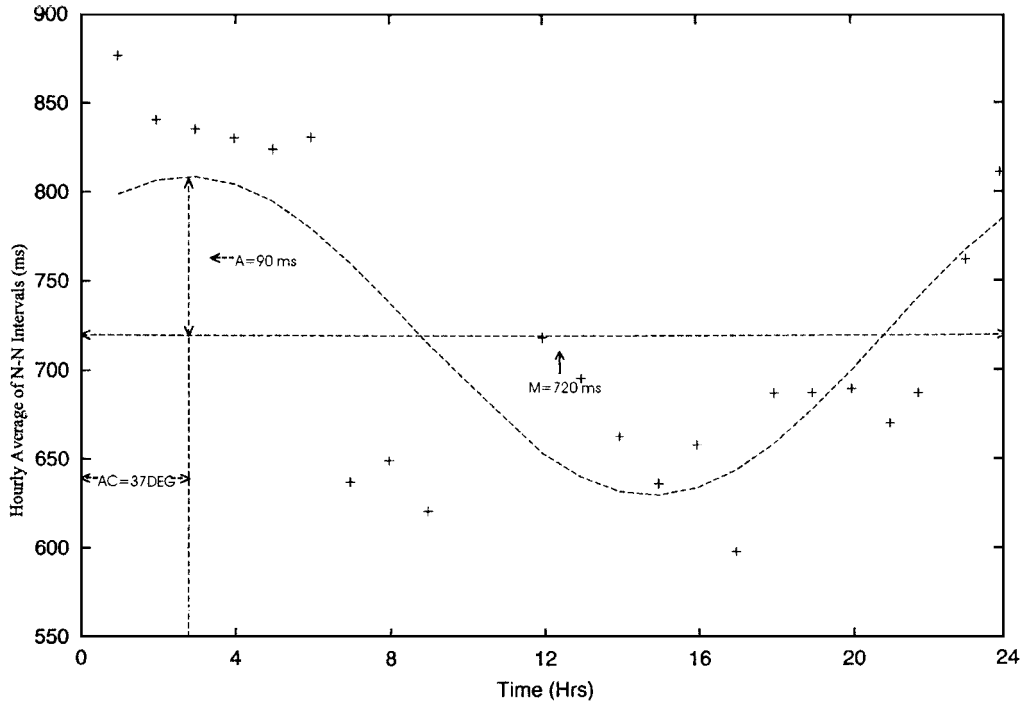

Fig. 1. *Example of 24-hour cosinor analysis. (N-N = Normal-to-normal interbeat intervals; A = amplitude; AC = acrophase; M = MESOR).*

sympathetic output is enhanced and heart rate increased, all of these indices have been found to decrease. Estimated trough values usually occurred between 10 AM and 2 PM [4–6]. During the nighttime, following sympathetic withdrawal and parasympathetic dominance, these measurements begin to increase, reaching their peak values between 12 AM and 6 AM. These changes, believed to be regulated mainly by the autonomic nervous system, enable the heart to adapt to circadian fluctuations in demand by adjusting both its electrical activities and mechanical function. It is worth noting that not only the Q-T interval, which is known to be significantly affected by heart rate, but also the Q-Tc shows diurnal changes [5]. Even in the patients with permanent implanted ventricular pacemakers because of atrioventricular dissociation [6], clear circadian changes in Q-T interval can still be found. These results suggest that there is a circadian rhythm in the duration of ventricular repolarization itself.

Cardiac Arrhythmias

Ventricular arrhythmias are the main cause of sudden cardiac death and circadian patterns have been extensively studied in recent years [7,8]. Most of the studies, whether based on Holter recordings or Implantable/Defibrillators, have shown that ventricular arrhythmias do have a circadian rhythm, with their peak frequency in the morning and trough during the sleeping hours, similar to most other cardiovascular parameters.

Goldstein et al. [7] examined a subset of patients entered into the Cardiac Arrhythmia Suppression Trial to clarify the relationship between the circadian character of ventricular premature beats and sudden arrhythmic death. They found that there was a cluster of arrhythmic events from 6:00 to 10:00 in the morning. However, they did not found any relationship between the circadian rhythm of ventricular ectopic activity and cardiac mortality, and concluded that the presence of a circadian rhythm in ventricular premature beats is not a predictor of sudden arrhythmic death in patients with a high frequency of this arrhythmia.

Peckova et al. [8] investigated diurnal variation in 6603 out-of-hospital cardiac arrests and found a circadian rhythm in these events with a low incidence at night and two peaks of approximately the same size, one from 8:00 to 11:00 in the morning, the other from 16:00 to 19:00 in the afternoon or early evening. They noted that the evening peak is attributable primarily to the patients found in ventricular fibrillation, whereas arrests associated with other rhythms exhibited a morning peak.

The circadian variations of atrial arrhythmias have been less studied, probably because of their

relative benign nature. Atrial arrhythmias (premature beats, tachycardias, atrial fibrillation and flutter) also appear to exhibit a circadian rhythm following the active-quiescent period (higher frequency in the daytime and lower frequency in the nighttime), with the abnormal atrial foci under the same long-term autonomic regulation as normal pacemaker tissue [9]. However, a study published by Yamashita et al. [10] suggests a unique circadian variation in paroxysmal atrial fibrillation with a nadir around 11:00 in the morning. Further studies are needed to clarify the circadian features of atrial arrhythmias.

Electrophysiological Phenomenon

Sinus node function

Although sinus node function could be monitored by using programmed electrical stimulation through esophageal electrodes, all available data are from invasive studies. It has been found that, sinus node function changes follow the circadian rhythm of the autonomic nervous system [11]. Sinus node recovery time, the main index of sinus node function, follows a circadian rhythm with an acrophase between 12 midnight and 7 AM. Coefficients of variation of sinus node recovery time over 24-hours may be as high as 10% [11,12].

Cardiac refractoriness and conduction

Atrial fibrillation patients are very good models for non-invasively observing the diurnal rhythm of atrioventricular conduction. Such studies have shown that during the night time the frequency of ventricular response is significantly lower than during the day time, implying that the A-V node refractory period is longer and A-V conduction is faster during night [13,14]. The trough value of ventricular response often occurs between 3 and 5 AM, and the peak value occurs between 10 and 12 AM, a pattern consistent with the circadian activities of autonomic nervous system. A significant prolongation of the effective refractory period of the atria and right ventricle in healthy subjects, and even the retrograde Kent bundle in patients with W-P-W syndrome has also been reported [12]. Coefficients of variation were 3–8% over 24 hours. In another study, in patients with dual AV nodal pathways, prolongation of the fast pathway effective refractory period was found at midnight, whereas conduction through the slow pathway followed an unpredictable daily variability [15].

Pacing and defibrillation threshold

Schuchert et al. [16] reported data about the pacing threshold in patients with cardiac pacemakers. They found that the pacing threshold for ventricular capture increased by 5% during the nighttime compared with the daytime. Circadian variation in the electrical stability of the heart, as reflected by the threshold for ventricular fibrillation induced by programmed electrical stimulation, has also been seen. In an animal study reported by Svorc et al. [17] a circadian rhythm of the ventricular fibrillation threshold was found, with the acrophase $= -338$ degrees, the mesor $= 2.58$ mA and the amplitude $= 0.33$ mA. The diurnal variation of the threshold for malignant ventricular arrhythmias may contribute, to some extent, to the uneven distribution of sudden cardiac death within a 24-hours day. Based on recordings from implantable cardioverter-defibrillators, Venditti et al. [18] found that there was a morning peak in defibrillation threshold and a corresponding morning peak in failed first shock frequency. These results suggested that, during the morning hours cardiac electrical instability is increased and, it is easier to introduce ventricular fibrillation but more difficult to stop it [17,18].

Non-Invasive Electrophysiological Measures

Heart rate variability

Heart rate variability (HRV) analysis, based on time domain and frequency domain methods, has proved useful for risk stratification of cardiac patients [19,20]. HRV also has a diurnal rhythm, a result of circadian variations in autonomic nervous system activity [20,21]. Importantly, this rhythm can reflect the sympathetic-parasympathetic autonomic balance [22]. In general, indices of HRV (except for the LF/HF ratio, the ratio of spectral power in the low frequency band to the spectral power in the high frequency band) decrease significantly during the daytime and increase during the nighttime [20–22]. The ratio of LF to HF, which is believed by some to reflect the sympatho-vagal balance, has an inverse rhythm: with a higher level during the daytime and a lower value during the night. In some pathological conditions, such as ischemic cardiac disease, diabetic mellitus, and stroke, which impair autonomic nervous function, the amplitude of the circadian rhythm of HRV can be altered or nearly absent [21,23].

Almost all physiological rhythms are affected by factors, such as age, gender, race, etc., as is the circadian rhythms of HRV. In children under 1 year of age, HRV often show no significant diurnal rhythm, due, it is believed, to the immaturity of autonomic nervous function and increased sleep time compared to older children [22]. Among the very old, reduced power

of the 24-hour circadian rhythm has been found, along with augmented power in an 8-hour period ultradian rhythm. Also, the circadian acrophase was found to be shifted to a later point in the cycle [24]. Gender can also affect circadian rhythm of HRV. In a study published by Yamasaki et al. [20] the low-frequency component of HRV showed high values for the 0800–1200 period in male subjects and the 1200–2400 period in female subjects. Furthermore, under pathological conditions that impair autonomic function, circadian parameters such as mesor (median value) and acrophase, as well as amplitude, can be significantly changed [21,23,25,26]. Lombardi et al. [21] investigated a group of patients with a myocardial infarction, and found that compared with the healthy subjects, circadian rhythm of HRV indices were changed significantly, with lower median value and amplitude, and earlier or later acrophase. Korpelainen et al. [23] reported that, in patients with acute stroke, circadian rhythms of HRV indices were reversibly abolished.

Signal-averaged ECG and ventricular late potentials

The signal-averaged ECG identifies areas of slowed conduction that are a prerequisite for reentrant ventricular arrhythmias. Although the substrate for late potentials identified by the signal-averaged ECG has been assumed to be fixed, some studies suggest that late potentials have a circadian rhythm and may alter with changes in the autonomic tone [27,28]. It is reported [28] that in patients with a history of ventricular fibrillation late potentials appeared significantly more often during the morning hours, especially during phases with heart rate accelerations. The prevalence of positive late potentials was relatively low during the rest of the day.

QT dispersion

QT dispersion calculated from interlead QT variability in a 12-lead ECG provides a simple way to evaluate the repolarization heterogeneity of the ventricular myocardium. Although there have been a large number of studies of Q-T dispersion, few have focused on diurnal changes [29,30]. Yetkin et al. [30] reported that QT dispersion shows diurnal variation with an increase in the morning hours in both patients with coronary artery disease and subjects without coronary artery disease. Manolis et al. [29] found a circadian rhythm of QT dispersion in patients with heart failure with higher values at night and lower during the day time. Manolis et al., however, did not find any day-night differences in subjects without organic heart disease.

T-wave alternans

T-wave alternans is a phenomenon of beat-to-beat variability in the amplitude, morphology, and sometimes polarity of the T-wave. A significant relationship has been found between T-wave alternans and life-threatening arrthymias. Based on limited reports, this phenomenon too shows a circadian variation with higher density during morning hours [31].

Underlying mechanism for the circadian rhythm of the cardiovascular system. The underlying mechanism for circadian rhythms in the cardiovascular system is not yet completely clear. Although most studies confirmed the existence of these circadian variations, it has not been determined whether these changes are associated the "clock" itself. However, there is an excess of arrhythmic event during the morning hours, as mentioned, but if patients get up later, the events will also occur later [32,33]. For this reason, most authors believe that circadian phenomena primarily link to the time schedule of life, but not the clock per se. In that case, it is reasonable to believe that the circadian rhythms of non-invasive EP indices are also linked to wake time or activity levels, although this question has not been systematically studied. Consistent with this hypothesis, it has been shown that there are a series changes in the body soon after waking and commencing activity, which may include a surge in heart rate, blood pressure, plasma catecholamines levels and renin activities [34]. As a result, the arrhythmic threshold is decreased and cardiac electrical instability increased, which bring about the electrophysiologic changes previously described.

Implications. Clinically, we should consider the circadian properties of some cardiac EP measurements when we decide whether or not a result is normal and/or whether it has been changed by an intervention. For example, we often monitor Q-T and Q-Tc intervals in patients treated with amiodarone to detect the prolongation of this index. It would not be reliable, for example, if we compare measurements taken at 7 AM and 5 PM, because even in normal subjects the Q-T values can differ by 30% at different times of the day [35]. Also, it would be not reasonable to compare a short-term heart rate variability result sampled at 10 AM one day with another result sampled at 5 PM on another day. Similarly, the same patient could theoretically be inducible in the early morning and not inducible in an EP study performed in the late afternoon. In high-risk population, a negative EP test result might not demonstrate that this patient is at low risk if the test is performed at a relative "safe" period of the day. Similarly, it has become

clear, that we must consider "time" as a factor when we treat patients, e.g., the anti-arrhythmic medications should cover the early morning hours when there is a higher prevalence of arrhythmic events and sudden cardiac death. It is important to conduct prospective studies of circadian rhythms in electrophysiology to determine which results may be affected by the "clock." Until that time, we must keep in mind that "everything is changing all the time," and try to make test-retest results as comparable as possible by obtaining them at the same time.

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