**Chronotherapy for Coronary Heart Disease**

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**SUMMARY**

Traditionally the therapy for coronary heart disease has been focused on the “how-to” problem. However, the clustering of cardiovascular events around the specific time of the day has been clarified. To solve the problems of the clustering would give us the clue to treat the coronary heart disease timely and in time. Therefore, the research has been stressed to solve “when-to” problem.

The circadian variabilities in coronary heart disease has been clarified to be the function of the biologic time. Therefore, three problems were discussed in this paper. 1) The circadian variabilities in biology should be assessed based on the biologic zero hour rather than the mid-night of the mechanical clock. Our concept of the biologic zero hours has been proposed to answer this problem. 2) Daily health care with circadian order and harmony for the prevention of the coronary risk factors should be recommended as the prevention of the acute coronary risk factors as the trigger mechanism of the cardiovascular events. 3) The chronotherapy to chronic coronary risk factors such as hypertension was discussed. In hypertension the anti-hypertensive therapy should be customized individually adjusting the circadian variability of blood pressure with the proper selection of agents and time of the administration. (Jpn Heart J 1997; 38: 607–616)

**Key words:** Circadian variability, Biologic zero time, Daily health care, Chronotherapy

In traditional cardiology, cardiac studies of coronary heart disease have focused on “how-to” problems. However, according to recent developments in chronobiology and medicine, the following issues have been pointed out. First, the clustering of the incidence of coronary heart events around a specific time of the day has been repeatedly shown by many epidemiologic associated changes throughout the world. Therefore, this clustering problem may provide a clue to preventing and treating problems. Second, functional changes in the heart should be assessed as a function of time, since the prevention and therapy of coronary...
heart disease have aimed to preserve or restore cardiac function. This time axis has been shown to comprise variable components from less than 1 min. to the whole life cycle. Furthermore, the long-term variability of data such as circadian cycle has been pointed out to have clinical significance in diagnosis and therapy in addition to short-term variability. Third, the clustering of coronary risk factors has also been observed in a specific patient. Many of these factors are inter-related. Chronic sympathetic over-activity has been proposed as a common denominator. Coronary risk factors such as hypertension are known to be time associated changes, including autonomic nervous system activity.

In order to assess these "when-to" problems in coronary heart disease, the following four components have been developed: 1) instrumentation for long-term biologic monitoring, 2) software to quantitate these time associated variables, 3) a large database of the cardiovascular system and 4) therapeutic and preventive tools to control the disharmony of cardiac function in coronary heart disease as "chronotherapy".

The objective of this article is to review some aspects in the chronotherapy of coronary heart disease, based mainly on our data.

**What Time is the "Biologic Zero Hour" to Assess the Circadian Rhythm of Blood Pressure in Hypertension?**

The idea of a biologic clock was developed during research on the circadian rhythm. The circadian rhythm is a ubiquitous phenomena present in all living organisms and is found at all levels of organization from subcellular particles to human beings. Circadian rhythm has been most extensively studied in biologic rhythms which have a variable time span, and has been shown to be composed of both genetic and environmental factors.

Blood pressure in hypertension is also thought to be regulated by the circadian rhythm, since every component to regulate blood pressure is under control of the biologic clock. Ambulatory blood pressure monitoring (ABPM) has been accepted as a useful clinical method with which to monitor the circadian variability of blood pressure. Most ABPM studies in the literature have been assessed based on the mechanical clock as the reference time, even though they wanted to assess the circadian biologic clock mechanism in hypertension. If we accept the theory of the biologic clock mechanism, we should not rely on the mechanical clock as a reference time.

Our concept of "biologic zero hour" as the reference time has been accepted to assess the circadian variability of blood pressure as the biologic clock. The sleep-awake and/or activity-rest cycles as individualized profiles are important for the recognition of circadian variability of blood pressure which shows
Figure 1. Circadian profiles of systolic blood pressure taking zero hour by the clock (a), awakening (b), physical activity (c), and mid-sleeping time (d) in dipper and non-dipper.

intra- and interindividual variabilities.

Nocturnal dipping and non-dipping blood pressure patterns which have been assessed since ABPM able us to approach this problem clinically. The impact of nocturnal hypertension is well appreciated. Moreover, elevated nocturnal BP profiles are associated with an increased risk of hypertension-induced cardiac, cerebral and renal organ damage.7,8) The prospective epidemiologic studies are now in progress throughout the world to confirm these data.

Therefore, individualized circadian variations in blood pressure in essential hypertension using biologic zero hour was assessed, paying special attention to dipper and non-dipper profiles of blood pressure (Figure 1).9) In systolic blood pressure, there were clearly significant differences in the circadian blood pressure variation between dipper and non-dipper, regardless of the differences in the zero
Figure 2. Circadian profiles of heart rate taking zero hour by the clock (a), awakening (b), physical activity (c), and mid-sleeping time (d) in dipper and non-dipper.

hours. In the dipper, the top panel shows the circadian variability of systolic blood pressure assessed when zero hour was considered to be 24:00 by the mechanical clock. Systolic blood pressure exhibited an abrupt decrease in pressure after midnight. It reached the circadian trough and then increased steeply to the peak of the variation during the day time activity span.

The circadian variation of systolic blood pressure using the diary time of individual patients showed a similar circadian variation as that of the clock time. The morning rise in pressure in the diary time seemed to be steeper than that of the clock time. The circadian profile of the midsleeping time clearly differed from the other profiles. The circadian trough was wider and the slope in the morning rise was steeper in the mid-sleeping time than the clock time. In the non-dipper, however, the circadian pattern was quite similar no matter how we obtained the
different zero hour as the zero reference. Therefore, in the non-dipper the circadian profile of blood pressure was completely different for all time settings compared with those of dipper. In diastolic pressure the discordance among four timings was quite similar to those in systolic blood pressure.

The circadian profile of heart rate in hypertension was also assessed in a similar manner (Figure 2). In the clock time the profile of the heart rate of the dipper reached a maximum during day-active time span, reached a trough during night-resting span and increased again in the morning. The heart rate profile based on the physical activity level was quite similar to that in the diary time. However, the profile based on the time of mid-sleeping exhibited a wider trough and this profile was clearly different from those based on the clock time.

The circadian variation of physical activity was quite similar between dipper and non-dipper no matter which timing we took as the biologic zero hour. These changes were quite different from those in blood pressure.

Therefore, the acceleration of heart rate, rather than blood pressure, might be more contributory to the genesis of cardiovascular events in the morning as a major component of the morning surge to form the trigger mechanism of coronary vascular events.

**DAILY HEALTH CARE WITH CIRCADIAN ORDER AND HARMONY AS PREVENTION OF RISK FACTORS**

A life style modification approach provides a means for preventing coronary heart disease while improving important cardiovascular risk factors such as hypertension, dyslipidemia, blood glucose/insulin level, obesity and fat distribution. Life style modifications rely basically on the daily health care of each individual. All efforts for health care will be successful only if we can begin, live and end each day with circadian order and harmony. Namely, regular and recurrent circadian rhythms counterbalance the irregular and arrhythmic daily stress of body and mind which are difficult to avoid in today's highly industrialized countries.

In healthy nurses in our hospital, blood pressure and heart rate were monitored every 30 min. and the number of movements of the upper limb was determined using a motormeter during 1 min. period for 48 hours on successive day and night shifts. The results of comparisons of the circadian rhythms of the blood pressure and heart rate between the day shift and the night shift are shown in Figure 3. The pressure decreased during the period of activity on off-duty but increased during the periods on duty. The circadian variations in the blood pressure were rapidly adapted to changes in the time of duty (Figure 3, left). The heart rate showed similar circadian variations to blood pressure (Figure 3, right).
These data indicate that sleep-wake and rest-activity cycles have strong influences on the biologic circadian parameters in shift work positions.

Presently, in highly industrialized countries, about 10% of the active shift workers are involved in night and shift work. Based on many chronobiologic studies it is no longer possible to state that anyone is able to perform any task at any time of day or night with similar efficiency. It is well documented that the accident risk has a circadian rhythmicity, with a prominent nocturnal peak.

Based on the results of night and shift work and transmeridian and space flights and our data we can fairly confidently presume that we should try to regulate each day by trying each day at the same hour to maintain our biologic clock. This daily health care is the basis for a life style to prevent and treat hypertension.

**CHRONOTHERAPY TO CHRONIC CORONARY RISK FACTORS SUCH AS HYPERTENSION**

A strong association between hypertension and other coronary risk factors is known. Therefore, out-of-office blood pressure monitoring with an ambulatory pressure monitoring device (ABPM) has become an important part of clinical hypertension assessment and management. This assessment greatly enhances the
clinician’s understanding of BP behavior in patients and aids in diagnosis and therapeutic decision making. Several diagnostic advantages with ABPM have actually been discovered as a result of findings such as night non-dipper in hypertensives.7)

Furthermore, the therapeutic implications of circadian rhythm in blood pressure have been assessed.4) Namely, at certain times of the day the pressure level derived from the conventional dosing schedule would likely be lower or higher than the actual BP, which should be controlled within the reference range. During night time, the drug level could be either greater or smaller than the requirement relative to the pathological biologic need. Thus, the theoretical means of improving the blood pressure level to vary the medication level in synchrony with the circadian pattern of blood pressure has been developed.8,14,15)

Chronobiologic observations lead to the hypothesis that the response of an organism to a drug may depend on the hour of the administration. If the time of administration of an anti-hypertensive drug influences the kinetics and its mode of action, chronotherapy for hypertension is concerned with the influence of the timing of a treatment on its efficacy in hypertensives. Chronotherapy for hypertension leads to the timely use of an anti-hypertensive agent in the treatment of hypertension and aims to improve the efficacy and/or tolerance of drugs by timing their administration.

As shown in Tables I and II,4) the chronopharmacodynamics and kinetics of

### Table I. Chronopharmacodynamics of Cardiovascular Active Drugs in Humans

<table>
<thead>
<tr>
<th>β-Blockers</th>
<th>Calcium channel blockers</th>
<th>Nitrates</th>
<th>Glycosides</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>Diltiazem</td>
<td>Isoboride dinitrate</td>
<td>Digoxin</td>
<td>Dipyridamol</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Isoboride 5-mononitrate</td>
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<td>Metildigoxin</td>
<td>Potassium chloride</td>
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<tr>
<td>Verapamil</td>
<td>(immediate and sustained release)</td>
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### Table II. Chronopharmacokinetics of Cardiovascular Active Drugs in Humans

<table>
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<tr>
<th>β-Blockers</th>
<th>Calcium channel blockers</th>
<th>ACE inhibitors</th>
<th>Diuretics</th>
<th>Nitrates</th>
<th>Others</th>
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</thead>
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<td>Acebutolol</td>
<td>Amlodipine</td>
<td>Captopril</td>
<td>Hydrochlorothiazide</td>
<td>Glyceryl trinitrate</td>
<td>Clonidine</td>
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<tr>
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<td>Enalapril</td>
<td>Indapamide</td>
<td>Isoboride dinitrate</td>
<td>Prazosin</td>
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<tr>
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<td>Nisoldipine</td>
<td></td>
<td>Pretanide</td>
<td>Isoboride 5-mononitrate</td>
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<td>Nittendipine</td>
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<tr>
<td>Mepindolol</td>
<td>Verapamil</td>
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<td>Sotalol</td>
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## Figure 4

The morning rise in blood pressure before and after treatment in dipper and non-dipper hypertensive patients with diltiazem-retard and ordinary diltiazem. Data points are mean ± SD. *p < 0.05; **p < 0.01, before vs. after treatment.
Chronotherapeutic studies were performed in our hospital as follows. In order to identify differences in the patterns of efficacy and duration of effect by diltiazem given in different dosage forms and schedules (Figure 4). Blood pressure and heart rate were monitored before and after treatment by ambulatory blood pressure monitoring for 48 hours every 30 min. Patients were divided into 4 groups—nocturnal BP dippers and nondippers, with two different formulations of diltiazem. In dipper hypertension, diltiazem-retard at 08:00 had the most marked antihypertensive effects during night-time rest. Diltiazem-retard at 19:00 exerted the greatest effect during daytime activity with inhibition of the morning BP rise. Ordinary diltiazem (t.i.d.) had the best effect during daytime activity. However, in non-dipper hypertensive patients, this ordinary diltiazem (t.i.d.) had the most pronounced antihypertensive effects during the nightly rest span.
Evening medication with diltiazem retard appears to be more efficacious than the other dosage schedules.

Furthermore, the efficacy in the differences by morning versus evening administration in antihypertensive therapy has been tried with great success.\textsuperscript{4,16,17} In our recent study,\textsuperscript{17} the efficacy of imidapril was assessed to identify the differences in the patterns of efficacy and duration of effects administered either in the morning or evening in dipper and non-dipper in essential hypertension (Figure 5). Evening medication with imidapril appears to be more efficacious than morning medication in dipper hypertension, whereas the opposite appears to prevail in non-dipper hypertension.

Therefore, chronotherapy for hypertension has been accepted clinically. This basic idea can be applied to any of the coronary risks since they have been assessed as chronorisks.\textsuperscript{13}

\textbf{REFERENCES}