Chronobiology and Chronotherapeutics Applications to Cardiovascular Medicine
Michael H. Smolensky

The concept of homeostasis, ie, constancy of the milieu interne, has dominated the teaching, research, and practice of medicine during the 20th century. According to this theory, biologic functions and processes are maintained in relative constancy over time. The emerging concepts of chronobiology, the scientific discipline of biologic rhythm study, and the findings from research in this field challenge the construct of homeostasis. Epidemiology studies document that the occurrence and exacerbation of many human diseases vary predictably in time over 24 h, the menstrual cycle, and year due to underlying rhythms of corresponding period. Advances in the chronobiology of cardiovascular disease have proceeded rapidly during the past decade and have influenced the manner in which diagnostic procedures are conducted and interpreted. Twenty-four-hour ambulatory blood pressure (BP) monitoring and Holter monitoring reveal the marked circadian (24-h) rhythms in BP in hypertensive patients and electrocardiographic events in patients with ischemic heart disease. Homeostatically devised pharmacotherapies, ie, medications designed to ensure constant drug levels over time, may be inadequate to optimally control diseases whose courses vary in risk or severity during the 24-h period. Chronotherapies—medications formulated to deliver varying amounts of drug at different times during the 24 h period to correlate with biologic need—theoretically could offer improved efficacy. A chronotherapy for cardiovascular disease already exists in the form of the evening administration for lipid-lowering medications. The chronotherapy for hypertension and of ischemic heart disease is forthcoming. Am J Hypertens 1996;9:115-21s

KEY WORDS: Chronobiology, chronotherapeutics, hypertension, ischemic heart disease, treatment, chronopharmacology, circadian rhythm.

The concept of homeostasis, which stipulates that there is constancy of the milieu interne, is a most powerful construct in biology, and has influenced not only the teaching and understanding of the medical sciences but also the practice of clinical medicine. According to this concept, the risk of the occurrence and exacerbation of disease is independent of the time of day, day of the month, and month of the year as is the response of patients to diagnostic tests and medications. However, new findings from the field of biologic rhythm study (chronobiology) challenge the concept of homeostasis, as well as many of the assumptions and procedures of clinical medicine based upon its tenets. It is now recognized that most—if not all—human functions are precisely organized in time as biologic rhythms, whose time frames comprise periods of 24 h, weeks, months, or even years (Table 1). The systems of all living things—plants and animals—are so organized.1-5

Most physicians, nurses, and pharmacists are unfamiliar with the field of chronobiology—the scientific discipline concerned with the definition, mechanisms, and significance of the so-called biologic time structure—because the teaching of biology in schools of...
Major rhythmic components, and circadian rhythms. Low frequency rhythms include 7-day (circaseptan), monthly (circamensual), and 1-year (circannual) rhythms.

Domains and regions [named according to frequency (f) criteria] delineated according to reciprocal f, ie, period (T) of function approximating rhythm. Several variables examined thus far exhibit statistically significant components in several spectral domains. Examples of rhythms include metabolic processes, generally.

<table>
<thead>
<tr>
<th>Domain</th>
<th>High Frequency (T &lt; 0.5 h)</th>
<th>Medial Frequency (0.5 h &lt; T &lt; 6 days)</th>
<th>Low Frequency (T &gt; 6 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major rhythmic</td>
<td>τ ~ 0.1 sec</td>
<td>Ultradian (0.5 h &lt; τ &lt; 20 h)</td>
<td>Circaseptan (τ ~ 7 days)</td>
</tr>
<tr>
<td>components</td>
<td>τ ~ 1 sec</td>
<td>Circadian (20 h &lt; τ &lt; 28 h)</td>
<td>Circamensual (τ ~ 30 days)</td>
</tr>
<tr>
<td>Examples of rhythms</td>
<td>Electroencephalogram</td>
<td>Infadian (28 h &lt; τ &lt; 6 days)</td>
<td>Circannual (τ ~ 1 year)</td>
</tr>
<tr>
<td></td>
<td>Electrocardiogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Respiration</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reproduced with permission from Halberg F.6

Several variables examined thus far exhibit statistically significant components in several spectral domains. High frequency rhythms (τ symbolizes period and mathematically equals 1/frequency) in the range of ≤ 1 sec are exemplified in the tracings of the electrocardiogram and electroencephalogram. Medial frequencies include ultradian rhythms, exemplified by pulsatile hormonal secretions and progression of sleep stages, and circadian rhythms. Low frequency rhythms include 7-day (circaseptan), monthly (circamensual), and 1-year (circannual) rhythms.

Domains and regions [named according to frequency (f) criteria] delineated according to reciprocal f, ie, period (τ) of function approximating rhythm. Several variables examined thus far exhibit statistically significant components in several spectral domains.

HUMAN CHRONOBIOLOGY—CONCEPTS AND PRINCIPLES

Before addressing the impact of chronobiology on the practice of medicine, particularly in terms of cardiovascular disease, it is necessary to first define key terms and concepts that are fundamental to this new science.6,7

A biologic rhythm is a self-sustaining oscillation with the period, that is, the amount of time between each repetition, being basically unvarying under normal conditions. Biologic rhythms are describable by a specific set of characteristics (Figure 1).8 The first is the period, for example, 24 h or 28 days. One of the most important bioperiodicities in medicine is the circadian rhythm. Almost every endpoint used in the diagnosis of human disease and the assessment of treatment outcomes varies in a systemic manner during each 24-h period. A second defining characteristic is amplitude—the predictable variability over time ascribable to rhythmicity. Some circadian rhythms, such as those of body temperature and heart rate, are of relatively low amplitude; others are of quite high amplitude, such as those of plasma cortisol, epinephrine, and lymphocyte number. A third characteristic is the level (baseline) around which the predictable variability in time is manifested. Finally, a rhythm is characterized by its phasing, that is, the occurrence of the peak and trough values with reference to a given time scale (eg, 24 h, or a month in the case of the menstrual cycle). Collectively, chronobiologists refer to the intricate rhythmic organization of life’s functions and processes as the biologic time structure.

Initially, many classically trained biologists believed that rhythms were the result of conditioning responses of the body to cyclic phenomena presented by the environment.9 This, however, is not the case. Through genetic transmission, life forms inherit specific clock mechanisms that drive observable biologic rhythms.10-12 The period and phasing of rhythms are coordinated by pacemaker clocks that are located at various levels of biologic organization, with those located in the brain believed to be the most important.13,14 Human circadian clocks are set or reset each day by environmental time cues, termed “synchronizers,” the most dominant one being the daily timing of lights on and off in conjunction with one’s wake-sleep routine.15,16 The circadian rhythms of persons dwelling under experimental conditions devoid of time cues, such as in caves or special study bunkers, continue. In the absence of normal social and environmental time cues, the biologic clocks tend to free-run, that is, their circadian period becomes slightly longer or shorter than 24.0 h, which is the norm in the usual environment.15-17 Under constant environmental conditions, the phase-relationships between all the body’s circadian processes and functions become scrambled and desynchronized from normal associations.18 This type of phenomenon, de-
synchronization of the circadian time structure, is experienced temporarily by persons who suddenly undergo alteration of their activity-sleep cycle due to shift-work rotation or rapid displacement across several time zones by high-speed aircraft; the latter is termed jet lag. The observation that biologic rhythms persist—although with a period different from 24.0 h—in human and other organisms when the environment is devoid of time cues, as well as phase shift with change in the sleep-wake routine, is evidence that rhythms are not simply conditioned responses to 24-h environmental cycles.

Although the biologic time structure is genetic in origin, its expression may be influenced by several factors. For example, in most healthy persons, the inherited amplitude of the endogenous circadian rhythm in blood pressure (BP) is relatively small in magnitude. However, day-night differences in activity and stress amplify the biologic variability; in normal persons, the peak-to-trough variation in systolic and diastolic pressures commonly amounts to 15 to 25 mm Hg. Disease can also affect the expression and characteristics of the circadian rhythm of BP. In hypertensive patients, both the 24-h mean level and amplitude of the circadian BP rhythm may be altered; in some cases the rhythm might be obliterated. The 24-h BP pattern of patients with essential hypertension is characterized by the occurrence of a peak during daytime activity and a dip to a trough during nighttime sleep. In patients with secondary forms of hypertension, the magnitude of the sleep-time dip is often moderated; indeed, there may be an absence of a nocturnal dip or even an increase in BP over daytime values, resulting in an altered phasing of the rhythm.

In everyday life, the phasing of human circadian clocks and rhythms is set, or said to be synchronized, primarily by the sleep-in-darkness—activity-in-light, 24-h routine. Shift workers assigned to night duty adhere to a different sleep-activity routine than when assigned to days. The timing of the peak and trough of circadian rhythms, with reference to external clock time, changes in conjunction with shifts in the synchronizing sleep-wake cycle. For example, in personnel working the morning shift from 06:00 to 14:00, the peak of the circadian rhythm in systolic and diastolic BP occurs early in the afternoon—about 14:00—at the end of the work shift. When working nights from 22:00 to 06:00, however, the peak of the BP rhythms now occurs at a different time of day, 06:00, but again at the end of this work shift (Figure 3). Although the clock-time occurrence of the circadian peak of the BP rhythms differs between the day and night work-shift schedules, it is comparably timed when expressed in reference to the sleep-wake cycle, ie, the peak in BP occurs at the end of the respective morning and night work shifts. Thus, the sleep-wake cycle is a useful reference for estimating the phasing of various circadian functions and processes. This point is important for the proper application of chronobiology in medicine, when interpreting diagnostic test results that might be influenced by high-amplitude circadian rhythms or when prescribing medications to meet circadian-rhythm determinants, for example.

CIRCADIAN RHYTHMS IN THE OCCURRENCE AND SEVERITY OF DISEASE

The physiology and biochemistry of human beings vary greatly during the 24-h period. Circadian rhythms in critical bioprocesses give rise to prominent day-night patterns in the occurrence and severity of a large number of human diseases and their symptoms. Among these are the following:

- Allergic rhinitis, with the major symptoms of sneezing, runny nose, and stuffy nose being worse on arising from nighttime sleep than during the middle of the daytime activity span.
- Asthma, with the risk of dyspnea, wheezing, and other symptoms of acute exacerbation being at least 100-fold greater during nighttime sleep than during daytime activity.
Essential Hypertension (n = 30)

- Systolic BP (mm Hg)
- Diastolic BP (mm Hg)
- Heart rate (bpm)

Time

180
160
140
120
100
80
60
40
20
0

FIGURE 2. Circadian rhythm in heart rate plus systolic and diastolic blood pressure (BP) (mean ± 1 SD) in 30 diurnally active essential hypertensives (top) and 30 renal hypertensives (bottom). Essential hypertensives exhibited rhythms with afternoon peaks and nocturnal (sleeptime) troughs. BP rhythms were differently phased in patients with hypertension secondary to renal disease. They peaked during nighttime sleep with lowest values during daytime activity. The heart rate circadian rhythm, with afternoon peak, was preserved. Reproduced with permission from Portaluppi F et al.26

Chronic Renal Failure (n = 30)

- Systolic BP (mm Hg)
- Diastolic BP (mm Hg)
- Heart rate (bpm)

Time

170
150
130
110
90
70
50
30
10
0

FIGURE 3. Twenty-four-hour pattern in systolic and diastolic blood pressure (BP) of 17 rotating shift personnel assessed while working morning (-06:00 to -14:00, open circles) and night (-22:00 to -06:00, closed circles) schedules. On the morning shift, BP peaked -14:00, at the end of the work period; it was lowest during nighttime sleep (-02:00). On the night shift, BP peaked at a different clock time, -06:00, but nonetheless, at the end of the work period. Reproduced with permission from Baumgart P.21

- Arthritis, with the signs and symptoms of rheumatoid arthritis being most intense at the time of awakening from nighttime sleep and those of osteoarthritis being worse around the middle to later portion of the daytime activity period.29,30

- Peptic ulcer disease, with the pain of the upper gastrointestinal (GI) tract at initial onset of disease or on its recurrence typically developing or worsening during the early hours of sleep.31

- Epilepsy, with the occurrence of overt seizures often restricted to particular times of the day or night.32

- Migraine, with headache being more common in onset or exacerbation in the morning when awakening from nighttime sleep or during the start of daytime activity.33

- Exertional angina, with ischemic events (chest pain and ST-segment depression) being most common during the initial hours of the daily activity span.34

- Prinzmetal's angina, with the manifestation of ST-segment aberrations mainly restricted to the sleep period.35

- Myocardial infarction (MI), with morbidity and mortality being approximately three-fold greater during the initial hours of the daily activity span than in the evening.36,37

- Stroke, with elevated incidence of the thrombotic form being most common at the beginning of the activity period and that of the hemorrhagic form being most common late in the evening.38

These are but a few examples of diseases that exhibit large variations in their occurrence or intensity over the 24-h period (Figure 4).2,27,28,35 For the sake of brevity, only chronobiologic examples relating to the circadian time structure have been highlighted. Important predictable-in-time alterations in human physiology and disease status occur over other time domains, such as the week, menstrual cycle, and year.2
BIOLOGIC RHYTHMS AND THE DIAGNOSIS OF DISEASE

Diagnostic procedures are commonly conducted and interpreted without consideration of possible chronobiologic influences. According to the construct of homeostasis, the timing of the majority of medical tests should be of little consequence. The results of various research investigations, as well as clinical experiences, however, fail to substantiate this expectation. For example, the airway patency of asthma patients varies greatly throughout the 24 h day; it is best during the daytime, during regular clinic hours, and poorest at night. The peak expiratory flow and 1-sec forced expiratory volume, as quantified by spirometry, are known to vary by 25% in mildly affected patients and as much as 50% in more severe patients. On average, the response of allergic patients to cutaneous antigen testing varies three-fold during the 24 h day; cutaneous reactivity is lowest in the morning around the time when daytime activity commences and greatest during the evening around bedtime. The results of certain laboratory procedures are also influenced by the circadian time at which they are conducted. Blood concentrations of cortisol and many other hormones exhibit high-amplitude circadian rhythmicity; thus, the time blood samples are drawn must be considered when interpreting laboratory reports. In this regard, so-called time-qualified-for-rhythms reference values are more sensitive than are conventional ones (Figure 5). Ambulatory patient assessment devices, such as Holter and BP monitors, clearly reveal the prominent 24-h rhythmicity in ischemia and systolic and diastolic BP.

The reference values used in making the differential diagnosis of normotension versus hypertension are often based on single, daytime BP measurements of presumably diurnally active normal persons. Physicians who regularly depend on ambulatory BP monitoring for the diagnosis of hypertension have first-hand knowledge of the extent of the circadian variation in BP and thus can appreciate the potential impact of chronobiology on the practice of clinical medicine. Nonetheless, of practical clinical concern is determining how to best use and interpret the 24-h BP data, especially with the conventional norms now used. Twenty-four-hour ambulatory BP monitoring provides a great deal more additional information about a patient's BP than once-a-day office assessment. The clinical implications of new chronobiologic endpoints based on 24-h ambulatory BP monitoring are currently under study, including:

- Daytime, nighttime, and 24-h BP means;
- Daytime, nighttime, and 24-h BP loads (the percentage of time that systolic and diastolic pressures are greater than specified limits);
- Morning BP surge (the rate of rise in BP between the termination of nighttime sleep and commencement of daytime activity); and
- Presence or absence of BP dipping during sleep.

Moreover, knowledge of the circadian patterning
of BP raises new questions, not only about the underlying rhythm-dependent mechanisms of hypertension but the pharmacotherapy of its management as well.11,42

**BIOLeGIC RHYTHMS AND THE BEHAVIOR OF MEDICATIONS**

Biologic rhythms can affect the behavior and effects of medications. For example, large-amplitude, 24-h bioperiodicities in gastric hydrogen-ion concentration, stomach emptying, and blood flow to the GI tract, liver, and kidney can significantly influence drug kinetics (ie, rate and extent of drug absorption; area under the time-drug concentration curve; and elimination rate).2,43-46 Rhythms in cellular and subcellular functions in drug-targeted tissues can also significantly influence therapeutic effects.2,43-46

 Chronopharmacology is the investigative science concerned with the elucidation of biologic rhythm dependencies of medications.2,43-46 Chronopharmacologic studies have yielded new insight and concepts germane to clinical medicine.

 Chronokinetics refers to administration time (according to circadian or other bioperiodicities) differences in the rate and extent of drug absorption, distribution, and elimination.2,46 Chronokinetic phenomena are related to the peculiarities of the dosage form, delivery technology, and parent drug. The chronokinetics of many different types of medications have already been demonstrated, including the benzodiazepines, β-antagonists and agonists, theophyllines, and nonsteroidal antiinflammatory drugs (NSAIDs), to mention but a few (Figure 6).46-51

 Chronesthesia refers to administration time dependent differences—according to circadian or other bi-periodic rhythms—in the desired and undesired effects of medications.2,44,45 Chronesthesies result from rhythms in receptor number or conformation, rate-limiting steps in metabolic pathways, and the free-to-bound fraction of medications. Chronesthesies are known for analgesics, anticoagulants, β-antagonists and agonists, bronchodilators, corticosteroids, NSAIDs, and others (Figure 7).2,48,52-55 In addition, chronesthesies give rise to rhythms in dose-response relationships, as has been documented for theophylline, β-blockers, and analgesic medications.56

 Chronotoxicity refers specifically to predictable-in-time variation in the undesired effect of medications as a function of their biologic time of administration. Significant circadian chronotoxicities are known to exist, particularly among antitumor agents.57

 The fundamental strategy underlying the pharmacotherapy of human disease today involves the application of drug-delivery technologies and treatment schedules to achieve the homeostatic goal of constancy of blood and tissue drug levels over time. It is assumed that the need for medication by patients is unvarying over the 24 h and that constancy of drug level translates directly into constancy of drug effect. Knowledge of day-night and other predictable-in-time variations in the intensity of symptoms or risk of disease, coupled with evidence of circadian rhythms that affect the kinetics, effects, and safety of medications, constitute the rationale for a new pharmacologic approach to treatment.

 **CHRONOTHERAPEUTICS—WHAT, WHEN, AND HOW**

 Chronotherapeutics is the administration of medications using modern drug delivery technologies in accordance with biologic rhythm considerations—chronokinetics, chronesthesies, and chronotoxicity—as an attempt to optimize desired effects and to potentially minimize or avert undesired ones.2,43-45 Most importantly, chronotherapeutics takes into account predictable-in-time variations in the risk, manifestation, and intensification of diseases that are due to underlying rhythms. Chronotherapeutics is especially relevant when:

- The risk or intensity of symptoms vary predictably over time (eg, 24 h day and menstrual cycle). Such variations characterize allergic rhinitis, arthritis, asthma, angina, myocardial infarction, stroke, peptic ulcer disease, and uterine contractions in preterm labor, to mention but a few examples.

- It is known that the therapeutic-to-toxicity ratio of a medication varies predictably according to chronobiologic determinants. This is best exemplified by NSAIDs and antitumor medications.

- The kinetics and dynamics of a medication are known to be biologic rhythm-dependent. This is the
case for several antihistamines, bronchodilators, anticoagulants, antihypertensives, antiarrhythmics, antihyperlipidemics, and NSAIDs.

- The goal of pharmacotherapy is hormonal substitution to mimic the temporal pattern of endocrine rhythms documented in healthy individuals. This has involved synthetic corticosteroid and reproductive hormones thus far.

- The desired effect of a medication can be achieved or optimized only by dosing in a time-modulated manner, as exemplified by the pulsatile dosing regimen of luteinizing hormone releasing hormone using ambulatory pumps for the treatment of hypothalamic amenorrhea.

- The morning daily or alternate-day dosing strategy for methylprednisolone (Medrol, Upjohn, Kalamazoo, MI) that became popular during the 1960s is considered to be the first chronotherapy incorporated into clinical medicine. Other commonly unacknowledged chronotherapies now being prescribed include:
  - Chronotherapy of peptic ulcer disease with evening, once-daily dosing of H₂-receptor antagonists or morning chronotherapy of proton-pump antagonists.
  - Evening, once-daily chronotherapy of asthma with specially formulated theophylline and β-agonist bronchodilator tablets or capsules.
  - Evening administration of lipid- and cholesterol-lowering medications, taking into account the circadian rhythm of their synthesis.
  - Unequal day-night, or nighttime-only, dosing of H₂-receptor antagonist medication for the management of the morning symptoms of allergic rhinitis.
  - Use of ambulatory, programmable infusion pumps to time the release of antitumor medications according to biologic rhythms as a means to minimize toxicity and enhance dose intensity in the treatment of cancer.
  - Use of programmable-in-time, drug-delivery devices to administer tocolytic agents according to the circadian rhythm in uterine contractions for the purpose of minimizing the risk of preterm birth.
  - Use of programmable-in-time ambulatory infusion pumps to administer luteinizing hormone releasing hormone in 90-min cycles for the treatment of hypothalamic amenorrhea.

THE CHRONOBIOLOGY AND CHRONOTHERAPY OF CARDIOVASCULAR DISEASE

Day-night patterns have been documented for BP, arrhythmias, angina, myocardial infarction, and stroke, among other cardiovascular maladies. The risk of ischemic events is highest during the first few hours of the daily activity span and lowest during sleep. This temporal pattern is dependent on both endogenous 24-h rhythms and environmental triggering events. The former include circadian rhythms in sympathetic drive, blood coagulation, BP, coronary blood flow, and myocardial oxygen supply versus demand. Environmental triggers include the morning-time change from the supine to upright post-
ture, commencement of daily activity, and the sudden increase in mental and emotional loads associated with work onset or other demanding morning tasks.

The initial homeostatic approach to managing the morning risk of ischemic heart disease was to ensure that patients were compliant in scheduling their conventional, sustained-released β-blockers and other cardioprotective medications before bedtime, the goal being to sustain therapeutic benefit through the subsequent morning. More recently, clinicians have relied upon once-a-day, ultra-slow-release drug delivery systems to attain relatively constant levels of medication throughout the entire 24-h dosing interval.

During the past few years, several pharmaceutical companies have begun working on cardiovascular chronotherapies. One such product, controlled onset extended release verapamil (verapamil COER-24), is a chronotherapy candidate for both essential hypertension and angina.4,6 Verapamil COER-24 is specifically designed for bedtime dosing so that elevated verapamil levels are achieved in the morning, at which time BP begins its surge to high levels in many individuals. During the remainder of the 24-h dosing interval, drug levels are designed to vary in a prescribed manner to correlate with the usual circadian rhythm in BP; ie, the verapamil drug level is maintained at higher levels during the hours of daytime activity than during nighttime sleep.

**SUMMARY**

Medical chronobiology focuses on understanding how biological rhythms influence the diagnosis, manifestation, and treatment of human disease. The biology of human beings is not constant over the 24 h day, menstrual cycle, or year, as is suggested by the concept of homeostasis. Instead, it varies predictably according to defined and inherited bioperiodicities. Thus, the risk of the occurrence or exacerbation of many diseases varies in a rather predictable manner during the 24 h. Much of the discussion in this paper has focused on the differences between homeostasis and chronobiology. Many scientists and practitioners have difficulty in rectifying the two concepts—constancy versus rhythmicity—in biologic function. In reality, the two are compatible; the set points that govern the activation and operation of homeostatic mechanisms undergo precise rhythmic variation over the 24-h day, menstrual cycle, and year. Homeostatic mechanisms are responsible for the moment-to-moment regulation of the internal environment, while chronobiologic mechanisms are responsible for pre-
paring the organism to cope with predictable-in-time challenges associated with work-rest, environmental, and reproductive cycles.

Traditionally, medicine has been concerned with addressing a specific set of questions—What is troubling the patient? Why and how should the patient be treated? What dosage of medication should be prescribed for the patient? Today, the answers to another set of important questions pertaining to when—When is the risk of disease greatest? When are symptoms most troublesome? When are diagnostic tests to be conducted? When are treatments to be timed?—bear increasing relevance. The past decade has witnessed very rapid advances in the field of medical chronobiology and chronotherapeutics. These are now having an impact on the clinical practice of medicine.

REFERENCES


60. Chiverton SG, Howden CW, Burget DW, Hunt RH: Omeprazole (20 mg) daily given in the morning or evening: a comparison of effects on gastric acidity, and plasma gastrin and omeprazole concentrations. Aliment Pharmacol Ther 1992;6:103–111.


