FROM CHRONORISK TO CHRONOTHERAPY, WITH FOCUS ON THE CARDIOVASCULAR SYSTEM

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ОТ ХРОНОРИСКА К ХРОНОТЕРАПИИ С АКЦЕНТОМ НА СЕРДЕЧНО-СОСУДИСТУЮ СИСТЕМУ

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An organism's response to a given stimulus changes predictably depending on the time of its administration, due in large part to the endogenous circadian system. Such changes in susceptibility to a wide variety of stimuli led to the concept of chronorisk to reflect the hours of changing resistance to external agents. Chronorisk also constitutes the foundation for the fields of chronotherapy and chronopharmacology, as circadian rhythms affect all aspects of pharmacology, from absorption and distribution to metabolism and excretion. Recent advances in chronobiology indicated how circadian disruption relates to increased disease risk, and brought awareness about inter-individual disparities in circadian phase (approximated by chronotype). The principle of chronotherapy has evolved accordingly. New studies bring evidence for the merit of determining the optimal time to administer a given medication on a personal basis in preference to making general recommendations in terms of time of day. Accounting for the chronodiagnosis in recommending a time to treat, known as chronotheranostics, is one way to personalize chronotherapy, as illustrated for the case of blood pressure disorders. We present different approaches to chronotherapy and discuss the relative merits of several study designs for personalized chronotherapy.

Keywords: biorhythms6 circadian rhythms, chronorisk, chronotherapy, chronoteranostics

Реакция организма на тот или иной стимул предсказуемо меняется в зависимости от времени его предъявления, что во многом обусловлено работой эндогенной циркадной системы. Подобные изменения восприимчивости к самым разным стимулам привели к появлению понятия хронориска, отражающего часы изменения устойчивости организма к внешним воздействиям. Хронориск также является основой хронотерапии и хронофармакологии, поскольку циркадные ритмы влияют на все аспекты фармакологии — от всасывания и распределения до метаболизма и экскреции. Последние достижения в области хронобиологии показали, как нарушение циркадных ритмов связано с повышенным риском заболеваний, и позволили осознать межиндивидуальные различия в циркадных фазах (аппроксимируемых хронотипом). Соответственно развивался и принцип хронотерапии. Новые исследования подтверждают целесообразность определения оптимального времени приема того или иного лекарственного средства в индивидуальном порядке, а не общих рекомендаций по времени суток. Учет хронодиагноза при рекомендации времени лечения, так называемая хронотераностика, является одним из способов персонализации хронотерапии, что показано на примере нарушений артериального давления. Мы представляем различные подходы к хронотерапии и обсуждаем относительные достоинства нескольких дизайнов исследований для персонализированной хронотерапии.

Ключевые слова: биоритмы, циркадианные ритмы, хронориск, хронотерапия, хронотераностика

Introduction

Living organisms are organized in space and time. Biological rhythms are periodically recurring changes in the intensity and nature of biological processes and phenomena [1]. They characterize all levels of biological organization, from intracellular processes, tissues, organs and organ systems to the individual, populations, and the biosphere [1, 2]. While they span a broad frequency range, circadian rhythms received particular attention since their partly endogenous nature was placed on a solid molecular basis [3–5].

Living organisms have an autonomous, evolutionarily conserved internal timing system [6]. The 24-hour alternation between light and darkness in the environment synchronizes the circadian clock in the suprachiasmatic nuclei (SCN) of the brain's hypothalamus [7]. Intrinsically photosensitive retinal ganglion cells in the

retina transmit light information to the SCN [8]. The SCN orchestrates circadian rhythms throughout the body. The molecular circuitry of the circadian clock, however, is present in almost all cells, including those of peripheral organs. Other external inputs, such as temperature, food intake, and exercise, also affect cells in peripheral organs [9]. Each cell contains a biochemical oscillator consisting of interlocked transcription-translation feedback loops, composed of several clock genes and their protein products. The primary loop, lasting about 24 hours, consists of the core clock genes *Bmal1* and *Clock* on the positive arm and *Per* and *Cry* on the negative arm of the primary loop [10–12]. Interlocking to this core loop, a molecular feedback loop regulates *Bmal1* transcription in which transcription factor RORα activates and REV-ERB suppresses *Bmal1* transcription [13]. In addition, the autofeedback loop of rhythmic *Dec* transcription also interacts with the core loop [14]. These multiple interlocked molecular feedback loops function to stabilize periodicity in cells and enhance the amplitude when cellular oscillators are synchronized [15]. Directly or indirectly, the network of core clock genes modulates the expression of multiple genes and biological processes throughout the body [16].

Circadian rhythms play an important role in many physiological and pathophysiological functions, including functions of the heart. Cardiovascular functions exhibit pronounced 24-hour variations, as observed in blood pressure [17], heart rate [18], circulating catecholamines [19, 20], markers of blood coagulation [21, 22] and vascular endothelial function [23]. Epidemiological studies also indicate a marked increase in the morning in adverse cardiovascular events, including myocardial infarctions, strokes, ventricular arrhythmia, and sudden cardiac deaths [24–29].

Hours of changing resistance: Chronorisk

As early as 1955, Halberg et al. reported on the 24-hour periodicities characterizing eosinophil counts and rectal temperature of I mice of different ages studied under standardized experimental conditions [30]. In addition, the susceptibility of these mice to audiogenic convulsions, and their ability to recover from convulsions also followed 24-hour rhythms of large magnitude, accounting for statistically significant differences in the occurrence of convulsions between 11% by day compared to 63% by night [30]. A susceptibility rhythm to E. coli endotoxin in C mice reported in 1960 was such that a dose of endotoxin compatible with survival of most animals when given during the middle of the daily dark span was highly lethal when given 8 to 12 hours earlier or later, Figure 1 [31]. Many other studies followed that provided evidence for the generality of circadian response rhythms to a host of external stimuli, including X-irradiation [32] and drugs [33].

The physiological response to external stimuli changes predictably as a function of circadian stage. Chronorisk thus constitutes the foundation for the fields of chronotherapy and chronopharmacology, as circadian rhythms affect all aspects of pharmacology, from absorption and distribution to metabolism and excretion. It thus becomes possible to optimize treatment by timing its administration in order to maximize its effectiveness while minimizing its side effects. This is the principle underlying timed treatment.

Principles of Chronotherapy and Chronopharmacology

Under the standardized conditions of the laboratory, timing repeatedly tipped the scale between health and disease, and even between death and survival. This is, for instance, the case for the exposure of mice to the same dose of an adrenal cortical inhibitor (SU-4885) as a function of circadian timing. Three experiments involved 70, 210, and 350 mice, which were tested at six different circadian stages, 4 hours apart in relation to the lighting regimen of 12 hours of light alternating with 12 hours of darkness (LD12:12). Depending on the dosage, most if not all mice died when exposed to SU-4885 late during the light (rest) span, but most if not all survived when exposed to the same dosage of the same agent earlier during the rest span [34]. These results indicate that timing is as important, if not more important than dosing.

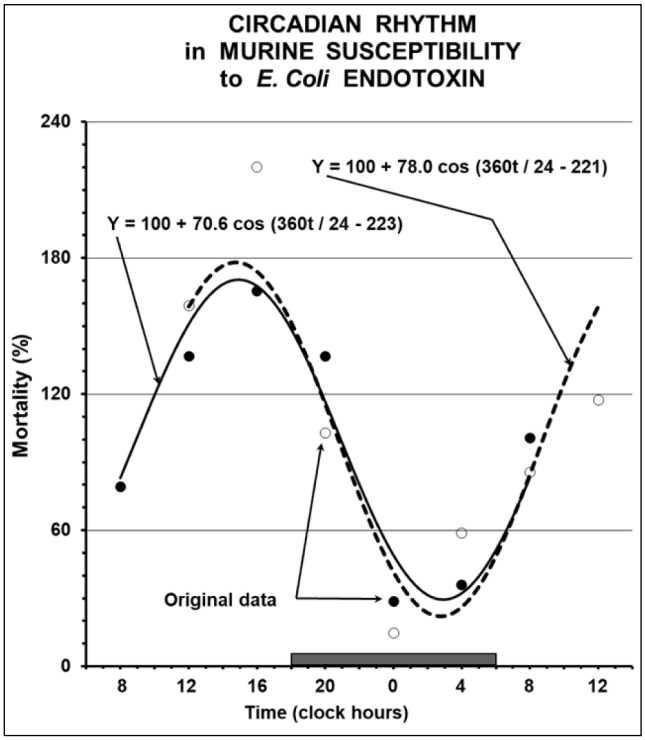

Fig. 1. Susceptibility rhythm to endotoxin and its reproducibility in two separate experiments. Percentage mortality from Difco's *E. coli* lipopolysaccharide (100 μg/20 g, i. p.) in separate groups of standardized mature C mice injected at 4-hour intervals. Evaluation at 1-week post-injection [31].
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The response to a single daily «meal» also makes the difference between life and death in a mammalian model of potentially fatal interactions between hunger, cold and rhythms, namely the singly-housed mouse abruptly restricted to a single daily «meal» [35]. Most singly-housed mice (but not multiply-housed mice) die when they have access to food for 4 hours during the first part of the light (rest) span each day, but if food is only available during 4 hours in the early part of the dark (active) span, most of the mice survive [35].

From a pharmacological viewpoint, changes in drug effectiveness depend on the sensitivity of tissues and organs and on circadian mechanisms of the signal transduction within cells, present at all stages of drug action, from absorption and distribution to metabolism and excretion (ADME). Biological rhythms characterize the pharmacokinetics of most classes of drugs, due to parallel changes in the physiological functions and variables involved in the ADME of drugs, but the peak and trough values of these functions and variables do not occur at the same hour of the day in every factor involved in drug disposition [36]. Considerable 24-hour variation described in the pharmacokinetics, efficacy, and side effect profiles of many therapeutics relates to 24-hour rhythms in ADME, as well as to pharmacodynamic variables, such as target expression [37]. Twenty-four-hour oscillations in abundance of proteins necessary for either drug absorption or metabolism result in circadian pharmacokinetics, and oscillations in the physiological systems targeted by these drugs result in circadian pharmacodynamics [38]. Chemical properties of the drug (such as its lipophilicity) affect its distribution rate [37]. Drug metabolism in the liver includes enzymatic processes that are circadian periodic [39, 40]: oxidation, reduction, and hydrolysis by monooxygenases; and conjugation by transferases, resulting in the production of conjugates that can be readily excreted [37]. Kidney function and its tissue-specific circadian clocks strongly modulate the excretion rate of metabolized chemicals and drugs. Glomerular function, xenobiotic-metabolizing enzymes and detoxification pathways, filtration rate, renal blood flow, tubular reabsorption, transporters, electrolytes, and urinary pH are all circadian rhythmic [41, 42].

While there is mounting evidence for the importance of drug dosing time in pharmacokinetics, pharmacodynamics, and toxicity and for the effect of circadian rhythms on drug ADME, challenges remain. In part, they relate to translational difficulties caused by interspecies differences, and from variability in study design and a lack of complete understanding of how the circadian clock affects physiological factors that strongly influence ADME [43].

Relative Merits of Different Study Designs in the Context of Blood Pressure Chronotherapy

Blood pressure (BP) chronotherapy presents the advantage that BP serves both as a marker variable and as a gauge of the response to timed treatment (chronotherapy). In clinical health and uncomplicated hypertension, BP undergoes a large-amplitude circadian rhythm with lower nighttime values during sleep and higher values during the active daytime [44, 45]. Because circadian characteristics of BP can also vary greatly from one day to another, measuring BP around the clock for several days, preferably by ambulatory BP monitoring (ABPM) is important to detect reliably abnormal variability patterns known as Vascular Variability Disorders (VVDs) [46], associated with increased cardiovascular disease risk, as shown in several outcome studies [47].

Typically, the chronobiologic interpretation of an ABPM record consists of fitting by least squares a model consisting of cosine curves with periods of 24 and 12 hours to approximate the circadian waveform more closely in most cases [48]. The monitoring of clinically healthy men and women in different age groups led to the derivation of time-specified (chronobiologic) reference limits (as 90% prediction limits) and reference values for the 24-hour parameters (MESOR, M, the rhythm-adjusted mean, amplitude, A, and acrophase, ϕ) that are qualified by gender and age [48]. Deviation from these norms identify VVDs: MESOR-Hypertension (MH), Circadian Hyper-Amplitude-Tension (CHAT), and ecphasia when the BP-M or BP-A are above the upper 95% prediction limit, or BP-ϕ is outside the 90% prediction limits of clinically healthy peers matched by gender and age. In addition, pulse pressure (PP) is considered excessive when it exceeds 60 mmHg and heart rate (HR) variability (HRV) is considered deficient when the standard deviation (SD) of around-the-clock HR measurements drops below 7.5 beats/min [47, 48]. Against this background, chronotherapy protocols were designed that aimed at lowering BP while also restoring a healthy circadian pattern of BP.

The optimization by timing of the once-daily administration of prazosin, an α_1-blocker acting as an inverse agonist at α_1 adrenergic receptors, was perhaps the first chronotherapy protocol of BP [49, 50]. The study involved only 10 patients, but its design is impeccable. The 10 patients with idiopathic hypertension participating in the study were admitted to a metabolic ward, where they were fed constant diets and were kept recumbent during the entire study. The intervention started after 3 days of monitoring to acclimate patients to hospital conditions. BP was measured around the clock at 30-minute intervals with the first available automatic BP monitor, the Roche Arteriosonde (an analog device) [51]. In this double-blind, placebo-controlled study, every patient received one capsule, either the active drug (1 mg prazosin) or placebo, every 4 hours for 7 days. Only one capsule per day contained prazosin, the time of its administration delayed by 4 hours every day. This study showed that the effect and duration of prazosin's action depended on the time of its administration [49, 50].

Randomized, double-blind, placebo-controlled trials of anti-hypertensive medications administered at one of six different circadian stages are very difficult to carry out,

notably when treatment needs to be taken for long enough times to obtain information on actual outcome. Different investigators have followed different approaches.

One early study included two arms, a chronobiologic approach compared to the then-conventional treatment of dosing three times a day [52, 53]. Chronobiologically, the time of the once-daily dosing was determined based on the circadian acrophase of BP measured around the clock and the pharmacokinetics of the anti-hypertensive drug: the selected treatment time targeted the anticipated time when the medication would be most effective when BP reached its highest daily peak. Three drugs were tested using this protocol: the β-blocker propranolol, the α_2-adrenergic agonist and imidazoline-receptor agonist clonidine, and the α_2-adrenergic agonist α-methyldopa. In each case, compared to treatment three times a day, using a smaller dose of the drug, chronotherapy (applied 1.5 to 2 hours before the daily BP peak) lowered BP to a larger extent, had a faster treatment response rate, and was accompanied by fewer complications and less over-dosage [52, 53].

Several pilot studies considered six different treatment times equally distributed between the time of awakening and bedtime, so that outcome measures can be fitted with a 24-hour cosine curve to determine the optimal treatment time when the zero-amplitude (no-rhythm) hypothesis is rejected with statistical significance. The rationale of these pilot studies is to determine in a first stage what the optimal circadian stage is to administer the treatment before selecting this test time in larger trials for comparison with conventional treatment. For such N-of-6 pilot studies to yield reliable results, it is important that study participants be a random sample of the target population and that they be randomly assigned to the different treatment times. One such N-of-6 pilot study tested effects of low-dose aspirin on blood coagulation and BP [54]. Another involved 24 dental patients undergoing periodontal surgery [55].

A particular case consists of the same patient switching among the six different treatment times. Such N-of-1 studies underlie the personalized optimization of treatment, recognizing that every patient is different, presenting with different diagnoses once the VVDs are also considered. Parameter tests [56] can assess the statistical significance of a change in average BP (MESOR) as well as that of a change in the circadian amplitude and/or acrophase of BP. In one study [57], switching the administration time of diltiazem hydrochloride (240 mg/day) from awakening time to mid-sleep in a 75-year old hypertensive man was associated with a reduction in systolic (S) BP MESOR from 147.7±2.1 to 141.7±1.0 mmHg (P=0.017) and in its circadian amplitude from 17.1±3.0 to 9.8±1.5 mmHg (P=0.039). The self-starting cumulative sum (CUSUM) control chart is another method capable of assessing the effectiveness of a given intervention for the individual patient [58]. As illustrated in Figure 2 (top), a breakout of one of the two (upward/downward) CUSUM curves outside the decision interval (shaded band) indicates that a statistically significant change (increase/decrease) in the endpoint examined took place. Following the CUSUM curve backwards to the time when it first deviates from zero provides an estimate of when the change took effect [59]. Since the start of intervention is known, if this time coincides with the time when the CUSUM line first departs from zero, a causal relation may be assumed. The MESOR of SBP of a man newly diagnosed with hypertension decreased almost immediately once valsartan hydrochlorothiazide (Diovan HTC) treatment started, its efficacy detected after about a month. Figure 2 (bottom) also shows that when the medication was taken in the evening, the circadian amplitude of SBP increased.

Two small clinical trials used this N-of-1 design. One enrolled 20 MESOR-hypertensive patients to optimize the administration of Micardis (Telmisartan, an angiotensin II receptor antagonist), with or without low-dose aspirin [60]. This cross-over, double-blind, randomized study consisted of three stages (placebo, Micardis, and Micardis with low-dose aspirin), each lasting 7 days. The treatment was administered each day at a different circadian stage, 3 hours apart, from the time of awakening to bedtime. Overall, treatment was most effective in decreasing BP when taken 6 to 9 hours after awakening. The other study recruited 30 hypertensive patients to optimize the administration of Hyzaar (Losartan/hydrochloride, an angiotensin II receptor antagonist combined with a diuretic) [61]. In this trial, treatment was given at the same circadian stage for at least one month before it was switched to another circadian stage, 3 hours later. Before the start of treatment and at the end of each about monthly stage when treatment was given at one of six different circadian stages, 3 hours apart between the time of awakening and bedtime, each patient provided a 7-day/24-hour ABPM record. Overall, a larger lowering of the diastolic (D) BP MESOR was achieved when treatment was administered in the early morning for more patients, while treatment upon awakening was the best choice for most patients to reduce the circadian BP amplitude the most. Importantly, the optimal treatment time differed considerably among patients [61].

When designing a chronotherapy trial, several factors need to be considered. Can one manage a protocol consisting of six test times, which may require a larger number of participants and complicate logistics? Or can one afford following a two-arm design without compromising the accuracy of the estimated optimal treatment time? If the protocol includes six different treatment times, equally distributed between the time of awakening and bedtime, should one use a transversal or longitudinal design? In other words, should one randomly assign different patients to each treatment time, or should one give the same dose of the same drug at different circadian stages to the same patients? In the latter case, how long should patients take the same dose of the same medication at a given circadian stage before switching to the next treat-

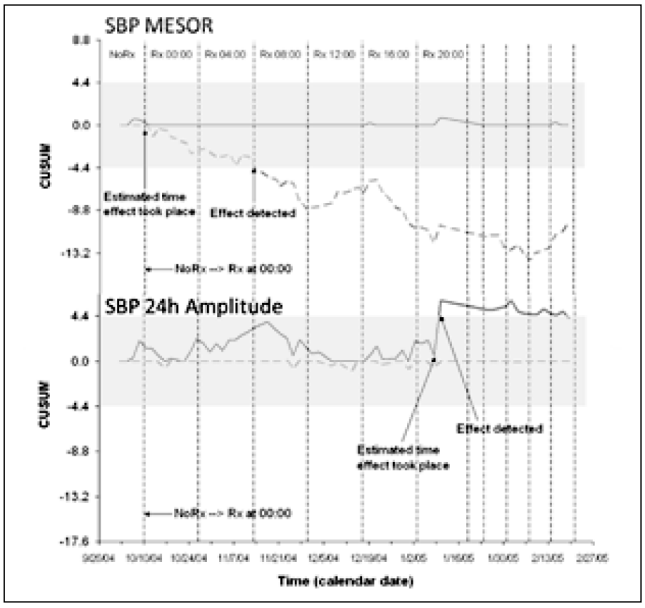

Fig. 2. The same dose of Diovan HTC (80/12.5) was taken at the same circadian stage for 17 days before the treatment time was advanced by 3 to 4 hours. After testing all 6 circadian stages, the protocol was repeated using shorter spans on each treatment time. Treatment was effective in bringing about a statistically significant decrease in the SBP MESOR, detected after about one month on treatment. When taken in the evening, treatment was associated with a statistically significant increase in the circadian amplitude of SBP.
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ment time? Choices made will depend on whether outcome variables are physiological changes or adverse cardiovascular events; they will also determine whether conclusions apply to a given population or to individual patients. Most large trials, however, focus on the question whether dosing is better in the morning or evening.

Current Debate of Morning Versus Evening Dosing of Anti-Hypertensive Medication

Despite the considerable variability in circadian rhythm characteristics from one day to another [62], most studies rely on ABPM records limited to 24 hours or at most 48 hours [63]. Moreover, in order to approximate the circadian variation in BP, clinicians typically rely on the day-night ratio (DNR) or night-to-day ratio (NDR) of BP, estimated from 24-hour ABPM records [64, 65]. The DNR is calculated as the difference between the daytime and nighttime means, expressed as a percentage of the 24-hour mean, whereas the NDR is computed as the ratio of the nighttime mean to the daytime mean. Whether considering the DNR or the NDR, four different kinds of BP patterns are defined: a healthy circadian BP pattern should dip by 10% to 20% by night (dippers). A nighttime dip less than 10% identifies non-dippers, while a nighttime dip exceeding 20% identifies extreme dippers; BP patterns such that the nighttime mean is higher than the daytime mean identify reverse dippers (or risers). These limits apply to all adults of both genders and do not account for the post-prandial dip in early afternoon that accentuates with increasing age [66].

While some studies report an increased cardiovascular risk in the absence of BP dipping, reverse dippers are generally found to carry the largest risk [67–76], as illustrated in Figure 3 based on data from Fagard et al [65]. Conditions such as diabetes [77, 78] and kidney disease [79–81] have long been known to be associated with changes in the circadian BP acrophase, and even with a reversal of the circadian BP rhythm, which can be associated with marked changes in the DNR or NDR (and corresponding dipping category), as illustrated in Figure 4.

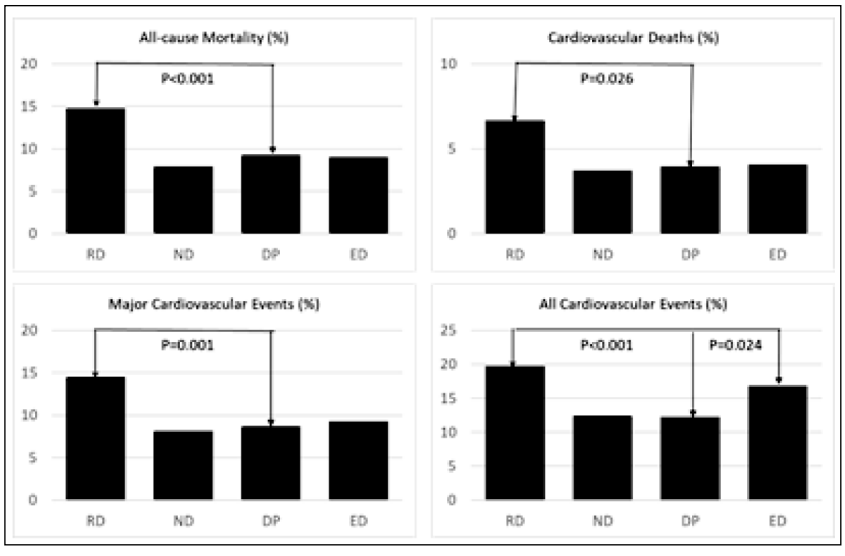

Fig. 3. Events after follow-up of 23,164 patient-years in 3,468 treated or untreated hypertensive patients from four prospective studies performed in Europe, classified by their night-day ratio as reverse dippers (RD, *N*=421), non-dippers (ND, *N*=1407), dippers (DP, *N*=1295), or extreme dippers (ED, *N*=345) based on 24-hour ABPM. Data from Fagard et al. [65].
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Risk associated with extreme dipping remains controversial [78]. Increased risk of stroke and silent cerebral disease was reported in several Japanese studies [82–86]. Risk associated with extreme dipping tends to be found in older patients in contrast to younger populations where it is reportedly protective [87–89]. While some have linked the risk of extreme dipping to that related to the morning BP surge [90, 91], others refute this association [92]. As shown in Figure 3, the risk associated with extreme dipping relates to all cardiovascular events, but not to major cardiovascular events. In our own clinical trial of an Asian population,

over-swinging (CHAT) related to the risk of cerebral ischemic events but not to coronary artery disease [93, 94].

Against this background, some investigators consider the additional benefit of achieving a nocturnal BP dip between 10% and 20% when treating hypertensive patients. Several trials compared outcomes between groups of patients receiving anti-hypertensive treatment in the morning or evening [95]. Since evening dosing tends to decrease nocturnal BP and hence increase the day-night ratio [96, 97], it is generally viewed as beneficial. Reduced adverse outcomes have primarily been achieved for patients with diabetes and chronic kidney disease who tend to have a weakened circadian BP rhythm, some even showing a reverse circadian BP pattern [97–00]. Little concern, however, seems to be given for the risk of achieving extreme dipping in some patients, which can lead to nocturnal hypotension and represents a known risk of optic neuropathy in glaucoma patients [101].

It has been recognized that activity [102], sleep [103], age [89, 104], and medications [105] all affect the day-night difference in BP, likely contributing to the poor reproducibility of the DNR or NDR [106, 107]. Moreover, the BP waveform can differ greatly among patients in need of treatment [108], including the exacerbation of the post-prandial dip with advancing age [66]. In this respect, a study showed that, like the nocturnal BP dip, the post-prandial dip in BP also modulates the risk of acute ischemic stroke [109]. The extent of the post-prandial dip in early afternoon also affects the DNR, as illustrated in Figure 5.

In view of these limitations, two questions need to be raised.

— First, the limitations of the DNR or NDR need to be better understood, the merits of assessing the circadian BP rhythm in terms of its amplitude and phase should be recognized, and means should be provided for their easy determination by clinicians.

— Second, the limitations of current clinical trials comparing morning versus evening dosing to draw across-the-board recommendations for treatment timing need to be better understood, and trials aiming at personalized chronotherapy that account for differences in circadian BP profile (chronodiagnosis) should be implemented.

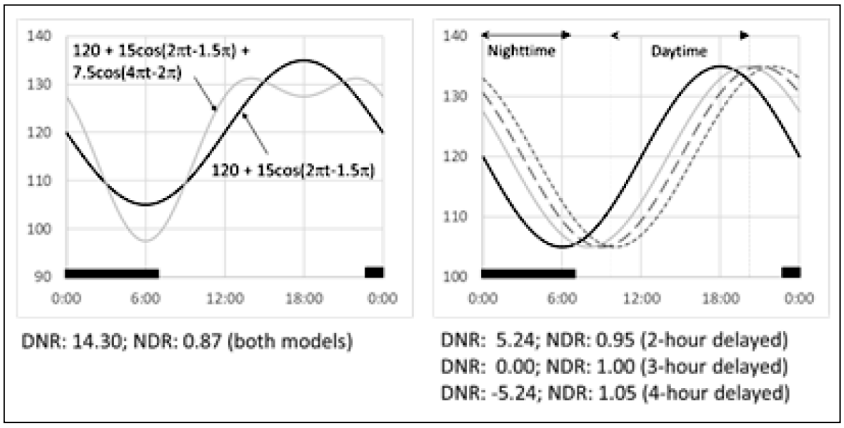

Fig. 4. *Left:* **One- or two-component models approximate the circadian variation in SBP. The Day-Night Ratio (DNR) is between 10% and 20% and the Night-to-Day Ratio (NDR) is between 0.8 and 0.9, both corresponding to a dipper pattern.** *Right:* **As compared to the one-component model shown on the left (solid black curve), similar models delayed by 2, 3, or 4 hours (solid, dashed, and dotted gray curves, respectively) are associated with non-dipper and even reverse-dipper patterns. Similar results apply to the two-component model: after a delay of 2, 3, or 4 hours, the DNR is 2.82, −2.78, and −7.65, respectively, and the NDR is 0.97, 1.03, and 1.08, respectively.**
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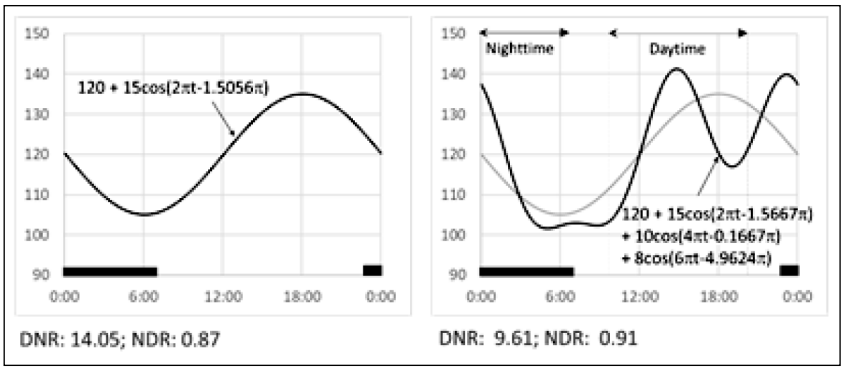

Fig. 5. *Left:* **The one-component model approximates the circadian variation observed in young adults. The Day-Night Ratio is between 10% and 20% and the Night-to-Day Ratio is between 0.8 and 0.9, both corresponding to a dipper pattern.** *Right:* **A composite model, differing mostly from the model on the left by a sharp post-prandial dip in early afternoon, approximates the circadian pattern likely observed in the elderly. Whereas the 24-hour amplitude is unchanged, the DNR is below 10% and the NDR is between 0.9 and 1.0, both corresponding to a non-dipper pattern.**
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Toward Personalized Chronotherapy

Figure 6 addresses concerns about reliance on the dipping pattern of BP. It also attempts to account for the apparent controversy in the literature regarding the risk associated to extreme dipping. Cardiovascular disease risk, gauged by the incidence of morbid events in a 6-year follow-up study [93, 94], has a nonlinear relation to the circadian amplitude of SBP (top) or DBP (bottom). Risk increases only after a threshold is exceeded [66], as illustrated by the up

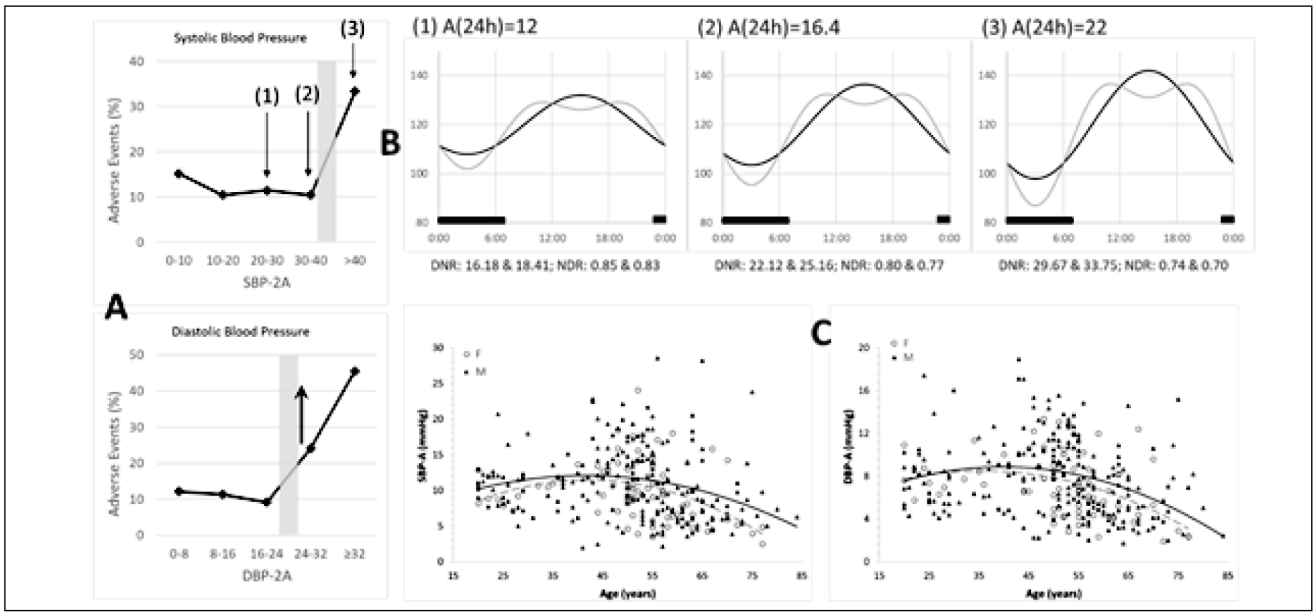

Fig. 5. A: The circadian amplitude of SBP (top) or DBP (bottom) has a nonlinear relation to cardiovascular disease risk. The up arrow indicates a statistically significant increase in risk.
B: Circadian profiles of SBP with acceptable [(1) and (2)] or excessive [(3)] amplitudes are displayed with their corresponding DNR and NDR values. DNR or NDR for intermediate amplitudes (middle) not yet associated with increased risk already indicate an extreme dipper pattern. Without or with the second harmonic term, models are simulated by the following equations: model (1): SBP = 120 + 12cos(22πt−1.25π) + 6cos(42πt−1.5π); model (2): SBP = 120 + 16.4cos(2πt−1.25π) + 8.2cos(42πt−1.5π); model (3): SBP = 120 + 22cos(22πt−1.25π) + 11cos(42πt−1.5π).
C: The circadian amplitude of SBP (left) and DBP (right) also changes nonlinearly with age, approximated by a quadratic polynomial for men (closed triangles and solid curve) and women (open circles and dashed curve). Fitted models are for SBP-A 5.1108 + 0.3354Age − 0.004Age2 (men) and 0.5387 + 0.5211Age − 0.0062Age2 (women), and for DBP-A 3.5836 + 0.2653Age − 0.0033Age2 (men) and 4.5127 + 0.2236Age − 0.0031Age2 (women). See text.
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arrow separating amplitude ranges where a statistically significant increase in risk occurs, the threshold represented by the gray area. Models (in Figure 6B) with circadian SBP amplitudes that are either below or above the threshold (in Figure 6A) have DNR and NDR values that do not indicate similarly acceptable of excessive dipping patterns. The DNR and NDR indicate a dipper pattern only for model (1), Figure 6B (left). However, they already indicate an excessive dipping pattern for model (2), Figure 6B (middle), associated with circadian amplitudes still in the acceptable range. DNR values well above 25% correspond to a circadian BP profile deemed to have an excessive amplitude, Figure 6B (right). As shown in Figure 6C, the circadian amplitude of SBP (left) and DBP (right) also changes nonlinearly with age, approximated by a quadratic polynomial for men (closed triangles and solid curve) and women (open circles and dashed curve). Accordingly, in clinical health, SBP-A varies from higher values of 12.1 (men) and 11.5 (women) mmHg around 40 years of age to lower values of 9.0 (men) and 6.6 (women) mmHg around 70 years of age. Similarly, DBP-A decreases from higher values of 8.9 (men) and 8.5 (women) mmHg around 40 years of age to lower values of 6.0 (men) and 5.0 (women) mmHg around 70 years of age. Since DNR values above 20% or NDR values below 0.8 are fixed, these values carry a different meaning for older than for younger patients. They represent a relatively larger excess in circadian variation for older patients than similar DNR or NDR values for younger patients. The difference that a fixed DNR or NDR value represents in terms of the expected deviation from chronobiologic norms in health likely accounts for results in the literature that report cardiovascular risk associated with extreme dipping in older but not in younger patients [89].

Studies aiming at personalized chronotherapy that account for all abnormalities of the circadian variation in BP, that is for the chronodiagnosis, do not need to be more difficult to implement than current clinical trials. Depending on outcome measures used to decide on the best treatment time, different protocols can be considered. If physiological outcome measures are used, each patient's response to treatment administered at several circadian stages tested one-at-a time sequentially can be assessed systematically. A decision can then be made, based on circadian characteristics determined from ABPM records over spans of several days carried out after the medication was taken for a long enough time to have reached a stable effect. Treatment can then continue at the presumed optimal time during follow-up when actual adverse events are recorded, for comparison with patients treated as usual. In the absence of physiological outcome measures, the optimal treatment time can be inferred based

on the circadian characteristics of the BP profile obtained by ABPM over several days and on the pharmacokinetics of the prescribed medication, as done earlier [52, 53]. In addition to immediate responses in BP, the incidence of adverse events can be recorded during follow-up, for comparison to a control group receiving treatment as usual.

The rationale underlying the above discussion assumes that the optimal treatment time can be determined using marker rhythmometry. Another approach often used in chronobiology is to estimate a person's circadian phase. Molecular [110] and genetic approaches to so doing are promising as they may also reveal the physiological mechanism underlying the abnormal BP pattern. Other avenues include the determination of dim-light melatonin onset [111], the monitoring of marker variables such as cortisol or temperature [41], or the assessment of chronotype by questionnaire [112, 113]. While these approaches all have merit, they remain limited by the fact that mechanisms underlying abnormal BP patterns are complex and far from being completely understood. Relying on marker rhythmometry and the monitoring of BP hence remains a good option at this time.

Concluding Remarks

Recent advances in chronobiology related to the determination of a person's circadian phase brought awareness about their wide inter-individual disparities. As illustrated above for the case of BP, different mechanisms may also underlie the presentation of abnormal circadian patterns in BP. Moreover, BP disorders represent a risk factor for different adverse cardiovascular outcomes. All these considerations support the need for a personalized approach to chronotherapy.

Recent work also indicated how circadian disruption relates to increased disease risk, including cardiovascular disease, diabetes, obesity, hypertension, sleep disorders, and metabolic disorders [114]. Several strategies emerged to counteract effects related to circadian disruption, all part of the broad concept of chronotherapy, as reviewed in a forthcoming book on Chronobiology and Chronomedicine — From Molecular and Cellular Mechanisms to Whole-Body Interdigitating Networks to be published by the Royal Society of Chemistry.

One approach to counteract or prevent circadian disruption consists of strengthening the circadian system by means of lifestyle modifications aimed at health maintenance and optimization. Exposure to light by day and dark by night, exercise, and meal schedules are features amenable to manipulation to strengthen the circadian system. As eating can influence peripheral circadian rhythms, adjusting meal timing may be a way to support circadian function [115]. More important than sleep duration, keeping a regular schedule [116] and avoiding social jetlag [117] also help consolidate the benefit derived from timed treatment since taking medication at the same, presumably best time of day may no longer remain the best treatment time when the daily schedule varies too much from one day to another. In addition to timing treatment administration to optimize therapeutic effects, developing small-molecule compounds targeting clock proteins directly to alter the circadian period, phase, or amplitude is a complementary approach to chronotherapy and an active area of research [118–120].

In future studies aimed at optimizing BP treatment from a chronobiologic perspective, it will be important

— to consider all lifestyle factors affecting the circadian system,

— to monitor BP around the clock for a span longer than 24 hours,

— to obtain reliable estimates of all circadian characteristics (MESOR, 24-hour amplitude and acrophase) in addition to the DNR or NDR, and

— to interpret these circadian parameters in the light of reference values accounting for gender differences and changes as a function of age.

The treatment plan also benefits from considering all features of the chronodiagnosis (i.e., alterations in the circadian amplitude and/or phase in addition to the MESOR) and any complicating condition (such as diabetes or chronic kidney disease). Finally, all aspects of the chronopharmacokinetics and chronopharmacodynamics are best kept in mind since not all anti-hypertensive medications have the same effect on the circadian amplitude of BP [121], and different drugs have different effects on other variables that also relate to cardiovascular health (such as heart rate variability) [122]. Adjusting the chronotherapy to the chrnodiagnosis in all its different aspects was termed chronotheranostics [57].

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