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ARTICLE

Chronobiologically interpreted ambulatory blood pressure monitoring: past, present, and future

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ABSTRACT

Research at the Halberg Chronobiology Center focused to a large extent on the monitoring of blood pressure (BP) and heart rate (HR). Self-measurements and later ambulatory BP monitoring yielded new knowledge of interest to basic science and clinical practice. After a brief review of BP measurement, we outline developments in methods of data analysis that paralleled technological advances in the measurement of BP. We review work done in cooperation with colleagues worldwide to illustrate how a chronobiological approach led to the mapping of spontaneous circadian and other rhythms for the derivation of refined reference values and to the assessment of response rhythms underlying chronotherapy. BIOCOS members work in different fields, spanning from cardiology and nutrition to obesity, diabetes, exercise physiology and rehabilitation, but all strive for "pre-habilitation". The early recognition of increased risk can prompt the timely institution of prophylactic intervention. As technology continues to improve, studies on groups are complemented by longitudinal self-surveillance for health maintenance. Longitudinal records serve for the investigation of environmental influences on human physiology, the topic of chronomics. As current advances in technology and wireless communication will likely impact the future of healthcare, chronobiological methods and concepts should be an integral part of this seachange.

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Introduction

The ongoing Project on the BIOsphere and the COSmos (BIOCOS) is a spin-off of our original "Womb-to-Tomb" study, which aimed at deriving time-specified reference

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Dedicated to the memory of Miguel A Revilla Ramos

values qualified by gender and age in health for the circadian variation of blood pressure (BP) and heart rate (HR). Replacing the current fixed limits by limits that account for the circadian variation, for gender differences, and for changes as a function of age, to delineate hypertension from normotension (or rather to distinguish between a deviant and an acceptable BP profile) in everyday clinical practice is one major line of research at the Halberg Chronobiology Center at the University of Minnesota. Doing so can identify cardiovascular disease risk early and prompt the timely institution of prophylactic intervention before there is target organ damage as true primary prevention.

The accumulation of longitudinal around-the-clock records of BP and HR spanning years and even decades has shed light on a set of shared periodicities between physiology and the environment. In addition to the weekly and yearly variations, low-frequency components with periods of about 0.42, 1.3, and even 11 years similar to changes occurring in solar flares, solar wind and sunspots have been detected in most cases, prompting the scrutiny of the influence from the cosmic environment on BP and HR, another area of research in our laboratory.

BIOCOS members have a common interest in the chronobiology of BP and HR. Their purpose, however, is varied, illustrating the richness of applications centered on the main theme. Some members are general practitioners. Others are researchers and educators, as well as clinicians specializing in cardiology, nutrition, obesity and diabetes, exercise physiology, and rehabilitation. Joint projects have centered on mapping rhythms in health and disease, studying effects of special diets, and optimizing anti-hypertensive treatments. Ambulatory BP monitoring (ABPM) has been carried out in research projects, in outcome studies from clinical trials, in epidemiological studies involving entire communities, and in longitudinal monitoring for self-surveillance. This article briefly reviews advances made in the measurement of BP and gives an overview of work the BIOCOS group did in relation to BP and of remaining tasks to be pursued.

Historical background: measurement of blood pressure

The Reverend Stephen Hales (1733) was first to measure BP directly by introducing a brass pipe into the crural artery of a mare. It took more than a century before a simple and convenient way of measuring BP was developed, despite several attempts at developing better methods of measurement, from Jean Léonard Marie Poiseuille's hemodynamometer to devices by Carl Ludwig and Jules Herrison, such as the kymograph, able to record BP waves noninvasively. In 1855, Karl von Vierordt postulated that in order to measure BP accurately noninvasively, it was necessary for the pulse to stop, which he did by applying weight on an artery and measuring the counter pressure that would just obliterate the radial pulse (Soto-Perez-de-Celis 2007).

Inspired by Vierordt's discovery, the Austrian physician Karl Samuel Ritter von Basch (1880) developed an apparatus to measure BP. In his latest model, instead of connecting a water-filled ball (placed over the radial artery) to a column of mercury, he used a calibrated aneroid manometer to measure BP. This innovation established the basis for the modern sphygmomanometer, as it made it possible to build portable devices. Using his sphygmomanometers, von Basch (1880) observed that the higher the BP was, the greater was the risk of stroke and kidney disease. His instrument was extensively tested

by Ignaz Zadek. By 1881, data from Zadek were available from four subjects to assess components with periods of about 24, 84, and 168 h (Otsuka et al. 2016).

BP became easy to measure when an Italian physician, Riva-Rocci (1896) developed what we would now recognize as a conventional mercury sphygmomanometer with a cuff around the arm, which was inflated until the pulsation of the artery could no longer be felt. A few years later, Nicolai Korotkoff (1905), a Russian army surgeon, realized that by listening with a stethoscope below the cuff over the artery at the elbow, characteristic sounds were heard at the systolic (S) pressure, and also at the lower (diastolic, D) pressure. Credit is due to Theodore Janeway (1904) who drew attention to the variability of BP and its response to external stimuli, such as surgery, tobacco and anxiety. He did not wish to "see a patient before collecting sufficient data to assess periodicities."

It is still customary to determine BP by static measurements in the physician's office, even though BP is essentially a fluctuating phenomenon (Pickering 1992). One of the first studies questioning the validity of clinic measurement of BP was based on self-measurements of BP (Ayman and Goldshine 1940). The BP readings from 34 hypertensive patients taken at home for an average of 22 months were invariably lower than those taken in the clinic by the doctor.

Using a noninvasive apparatus that employed a Gallavardin double cuff, the group of Sir George Pickering at Oxford showed for the first time how profound was the fall in BP recorded during sleep, and demonstrated fluctuations in BP during the course of 24 h (Richardson et al. 1964). As this system was not portable, measurements could not be obtained during unrestricted activity. To overcome this limitation, Pickering's group developed an ambulatory technique whereby BP could be measured directly from the brachial artery with a small plastic catheter (O'Brien and Fitzgerald 1994), leading to the first publication reporting BP changes in unrestricted subjects (Bevan et al. 1969). It became possible to determine the BP-lowering effects of antihypertensive drugs and their duration of action, as well as the 24-h changes in BP (Pickering 1968).

Limitations of invasive intra-arterial measurements, however, prevented their use in everyday clinical practice. The development of noninvasive ABPM originates with the work of Maurice Sokolow who developed with his colleagues the initial semi-automatic ABPM (Hinman et al. 1962). It consisted of a BP cuff that was manually inflated by the subject, and a tape recorder on which the Korotkoff sounds were recorded. The system was developed commercially by the Remler Company in California. Sokolow et al. (1966) were first to show that ABPM data correlate more closely than clinical BP measurements with damage to the heart and arteries caused by hypertension; ABPM also improved the ability to predict risk (Perloff et al. 1983). ABPM largely circumvents the limitations of clinic measurements since a much larger number of BP readings can be taken automatically under usual living conditions.

Because the Remler device depended on inflation by the subject, recordings were confined to waking hours and rarely spanned more than 12–14 h (Stanton and O'Brien 1993). With the development of compact pumps and solid-state memory systems, the Remler system was replaced by devices capable of automatically inflating the cuff and providing BP profiles over 24 h. Fully automated systems that were portable and eventually ambulatory became available by the late 1970s. In many early ABPM devices, BP was measured auscultatorily, and sometimes also oscillometrically. In more recent models, BP is usually measured oscillometrically.

Since these early days of ABPM use, further advances in BP monitoring include the development of continuous beat-to-beat recording of BP made possible with the Finapres. It is a device conceived by Jan Penaz (1973) as a servo-plethysmomanometer based on the vascular unloading principle using a light source and photocell in a finger cuff. It was further modified by Karel Wesseling (1990). It allows the investigation of the BP waveform without the need for invasive catheterization. Recently, a novel completely digital approach of the method for continuous noninvasive arterial pressure monitoring has been designed for patient surveillance in perioperative, critical and emergency care. It is based on concentrically interlocking control loops, which enable beat-to-beat correction of changes in vasomotor tone by means of a fast pulse wave analysis (Fortin et al. 2006).

Tonometry is based on the old sphygmograph technology as it describes a mechanism for the automatic non-invasive palpation on the radial artery. In order to obtain a stable BP signal, the tonometric sensor must be protected against movement and other mechanical artifacts. Using this technique, around-the-clock ambulatory, noninvasive, cuffless, wrist-type devices can now measure central aortic systolic pressure (CASP) and central pulse pressure (CPP) (Williams et al. 2013). In view of differences with brachial ABPM and with intra-arterial measurements, the prognostic significance of CASP and CPP remains to be determined in follow-up studies.

Pulse transit time (PTT) is the time it takes for the BP wave to arrive in the periphery; it depends indirectly on BP: the higher the pressure, the faster PTT. Pulse wave velocity (PWV) is the velocity at which the arterial pulse propagates through the circulatory system; it is clinically used as a measure of arterial stiffness. The determination of PTT and PWV is another approach currently being considered for the noninvasive detection of BP changes, but this method needs calibration (Fung et al. 2014). Pulse Decomposition Analysis (PDA) is another approach being used to noninvasively measure BP. The CareTaker is a device based on this principle (Baruch et al. 2011). It is a physiological sensing system that communicates physiological data wirelessly via Bluetooth. The device uses a low-pressure, pump-inflated, cuff surrounding the proximal phalange of the thumb that pneumatically couples arterial pulsations via a pressure line to a custom-designed piezo-electric pressure sensor. The sensor converts the pressure pulsations, using trans-impedance amplification, into a derivative voltage signal that is digitized and transmitted to and recorded on a computer. PDA is used to derive BP based on the concept that five individual component pressure pulses (due to the left ventricular ejection and the reflections and re-reflections of the first component pulse from two central arteries reflection sites) constitute the peripheral arterial pressure pulse (Baruch et al. 2011).

Parallel to these developments, home BP monitoring has rapidly progressed: devices for recording pressures taken at home have improved and become widely available (Krakoff 2014). They have the advantage that BP can be measured longitudinally over long spans, that data can be recorded in memory, and that in the newer devices, results can be sent to a data center or individual care providers for review and management, as part of telemedicine. Whereas many such devices use arm cuffs, wrist monitors have become available and their performance has increased in recent years. Whether wrist devices can be modified for accurate ambulatory automatic BP measurements is being investigated by the Phoenix Study Group of volunteering members of the Twin Cities chapter of the Institute of Electrical and Electronics Engineers (http://www.phoenix.tc-ieee.org) (Beaty et al. 2012).

Methodological considerations: chronobiological analysis of blood pressure records

Early studies of BP at the Chronobiology Laboratories of the University of Minnesota were based on self-measurements taken a few times a day, in some cases for only a couple days, and in others for much longer spans of years and even decades. Halberg had developed a simple method for the quantification of circadian rhythms in short and sparse data: the single cosinor. This method consists of fitting a cosine curve of known (or approximately known) period to the data by least squares (Halberg et al. 1967). Rhythm detection was done by an F-test of the zero-amplitude (no-rhythm) null hypothesis. Rhythm quantification consisted of the estimation of the MESOR, a rhythm-adjusted mean, and of the amplitude and acrophase, measures of half the predictable extent of change within a cycle and timing of overall high values recurring in each cycle, respectively. The method was extensively applied in school projects as well as in clinical research.

The method was later extended to include more than a single component, for a more precise representation of the circadian waveform. Adding the second harmonic with a period of 12 h to the 24-h fundamental component greatly improved the fit, accounting for the shorter and more pronounced dip of BP by night, the rapid increase in the morning, a postprandial dip accentuating with increasing age, and a slow decrease in the evening. Another extension of the method consisted of fitting a given model to the data over a fixed interval that was progressively displaced throughout the time series. This method is known as the chronobiological serial section (Halberg et al. 1977). It is useful to illustrate how rhythm characteristics change as a function of time, thus allowing the analysis of non-stationary time series. Methods were also developed to compare rhythm parameters between two or more time series or between two or more populations (Bingham et al. 1982).

When BP measurements could be recorded automatically in the mid-1970s, it became clear that fixed limits to delineate hypertension from normotension did not account for the large circadian variation in BP. Methods were developed to derive time-specified reference limits that accounted for the circadian rhythm in BP. Originally, these "chronodesms" were computed as tolerance intervals around the fitted 24-h cosine model (Halberg et al. 1978). As ABPM data became available from clinically healthy people of all ages, another kind of chronodesms was developed as time-specified prediction limits qualified by gender and age (Nelson et al. 1983). Prediction intervals were also computed for the MESOR, and for the 24-h amplitude and acrophase of BP and HR, based on a two-component cosinor model, separately for men and women in different age groups.

With denser data automatically collected around the clock, the question whether BP was acceptable, too high or too low no longer had a straight answer: only in a few cases were BP measurements all inside or outside the reference range, and in many cases there were readings both inside and outside the acceptable limits. New questions had to be asked, such as: (a) how many BP measurements are above acceptable limits; (b) by how much does BP exceed acceptable limits; and (c) when is BP most deviant? To answer the first question, one can compute the percentage time elevation (PTE) as the percentage of elevated readings over 24 h. This was an index similar to the BP load

introduced more or less at the same time by the Mayo Clinic, except that instead of fixed limits, we used time-specified reference limits qualified by gender and age (Cornelissen et al. 1993). However, different patients can have a similar PTE but still be at considerably different risk for cardiovascular disease if the excursion of their BP above acceptable limits is larger or smaller. The amount of excess or hyperbaric index (HBI) is computed as the area delineated by the BP profile when it is excessive and the upper limit of acceptability itself; it is expressed in mmHg x hour over 24 h. Depending on the circadian waveform of BP, excess can occur at different circadian stages in different patients. The timing of highest excess is computed as the time corresponding to the center of gravity of the area of excess. It is a useful guide for timing the administration of antihypertensive medication.

In order to summarize results from these parametric and nonparametric approaches, the "sphygmochron" was designed (Cornelissen et al. 1993). It is a form that lists on the one hand, the MESOR and 24-h double amplitude and acrophase of SBP, DBP, and HR from the composite model, together with the 90% prediction limits from clinically healthy peers matched by gender and age, and on the other hand, the PTE, HBI, and timing of excess. Abnormal circadian BP patterns can thus be readily identified. MESOR-hypertension is defined as a BP-MESOR above the upper 95% prediction limit from gender- and age-matched healthy peers. CHAT (Circadian Hyper-Amplitude-Tension) is defined as a 24-h amplitude of BP above the upper 95% prediction limit from gender- and age-matched healthy peers. Ecphasia is a 24-h acrophase outside the 90% prediction limits from gender- and age-matched healthy peers. In addition, pulse pressure is considered to be excessive when it exceeds 60 mmHg, and HR variability (HRV) is considered to be deficient when the 24-h standard deviation (SD) of HR is less than 7.5 beats/min. These abnormalities are referred to as "vascular variability disorders" (VVDs) when they are found to consistently characterize BP profiles from a given person. The thresholds that define VVDs have been used in several outcome studies, and their performance has been compared to a classification of the day-night ratio (DNR) in terms of dipping (Halberg et al. 2013).

Lessons learned from blood pressure monitoring

Self-measurements and manual measurements by staff

In the 1970s, self-measurements of BP were introduced in schools in different states in the United States as well as in several European countries, using mercury sphygmomanometers. These studies indicated for the first time that the circadian amplitude of BP was larger in children with a positive family history of high BP and/or related cardiovascular disease (Halberg et al. 1974), just as experiments on the stroke-prone Okamoto rat had shown an increase in the circadian amplitude of BP preceding the elevation in the BP MESOR (Halberg et al. 1980).

These studies also documented the critical importance of measuring BP during the night as well as during the day in order to correctly characterize the circadian amplitude of BP (Halberg et al. 1988). By 1966, circulatory circadian rhythms were also shown to persist for at least several months in the absence of known time clues, as three healthy subjects spent 2–4 months in isolation in separate caves, their period differing slightly from precisely 24 h (Halberg et al. 1966). Moreover, apart from external circadian

desynchronization, around-the-clock manual measurements by staff showed that SBP desynchronized from 24 h, whereas temperature and other physiological variables remained 24-h synchronized in the case of a child with a history of fever of unexplained origin recurring at intervals of several weeks (Halberg et al. 1966). These results clearly implied that the circadian rhythm in BP was partly endogenous and not a mere response to activity, a misconception that persisted at least until 1993 (Stanton and O'Brien 1993), when Lemmer et al. (1993) clearly showed in transgenic hypertensive rats that BP could desynchronize from activity.

The risk of misdiagnosis based on BP measurements in the physician's office was elegantly demonstrated by Frederic C Bartter (1974) who also advocated that data be analyzed by cosinor. Around-the-clock measurements of BP by staff for several weeks illustrated that ignoring the circadian variation in BP could lead to opposite diagnoses depending on when BP is measured in the clinic. The impact of when BP is measured was later assessed from a conceptual viewpoint, based on simulations (Cornelissen and Halberg 1996).

Automatic around-the-clock measurements of blood pressure as part of international epidemiological study

The first automatic around-the-clock measurements of BP obtained in our laboratory used the Arteriosonde, an analog device that necessitated the manual calibration of BP and time, as well as the taking off of data from graphic recordings to be transferred onto punched cards prior to analysis on a PDP II computer. The collection of BP data was part of an ambitious international study known as the Minnesota-Kyushu study of breast cancer risk. The original protocol developed in Minnesota and Japan also included several satellite studies carried out in Italy, Great Britain, Sweden, and Mexico (Halberg et al. 1981b) .

The Roche Arteriosonde was used at the Clinical Research Center of the University of Minnesota to compare healthy women in three age groups who were either at a low or high risk of developing breast cancer. They were monitored once in each season. A battery of hormonal determinations was concomitantly obtained. Despite the limitations stemming from analog data, results showed a correlation of the circannual amplitude of aldosterone with both DBP and cardiovascular disease risk (Halberg et al. 1981b, 1988). With BP data covering the full 24-h day in clinical health, time-specified reference limits were computed as tolerance intervals around the 24-h cosine model.

Reference values from womb to tomb

In the 1980s, Masayuki Shinoda's Nippon-Colin Company (Komaki, Japan) developed a portable automatic BP monitor. The BP-203X model we used was a big blue box weighing 9.1 kg. It was provided with an automatically inflatable cuff. It had a handle that allowed its transportation back and forth between home and the laboratory. Auscultatory and oscillometric measurements of BP and HR could be obtained at different intervals ranging from 1 to 99 min, initiated upon start. Numerical data were printed on thermal paper together with the date and time when they were collected. They also had to be transferred to punched cards prior to analysis.

The BP-203X Nippon-Colin monitor was used in several cross-sectional studies, examining, among others, the effect of sodium restriction and sodium loading on BP. With the

availability of methods to compare individual rhythm parameters, we showed that in addition to salt responders and nonresponders, there were some cases who responded to salt restriction with an increase in BP (Halberg et al. 1988). This monitor was used to study the effect of different procedures on BP. Examples are the persistence of the circadian rhythm in BP during bedrest, the circadian stage-dependent effect of the cold pressor test on BP, and the BP response to dental procedures (Halberg et al. 1988).

Longitudinal records of around-the-clock BP data could then also be obtained. They were instrumental in demonstrating that BP increases toward mid-sleep, well before awakening, the latter associated with a larger and faster increase in BP (Halberg et al. 1981a). They also served to show how the uncertainty on the estimation of circadian parameters could be reduced by 35% (and 45%) by extending the monitoring span from 1 to 2 (and 7) days (Halberg et al. 1984). Eventually, it was recommended at several consensus meetings that BP be monitored around the clock for at least 7 days at the outset in order to obtain more reliable estimates of the circadian rhythm, and to also obtain a rough estimation of the weekly variation in BP and HR (Halberg et al. 2013). Monitoring for longer than 24 h recognizes the need to account for the novelty effect and for the large day-to-day variability in circadian rhythm characteristics.

The Nippon Colin Company also had a neonatal model. It was a little smaller than the BP-203X and it was provided with tiny arm cuffs of different sizes. This neonatal BP monitor was extensively used by us in Minnesota as well as by a number of coinvestigators in Italy, Japan, the Czech Republic, Russia, Germany, and Spain. We showed that the circadian rhythm in BP and HR could be detected early after birth on a population basis, that its phase was almost in antiphase with that of the mother, peaking shortly after midnight, and that it had a larger amplitude in babies with a positive family history of high BP and/or related cardiovascular conditions than in babies with a negative history (Schuh et al. 1989), extending results obtained earlier with self-measurements in school children (Halberg et al. 1974).

The major new finding stemming from these studies was the presence of a prominent circaseptan (about-weekly) variation in BP and HR during the first few weeks after birth. First detected cross-sectionally in data from Italy, it was confirmed longitudinally in Russia, Japan, the Czech Republic and Minnesota (Cornelissen et al. 2002b). In the data from the Czech Republic, we found that the phase of the circaseptan rhythm was determined by the time of birth (developmental age) rather than by the day of the week. In records spanning several weeks, we learned that the period could differ from precisely 7 days, a sign of partial endogenicity, further supported in Minnesota where data on twins were examined by intracorrelation analysis (Cornelissen et al. 2002b).

The first truly ambulatory BP monitor we used was the ABPM-630 from Nippon Colin. It operated on gas cartridges. BP was measured by auscultation and oscillometrically. The monitor could be programmed to automatically inflate the cuff at intervals and to vary the sampling rate in four fractions of the 24-h day. It also had an event recorder to mark times of waking up, going to bed, meal times, times of exercise or times when medication was taken. Data stored in solid-state memory could be downloaded to a personal computer by means of an interface.

The ABPM-630 was extensively used to collect data in clinical health. Typically, data were collected at 15-min intervals for 2 days. As part of our “Womb-to-Tomb” study, around-the-clock records were obtained from clinically healthy individuals on three

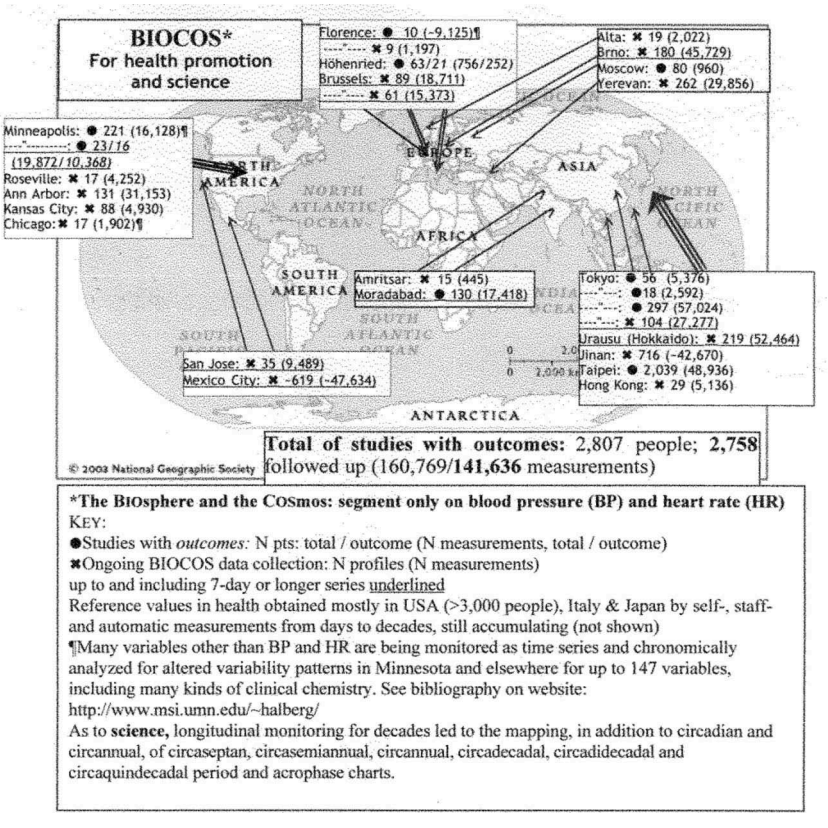

Figure 1. 2004 map of BIOCOS participation.
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continents from children to centenarians, and during pregnancy, Figure 1. These data were essential to derive time-specified reference values qualified by gender and age, on which our sphygmochron analysis is based. They also helped assess changes as a function of age, namely, a reduction in circadian amplitude, an advance in circadian acrophase, and an increased prominence of the circaseptan component.

Outcome studies

The ABPM-630, and later the TM-2421 and the TM-2430 from A&D (Tokyo, Japan) were also critical for the assessment of outcomes from prospective clinical trials and retrospective studies. Outcome studies carried out in Japan, Taiwan, the Czech Republic, Germany, and Minnesota corroborated the risk associated with an excessive circadian amplitude of BP (CHAT) (Halberg et al. 2013). They also identified other abnormal BP and/or HR patterns (VVDs), which all contribute to cardiovascular disease risk and which can also be associated with an increase in risk in the absence of MESOR hypertension. In contrast to the almost linear relationship of cardiovascular disease risk with the BP MESOR, its relation to the circadian amplitude of BP is nonlinear, risk being increased only once a threshold amplitude is exceeded. A similar nonlinear relationship holds for HRV.

Whereas uncomplicated MESOR-hypertension was associated with less than 10% adverse outcomes within 6 years in one outcome study, the presence of one or two additional VVDs increased that risk to 29% and 53%, respectively. Risk assessment based on the screening for VVDs was also found to outperform predictions conventionally based on a classification in terms of "dipping" derived from the DNR (Halberg et al. 2013).

Marker-rhythms-based chronotherapy

The chronotherapy of BP benefits from the fact that BP, which can now be easily measured noninvasively around the clock, can serve as both a marker variable and as a gauge of the response to timed treatment (chronotherapy). Several transverse and longitudinal chronotherapy designs have been used and their relative merits have been reviewed (Cornelissen et al. 2017), from small studies on groups and N-of-6 pilot studies to larger clinical trials. Some chronotherapy designs were aimed at optimal results for the average patient in a given target population, while others aimed at personalized chronotherapy, where each patient in the study was considered as an N-of-1 pilot.

The first optimization of an antihypertensive medication by timing designed by Franz Halberg in cooperation with Frederick C Bartter and Hans-Georg Güllner was an impeccable double-blind, placebo-controlled study involving 10 patients (Güllner et al. 1979). The anti-hypertensive treatment tested was the once-daily administration of prazosin, an α1-blocker with a plasma half-life of about 1.5 h. Patients were admitted to a metabolic ward, fed constant diets and kept recumbent during the entire study. BP monitoring started 3 days before the start of intervention, which consisted of the administration of one capsule, either active drug (1 mg prazosin) or placebo, every 4 h for 7 days. Only one prazosin capsule was given every day. The time of prazosin administration was delayed by 4 h every day. BP data were collected at 30-min intervals around the clock with the Arteriosonde. The effect and duration of prazosin's action were reported to depend not only on dosage, but also on the time of its administration.

Another chronotherapy protocol was aimed at treating at the anticipated optimal circadian stage, based on the circadian BP profile and the pharmacokinetics of the drug used (Cornelissen et al. 1994). In this approach, results from the sphygmochron were used as a guide to time treatment, targeting the time of peak drug action to the time of highest BP excess. This design from Dr. Rina Zaslavskaya was tested by her versus conventional treatment at the time, which consisted of dosing three times a day. She tested three drugs: propranolol, clonidine, and α-methyldopa. As compared to once-traditional treatment three times a day, in all three cases, chronotherapy was associated with a larger reduction in BP using a lower dosage, and it resulted in a faster response with fewer side effects.

Before undertaking large clinical trials, it is often cost-effective to first proceed with smaller pilot studies aimed at determining the optimal circadian stage at which to administer a given treatment. Such pilot studies can be as small as N-of-6 studies, wherein six different circadian stages are tested, equally distributed along the 24 h, or at least during the waking span from the time of awakening to bedtime. 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

(Cornelissen et al. 1991) and also on BP. Lipoperoxides in platelet-rich plasma and the affinity of lymphocyte-b_2-adrenoceptors for ^{3}H-dihydroalprenolol were determined around the clock for 2 days before (reference) and at the end of a 1-week intervention span. The circadian stage-dependent response of these two variables to low-dose aspirin was demonstrated by the fit of a 24-h cosine curve to the treatment-versus-reference differences assigned to the respective times of treatment administration.

Ultimately, preference should be given to N-of-1 investigations since they underlie personalized optimization of treatment, recognizing that every patient is different. Individualized chronotherapy is made feasible by the availability of BP monitors for the automatic collection of around-the-clock data, preferably for longer than 24 h, and of statistical methods for their analysis. The latter include parameter tests (Bingham et al. 1982) and the self-starting cumulative sum (CUSUM) control chart (Hawkins 1987). As opposed to applications in industry, in medicine the start of treatment is known (recorded); if this time coincides with the time when the CUSUM line first departs from zero, then a causal relation may be assumed (Cornelissen et al. 1997).

Studies on groups of patients are best designed to include more than two test times, as is often the case when comparing the efficacy of antihypertensive treatment given in the morning or evening. Depending on the response rhythm to the given treatment, selecting two treatment times about 12 h apart, such as morning and evening, may correspond to the midline crossing of the response rhythm. If so, no difference will be detected, even if benefit could be derived from treating at a different circadian stage. It is also recommended to measure BP around the clock, so that the circadian variation can be assessed, since treatment can also affect the amplitude and/or acrophase of the circadian BP rhythm, in addition to lowering the MESOR. Some, but not all antihypertensive medications affect the circadian amplitude of BP.

One example of a small clinical trial using six different test times between 08:00 and 18:00 enrolled 24 presumably normotensive individuals, who were randomly assigned to one of six times to undergo periodontal surgery (Raab et al. 1998). The BP response to periodontal surgery was shown to be circadian stage dependent, with a decrease rather than increase in BP found when periodontal surgery was performed in early afternoon. Transverse clinical trials like this one have the advantage that patients can be kept in their respective arms of the study for long enough spans to be followed-up until a sufficient number of adverse events occurred to make global recommendations for the population, not only in terms of BP lowering, but also in terms of actual target organ damage.

Studies based on a longitudinal design require repeated ABPM profiles, before treatment is initiated, and at the end of each stage corresponding to a different circadian stage at which medication is administered; the time of treatment is then changed from one stage to another, preferably covering at least six circadian stages equally distributed between the time of awakening and bedtime. One key feature of longitudinal designs relates to the duration of treatment at any given administration time. Some studies have considered an interval as short as one day, in which case results can be obtained after 7 days during which BP is continuously monitored around the clock (Prikryl et al. 2005). Other studies opted to keep the same treatment time for at least one month before switching the administration time to the next circadian stage, in which case the effect of treatment can be more reliably evaluated based on 7-day/24-h ABPM at the end of each

stage (Watanabe et al. 2013). The optimal duration of treatment on any administration time, however, has not been determined yet. It should be long enough for its full effect to have taken place and to be reliably assessed, but not too long to avoid interference from other sources, such as the modulation of the circadian BP rhythm by the circannual variation.

One important lesson learned from international studies using different chronotherapy protocols is the merit to consider more than two test times since the optimal treatment time for a given population of patients and a given intervention may differ from morning or evening. Another important lesson learned is that even if one time seems to be superior overall, it may not fit all patients. In part, this is because the optimal time to treat depends on the chronodiagnosis: patients with CHAT have most of their BP excess by day, but patients with a reversed BP pattern have most of their BP excess by night.

Chronomics

Chronomics is the study of rhythms in biota as they are influenced by rhythms in the broad environment. The tenet is that since biota live in an open environment, all periodic phenomena in the environment are susceptible to influence the time structure of life forms in that environment, from the about weekly variations in weather conditions on earth to the multiple oscillations characterizing the sun, the interplanetary space and the cosmos, including the about 10.5- and 21-year cycles in solar activity.

Work with colleagues in the United States, Russia, Japan, Norway, China, the Czech Republic, and Ukraine led to the finding that magnetic storms are associated with a decrease in nocturnal melatonin and in HRV. Not surprisingly, these variables relate to the two organs generating strong electrical signals. The decrease in HRV may be a mechanism underlying the higher incidence of mortality from myocardial infarctions observed in Minnesota during years of maximal solar activity by comparison with years of minimal solar activity (Cornelissen et al. 2002a).

Quo vadis?

Ongoing monitoring worldwide (Figure 1) continues to accumulate evidence for the need to routinely screen for VVDs and to better understand how variability in BP and HR can be influenced by the broad environment. VVDs like CHAT have been diagnosed in all geographic locations examined thus far, Figure 2. Because antihypertensive medications can affect the circadian amplitude in addition to the BP MESOR, treatment effects should be assessed on all characteristics of the circadian BP rhythm. Because abnormal variability in BP and HR also relates to cardiovascular disease risk, antihypertensive treatment should target not only the lowering of BP, but also the restoration of an acceptable circadian variation. Methods to analyze individual BP records now make it feasible to determine personalized optimal treatment times. Outcome studies remain to be performed to assess the gain to be obtained from personalized chronotherapy in terms of an actual decrease in adverse cardiovascular events.

Clinical trials based on a longitudinal design have thus far been limited to assessing benefit derived in terms of changes in the marker variable(s) (BP and HR). Outcome

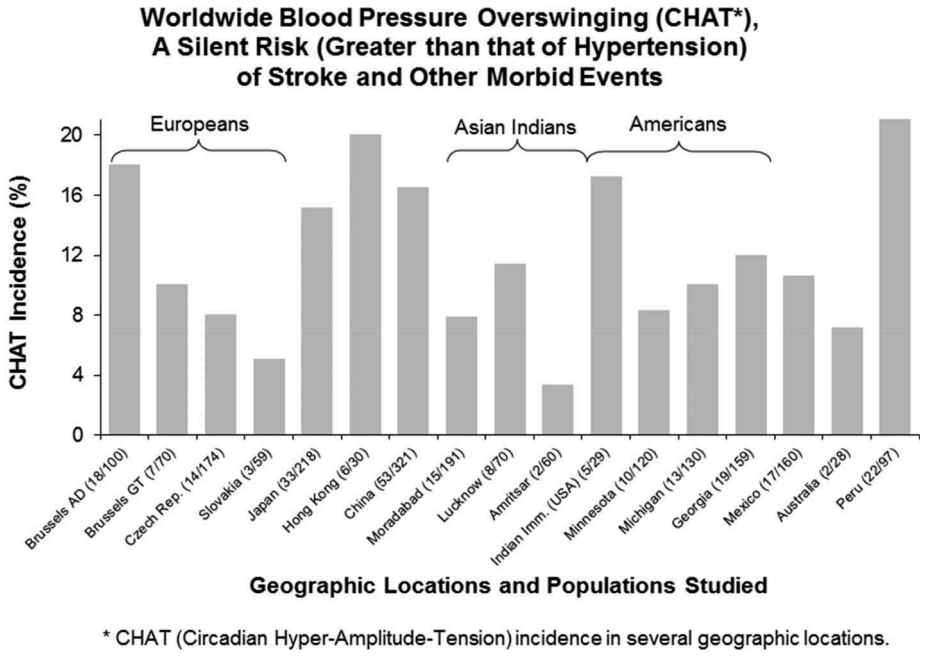

Figure 2. Summary of 247 cases of CHAT in 2016 ABPM profiles collected worldwide, detected in the presence or absence of MESOR-hypertension.

studies focused on benefits to be derived in terms of the incidence of adverse cardiovascular events will need to first determine for each patient the optimal treatment regimen, then compare the occurrence of adverse events between patients thus treated chronobiologically versus similar patients treated conventionally, without consideration of timing, since the optimal treatment time will differ among patients.

Much progress has been made not only in terms of measuring BP but also of doing so around-the-clock automatically and noninvasively. Much progress has also been made in terms of interpreting BP data and taking BP variability into account in making a treatment decision. Much work, however, still needs to be done. First and foremost, the knowledge gained on how to improve the diagnosis, prognosis and treatment of BP disorders needs to enter mainstream medicine. ABPM should not be reserved for special cases. Like in the case of high BP, there are no symptoms in the presence of VVDs, and abnormal BP variability is associated with a marked increase in cardiovascular disease risk even in the absence of an elevated BP. For these reasons, we have recommended that ABPM be available for everybody, for at least 7 days at the outset (Halberg et al. 2010).

The shortcomings of ABPM restricted to 1 or 2 days interpreted only in terms of mean values and on day-night differences, and the need for longitudinal monitoring for patients on antihypertensive medication are reflected in the new ACC/AHA 2017 Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults that give higher emphasis on home BP than on ABPM (Whelton et al. 2017). While home BP facilitates longitudinal monitoring, the merits of ABPM should not be overlooked, once the current shortcomings associated with its current usage are

overcome. To account for the novelty effect and for the usual large day-to-day variability in circadian characteristics of BP, monitoring should be done for several days. The data also need to be interpreted chronobiologically, recognizing that references values should be time-specified and qualified by gender and age.

Recent advances in technology and wireless communication provide new opportunities and are likely to also impact the healthcare system. Miniaturized sensors communicating with wearables such as watches and smart phones are increasingly being used for self-surveillance by ordinary citizens interested in their own health and performance. This is evidenced for instance by the "Quantified Self" movement. While variables such as activity, temperature and HR are relatively easy to measure, however, this is not yet the case for BP. The arm cuffs used in ABPM devices are uncomfortable. Wrist devices available for home BP monitoring could be made ambulatory but would need to incorporate a correction for position. Devices based on the analysis of the BP waveform also require calibration. Photo-plethysmography has recently been used to measure BP on the wrist, but the accuracy of devices based on this technique remains questionable. As algorithms and technology further improve, it may soon be possible to measure BP effortlessly and to derive information about the heart's function itself. This represents a unique opportunity to integrate chronobiological methods and concepts into these evolving systems to make sure that massive data collection does not happen at the expense of quality data analyses.

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