PERSONALIZED CHRONOME (TIME STRUCTURE) COMPLEMENTS GENOME DETECTING VASCULAR VARIABILITY DISORDERS (VVDS), INCLUDING MESOR-HYPERTENSION

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Computer-aided, automatic, inferential statistical, self-help-based preventive health care is better and cheaper when the personal surveillance is done by a secure Internet, without the need for a care provider. The introduction of such a system in a medical faculty and then university-wide, and extended to secondary education, could lead to a universal scientific literacy of the entire population, while it also promises dividends from research on space weather in the spirit of Alexander Leonidovich Chizhevsky, that was not possible in the pre-computer era.

Key words: time structure, chronome, monitoring, blood pressure, vascular variability disorders (VVDs).

Introduction

As compared to a genome-based personalized care in the future, self-care based on monitoring key marker variables, with data analyzed by computer and interpreted for their time structure (chronome) as-one-goes could involve most people treated for high blood pressure (BP). Data analyses can be handled by a computer-savvy individual in a circle of family and friends, as well as offered as part of community services, e.g., in schools. The complexity and cost of a chronobiologic system could be greatly reduced by automating analyses on a secure website that also offers educative materials. A summary of results could be returned cost-free to participants, while the data are archived for later interpretation in the light of outcomes as they become available. This is now ongoing on a small scale in a project on The Biosphere and the Cosmos, BIOCOS (corne001@umn.edu). Decades-long time series of around-the-clock measurements have become available for the BP and heart rate (HR) of clinically healthy subjects, which served to derive reference values, computed as 90% prediction intervals qualified by gender, age and ethnicity for circadian parameters as well as for time-specified values along the 24-hour scale. Outcome studies assessed the relative risk of morbid events associated with deviations from these norms, thus identifying Vascular Variability Disorders (VVDs). Among them are MESOR-hypertension, an elevation of the BP-MESOR (M, Midline-Estimating Statistic Of Rhythm), and CHAT (Circadian Hyper-Amplitude-Tension), a BP overswing. These chronobiologically-interpreted records are useful for diagnosis and treatment validation and must be rendered affordable as a step toward a chronome-based personalized health care, experimentally validated in the context of BP and HR.

Chronobiologically, i.e., time-structurally-interpreted 24-hour/7-day monitoring of BP and HR is ongoing on a small scale in several geographic locations and, as a demonstration of its feasibility, also at the People's Friendship University of Russia in Moscow. When the chronobiologic interpretation of a 24-hour/7-day screening record of data collected automatically at 30-min intervals shows abnormality, and the presence of one or several VVDs is validated in a repeated monitoring session, treatment is instituted, and its kind and timing are guided by the kind of VVDs diagnosed (chronotheranostics). Once treatment is started, continued weekly analyses of years-long half-hourly around-the-clock (briefly 24-hour/7-/365-day) records are recommended for the surveillance of treatment efficacy to validate the presence of desired effects and to identify any undesired effects, such as iatrogenic CHAT as early as possible, so that they can be eliminated or at least reduced.

As a dividend from the follow-ups on the data flow aimed at the prevention of life-threatening diseases, of benefit to the individual being screened, medical science may gain improved reference standards from those who die uneventfully at an advanced age while from those experiencing an adverse event, new harbingers and/or mechanisms of disease may be detected. Further, these same databases may provide important information regarding the roles played in human health, disease and other affairs by the earth, the sun and the broader cosmos, and even help in the development of rational countermeasures to undesired, heretofore undetected environmental effects. This is the topic of a novel transdisciplinary science in the sense of Vasily Vasilyevich Dokuchaev and Vladimir Ivanovich Vernadsky, as visualized by Alexander Leonidovich Chizhevsky in the era before computers, and implemented in the laboratory by one of us (Sergei Mikhailovich Chibisov) with electron microscopy and physiological studies of association with magnetic storms, amenable to statistical validation (1).

The conceptual formulation of home- and Internet-based self-help in medicine has been eloquently and thoroughly visualized as cybercare for 2028 or 2033 by former U.S. Surgeon General C. Everett Koop et al. (2). Recognizing the magnitude of the problem, these authors start by citing Machiavelli: «There is nothing more difficult to take in hand, more perilous to conduct, or more uncertain in its success, than to take the lead in the introduction of a new order of things». One of us learned it in person when the pursuit of what he called circadian rhythms was dismissed as his «paranoia». He lost his laboratory and had to perform his experiments in a former paint room at a state hospital in the 1950s (3). Ignaz Zadek must have learned this by the end of his life in 1931, after he wrote as a young fellow in 1880 in his thesis for his medical degree, as published for the medical profession in 1881, that he was interested (not in inter-individual differences but) in the (we add personalized) changes of BP within a given person (4). In 1904, Theodore C. Janeway, an opinion leader at Johns Hopkins University, advocated that frequent readings of patients' BP be taken before a physical examination to establish (we add personalized) normal ranges and to assess periodic variations (4). And in 1974, Frederic C. Bartter (of Bartter's hypokalemic syndrome fame), then head of the Hypertension-Endocrine Branch at the

U.S. National Institutes of Health and later the head of the institutes' clinical center, checked on his patient whose BP was previously diagnosed differently by spotchecks made by two physicians who saw him at different times of day (4). Around-the-clock monitoring at NIH for 17 days provided an explanation for the discordant diagnoses, as shown in Figure 1. Bartter concluded in print (4).

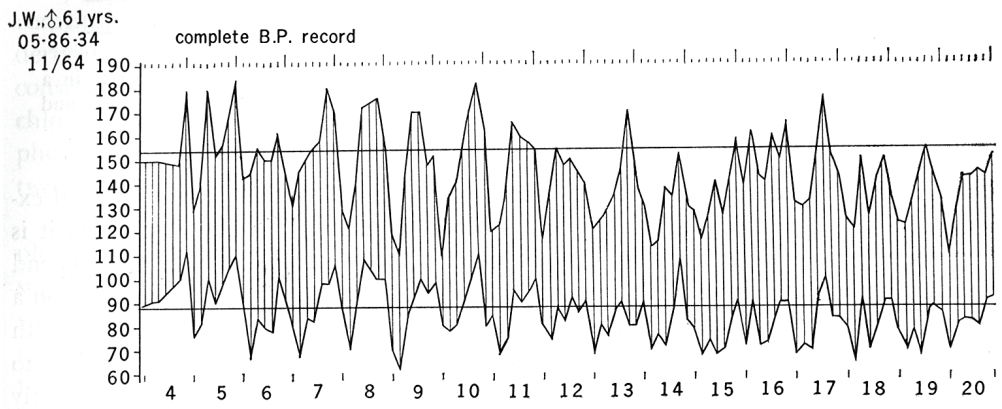

Figure 1. Blood pressure (BP) measurements taken 6 times each day for 17 days by staff at the Clinical Center of the U.S. National Institutes of Health on a 61-year-old patient show the large within-day variation that accounts for his diagnosis as «normotensive» by a physician habitually seen in the morning and as «hypertensive» by another physician regularly seen in the late afternoon. Guidelines of BP assessment can use time-varying rather than fixed limits and can assess day-to-day and longer-term variability. The diagnosis of «borderline hypertension» based on casual office measurements assessed by WHO limits resembles flipping a coin to decide whether to see a physician in the morning or the evening. (Even for patients with a 24-hour mean of SBP/DBP around 149/90 mmHg, «hypertension» is not detected 22% of the time because of the lack of consideration of circadian variation in computations based on a circadian amplitude of 20 mmHg [near, but still below the upper 95% prediction limit in clinically healthy adults] and acrophase of –240° [4 PM].) Limitations in dealing with casual measurements or office-hour profiles of BP interpreted by fixed limits, irrespective of gender and age, can be replaced by time-varying reference standards (chronodesms) and one must rely on more than one or a few casual BP measurements. In the absence of a measurement error, the circadian rhythm in BP results in contradictory diagnoses at different clock-hours. © Halberg.

By conventional standards, this patient is clearly normotensive every morning. Yet the blood pressure determined each day at 6 in the afternoon provides especially convincing evidence that this patient is a hypertensive... My plea today is that information contained in such curves [cosinor fits] become a routine minimal amount of information accepted for the description of a patient's blood pressure. The analysis of this information by cosinor should become a routine. It is essential that enough information be collected to allow objective characterization of a periodic phenomenon, to wit, an estimate of M... an estimate of [the amplitude] A itself, and finally an estimate of acrophase, «phi» [a measure of timing]. In this way, a patient can be compared with himself at another time, or under another treatment, and the patient can be compared with a normal or with another patient.

In 1984, the «chronobiology of blood pressure» appeared in extenso under the title «Chronobiology of blood pressure in 1985», a modification in italics in the title which had originally been «...in 1984», made by the late, and to us dear, physician/industrialist/publisher Agostino Carandente, whom we then considered a pessimist. In

2010, when we still have to explain what the Chronobiology of BP ought to be, we realize that Agostino was an optimist (4).

Koop et al. (2) advocate a system change from centralized hospitals to focus on neighborhoods and the home through technology and aim to merge private health care, public health care, national security and education. In the broad context of their detailed, scholarly and hardly improvable vision as to communication, we record what has already been implemented by us since 2000, in terms of BP and HR monitoring, not only toward their goal of modernizing conventional spotcheck-based care but also with respect to an improved quality of care, based on self-collected time series rather than upon spotchecks at home, if not in the office of a care provider. Such screening has been implemented on students at the People's Friendship University of Russia in Moscow. The same kind of BP and HR self-surveillance is also under way in two Japanese towns, a university hospital in Japan, one in Hong Kong and another in Italy, a university clinic in the Czech Republic, two hospitals in India, a research facility in Mexico, and in general practice settings in Belgium. With current technology, this approach can be extended further on an international scale as an immediate answer to the demands of at least one important BP-related aspect of universally available computer-aided preventive care at affordable cost, with BP chronobiology being the first step pertinent to a large segment of the population (4).

Internet-aided self-help in monitoring BP and HR constitutes a step toward changes from a manual spotcheck-based to cyber-collected and automatically-analyzed data, yielding diagnoses and treatment recommendations based on the chronomes of BP and HR time series. For screening or self-surveillance during treatment, the chronome-based approach is cheaper since it does not require a care provider, yet it automatically provides what is already a sine qua non in research, namely inferential statistical analyses that include both hypothesis testing and point as well as interval estimates of parameters. Hence, decisions are better than those based on spotchecks that may depend on the time of day when a patient is seen by a care provider (4). It seems pertinent that the complexity of these analyses is no problem when they are provided automatically by a website or currently by BIOCOS.

Why MESOR and other characteristics rather than only the mean?

It is well recognized that BP is highly variable. Since part of this change is rhythmic, a diagnosis based on single, albeit repeated measurements runs the risk of being dependent on the time of day when they were taken, affecting the recommendation of treatment, perhaps for a lifetime. The least squares fitting of models consisting of one or more cosine curves with anticipated periods (of 24 and 12 hours) accounts for part of the variability, yielding estimates of the circadian amplitude and acrophase, together with a measure of location, the MESOR, that is usually more accurate and/or more precise than the arithmetic mean. The circadian parameters further allow the detection of VVDs that today are not screened for in health care. Examples of VVDs are illustrated in Figure 2, screened for in a summary called «sphygmochron» (4). Some of these conditions can be induced by treatment aimed solely at decreasing the BP-MESOR, whereby iatrogenically, one may trade a bigger risk, such as CHAT for the lowering of an elevated BP. Taking the chronome into account is now possible in the context of an improved yet more affordable health care (4).

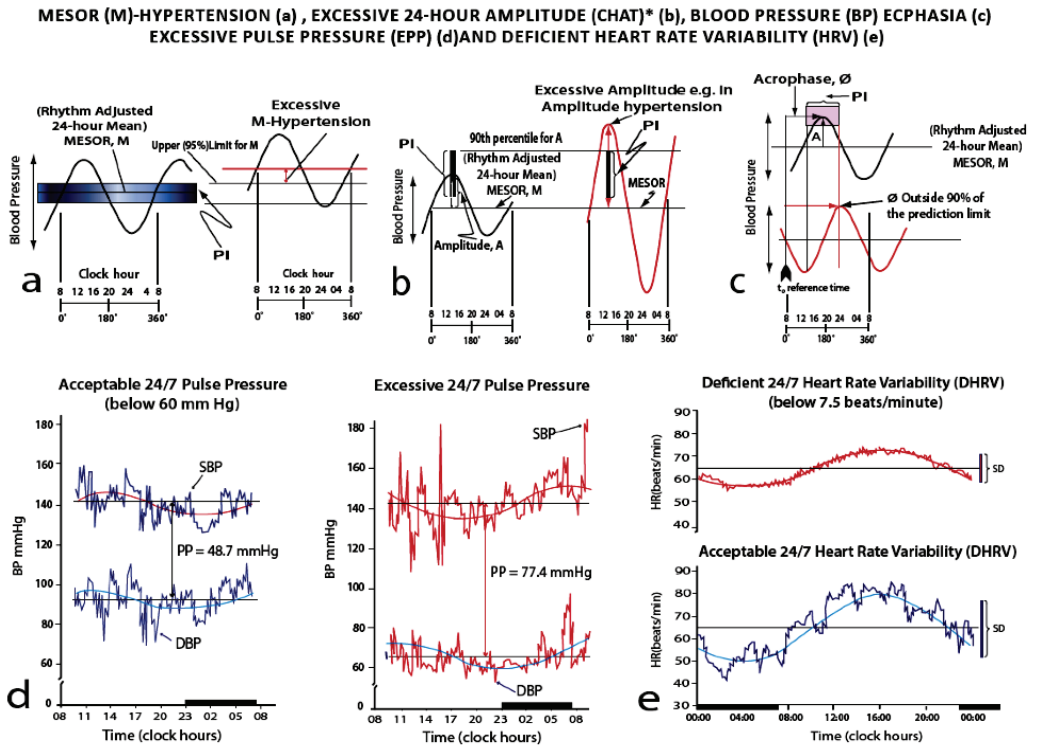

Figure 2. Definitions and illustrations of abstract vascular variability disorders, (a) to (c) diagnosed by cosinor (parametrically), (d) and (e) diagnosed by thresholds:

(a) MESOR-hypertension (MH), can be systolic (S-MH), diastolic (D-MH), mean arterial (MA-MH), or a combination of these conditions, incomplete when demonstrated only parametrically (complete when complemented non-parametrically by an extent of excess during 24 hours > 50 mm Hg x hour).
(b) Circadian Hyper-Amplitude-Tension (CHAT), which can also be systolic (S-CHAT), diastolic (D-CHAT), mean arterial (MA-CHAT) or a combination of these conditions.
(c) Odd timing of the circadian rhythm of BP but not of that in HR (BP ecphasia).
(d) Excessive pulse pressure (EPP), when the difference in the MESORs of SBP and DBP for adults exceeds 60 mm Hg, a threshold that remains to be replaced by reference values from clinically healthy peers (eventually with disease-free long-life outcomes) specified further by gender, age, ethnicity and geography.
(e) A deficient HR variability (DHRV), defined as a standard deviation of HR less than 7.5 beats/minute, a threshold that remains to be replaced by reference values from clinically healthy peers (eventually with disease-free long-life outcomes) specified further by gender, age, ethnicity and geography. © Halberg.

Chronomes and genomes are complementary structures in time and space, respectively. The genetic aspect of a personalized medicine has been thoroughly discussed by Richard Gallagher (5). He rightly lists goals: «First, everyone's genome will be sequenced cheaply and the sequence will be interpretable, and predictive. Second, [a person's] medical problems, discerned by analysis of the sequence, will be avoided by genetic, lifestyle or therapeutic means. And third, where a disease has to be treated, [medicines will be] exquisitely tailored to... patient and ailment. No risk, no mess, no problem». Specifically, Gallagher anticipates a $1,000 genome assessment and notes that it would not be useful at $10,000 an interpretation. Gallagher also notes that the genome is a moving and complex target, and refers to a commercial use, «Direct-to-Consumer genotyping», indicating that it «isn't a success. A handful of companies continue to provide information on ancestry (whimsical), findings on traits (trivial), and a little advice on disease risk. They need time for research to turn them into a ge-

nuinely useful service». In other words, its promise notwithstanding, a genetically personalized medicine is, to date, too high in cost and too low in benefits.

By comparison, routine chronobiologic 24-hour/7-day screening currently detects, among others, more reliably than conventional care, MESOR-hypertension (MH, an elevation of the rhythm-adjusted systolic (S) and/or diastolic (D) BP average or MESOR, M). MH is one of several vascular variability anomalies that become disorders, VVDs, Figure 2, if they are detected in a 7-day record analyzed as a whole. If replicated, a VVD can constitute a risk of stroke exceeding that of MH in Asians. A circadian BP overswing (CHAT), another VVD, is a feature common in two components of a pre-metabolic syndrome, namely pre-hypertension and pre-diabetes. CHAT and/or other VVDs can combine into Vascular Variability Syndromes (VVSs) (4).

In some cases and/or at some clock-hours, depending on the individual, the lowering of a high BP-MESOR is associated with a complication by CHAT, Figure3. The treatment-induced CHAT can represent a risk of stroke higher than that of MH. Hence, lasting CHAT and other VVDs should be reduced or eliminated, something that can be done on occasion by timing, Figure 3. Education of the public in the relative risks of alterations in BP-M and in other circadian parameters (amplitudes, A, and/or acrophases, «phi») of BP and/or HR and in the detection, treatment and further research on altered circulatory dynamics is within the mandate of state, national and international health and education departments and related foundations and agencies.

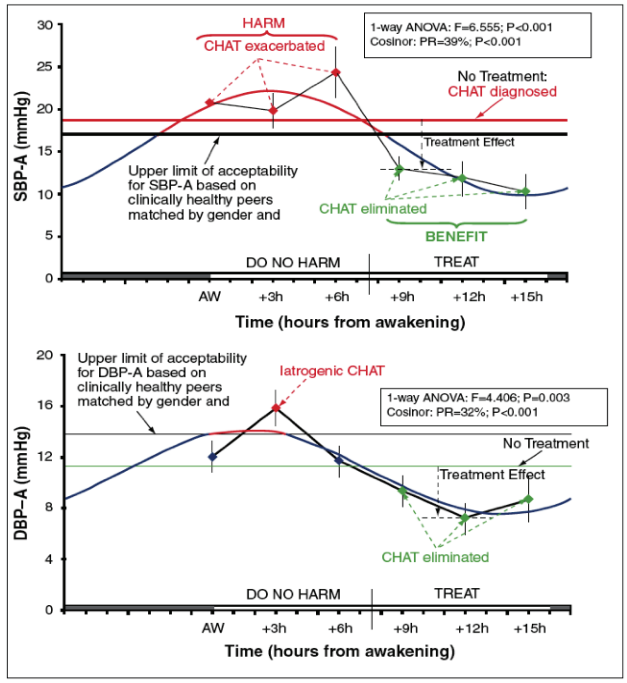

Figure 3. A popular drug, if prescribed without personalized surveillance, can induce a vascular variability disorder, VVD, such as Circadian Hyper-Amplitude-Tension (CHAT). A change in the time when the drug is taken can make the same dose of the same drug in the same person beneficial or vice versa. At one administration time (before noon), Hyzaar induces CHAT in diastolic BP and exacerbates a preexisting CHAT in systolic BP. At another time of administration, Hyzaar eliminates a pre-existing VVD. These opposite effects were found in tests at six medication times, each administered for about a month, with half-hourly surveillance of BP during the last week of each span. These differences occur as a function of the timing of the drug's use along the scale of 24 hours. Original study by Dr Yoshihiko Watanabe. © Halberg.

Chronome-based care is being implemented cost-free in adults today, although as yet on small scales. In the future, its application will have to be enlarged as a service available for everyone, starting not later than in early schooling, in middle school or earlier, preferably at birth, as well as by adult education, including in particular pregnant women, where it is particularly cost-effective. Starting with the BP and HR, already-documented great risks that escape conventional diagnoses have been detected and treated by available lifestyle modification and/or by changing the timing of medications (4). Where a disease has been found, the timing of lifestyle change, such as exercise, diet or medications, can be tailored according to the chronome determined on the basis of self-monitoring. Harm from any iatrogenic CHAT is detected and eliminated. Risk may be removed and some handicapping and life-threatening problems may be avoided. For a chronobiologically-implemented diagnosis about the chronome of BP and HR, the cost of an automatic ambulatory monitor via BIOCOS (corne001@umn.edu) is $450, a cost that could be lowered (4).

More than a century after Zadek's and Janeway's time, the study of periodic variations is facilitated by computers. A website is under construction, with an endeavor to build affordable tools at a cost below US $100, already demonstrated as practical (4) (as compared to the as-yet abstract goal of US $1,000 for a personalized genome; 5). It seems desirable and more important to educate the public and medical students than to offer postgraduate courses to care providers before the evidence accumulated with respect to the cost-effectiveness of computer-delivered chronobiology has become part of the business plans of care providers' compensation. False positive and false negative diagnoses of high BP can be reduced by replacing the BP cuff in a physician's office used before a physical examination by the results of a chronobiologically-interpreted self-collected and automatically website-analyzed ambulatory monitoring BP profile (C-ABPM) of 24-hour/7-day for screening and of 24-hour/365-day when consistent alterations are noted. This education may be more successful when involving the public than when addressed to care providers paid by the number of patients seen or by procedures used, rather than by the outcomes of their services. Involving the public may also be more successful than addressing those insurance executives who fail to see the savings in both suffering and cost when a program of prehabilitation, notably of stroke prevention, is implemented by computer-aided self-help for a better and universal as well as cheaper health care.

Gallagher (5) starts his discussion of the 3-way promise of genetically-personalized medicine under the fitting title «Stumbling Towards Nirvana». He concludes «Nirvana is the antithesis of ignorance. And dispelling ignorance of disease is progressing. So far we've stumbled forward a little on the road to (genetic) personalized medicine, but it looks like the pace towards Nirvana is about to pick up». Let us also sprint, rather than stumble, towards chronobiologic chronome-based personalization, an experimentally-validated approach in hand. It is inferentially statistically validatable, and results given based on appropriate time series can be automatically provided by a website. Complexity is thus removed, and a much-improved diagnosis and the validation of treatment can be personalized. If, at its current cost, the available instrumentation is used for screening by a neighborhood or a circle of family and friends,

the cost of a 24-hour/7-day record is already reduced to below $2 per weeklong profile, as compared to thousands of dollars for a personalization via the genome. If an instrument is to be used to 24-hour/365-day records, the cost is now reduced to $450 a go (within the BIOCOS project) in exchange for the data (corne001@umn.edu) and with cost-free analyses. The cost can be reduced to below $100 an instrument by currently available instrumentation in a government or other public health plan (4). Introduction into secondary education of the already available «why» and «how» of chronobiology can be accompanied by a yet-to-be updated book (4).

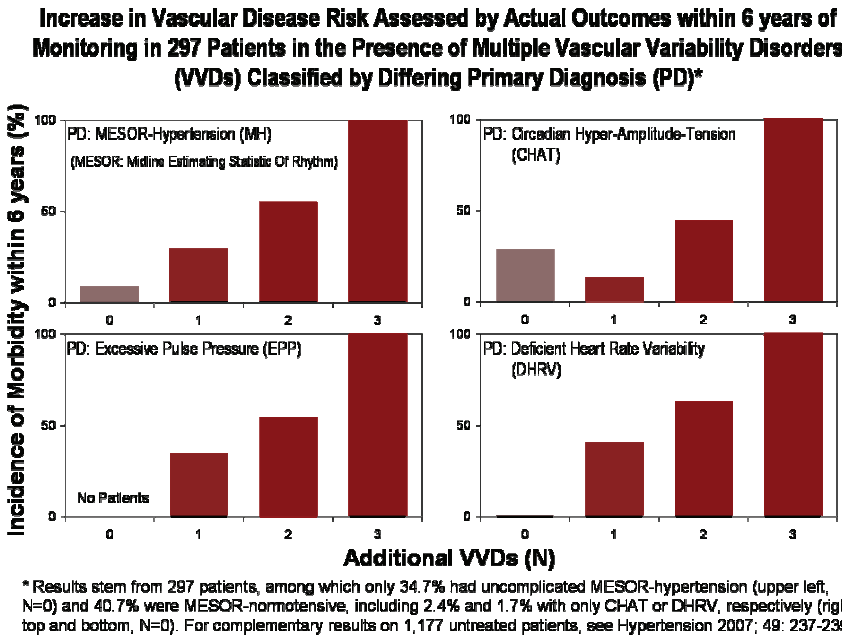

Figure 4. The incidence of VVDs is assessed herein in a clinic population of 297 patients. Blood pressure (BP) and heart rate (HR) of each subject were monitored around the clock for 2 days at 15-minute intervals at the start of study. Each record was analyzed chronobiologically and results interpreted in the light of time-specified reference limits qualified by gender and age. On this basis, MESOR-hypertension, MH (diagnosed in 176 patients), excessive pulse pressure (EPP), CHAT (a circadian overswing) and a deficient heart rate variability (DHRV) were identified and their incidence related to outcomes (cerebral ischemic attack, coronary artery disease, nephropathy, and/or retinopathy). Outcomes, absent at the start of study in these non-diabetic patients, were checked every 6 months for 6 years, to estimate the relative risk associated with each VVD alone or in combination with 1, 2, or 3 additional VVDs, shown in columns. Earlier work showed that CHAT was associated with a risk of cerebral ischemic event and of nephropathy higher than MH, and that the risks of CHAT, EPP, and DHRV were mostly independent and additive. It thus seemed important to determine the incidence of each VVD, present alone or in combination with one or more additional VVDs. The 176 patients with MH were broken down into 103 (34.7% of the population of 297 patients) with uncomplicated MH, 55 (18.5%) with MH complicated by one additional VVD, 15 (5.1%) and 3 (1.0%) with MH complicated by two or three additional VVDs (top left). In the latter group, all 3 patients had a morbid outcome within 6 years of the BP monitoring. Ambulatory BP monitoring over only 48 hours, used for diagnosis, is much better than a diagnosis based on casual clinic measurements, yet its results apply only to groups. With this qualification, of the 176 patients with MH, 73 (42.2%) had additional VVDs that further increase their vascular disease risk, and that are not considered in the treatment plan of these patients since current practice does not assess these VVDs. This proportion may be smaller in 7-day records. Results related to an excessive pulse pressure, EPP (bottom left), CHAT (upper right), and a deficient heart rate variability, DHRV (bottom right), illustrate that these conditions can be present in the absence of MH in as many as 12 (4.0%) of the 297 subjects. Since they do not have MH, it is unlikely that these subjects would be treated from a conventional viewpoint, even though their vascular disease risk can be as high as or even higher than MH.

Evidence exists to suggest that treatment of these conditions may translate into a reduction in morbidity and/or mortality from vascular disease. Another lesson from these results is that around-the-clock monitoring of BP and HR interpreted chronobiologically is needed, even in the absence of MESOR-hypertension, to detect vascular disease risk associated with VVDs such as CHAT and DHRV, that cannot be assessed on the basis of casual clinic measurements, so that non-pharmacologic and/or pharmacologic intervention can be instituted in a timely fashion before the occurrence of adverse outcomes. Once implemented across the board rather than in selected patient populations, vascular disease could be curbed to a much larger extent at relatively low cost if the monitoring is offered directly to the public and care providers become involved only after detection of a VVD. A website has to be built to interest many people and to provide cost-free analyses in exchange for the data, as is now provided worldwide by the BIOCOS project on a small scale (corne001@umn.edu). © Halberg.

Dividends as one goes

The merits of chronobiologic monitoring, if the data are saved, as could be done on a website, could serve for more than stroke and other life-threatening disease prevention. It would reveal the mechanisms underlying more than the circadian component documented thus far (6, 7). Each newly mapped spectral component could greatly increase the merits of «sequencing» the chronome for translation from research to clinical practice. More specifically, a dividend from monitoring BP and HR would allow the uses of novel spectral components to the extent that the mechanisms of these new entities are clarified by 24-hour/365-day or 24-hour/lifetime data on population outcomes. Already mapped are about 5-month quinmensal rhythms not only in solar flares and other environmental features, but also in human physiology, including BP, HR and melatonin, and in pathology, such as sudden cardiac death (7). Quinmensals and other newly found frequencies such as transyears (10) are reflected in the breakdown products of steroidal hormones in urine and in the melatonin of circulating blood. Mapping the chronome is the indispensable counterpart to sequencing genomes. The latter widely heralded endeavor is but a complement to the former. A decrease in circadian amplitude was associated with a reduction by one half of cardiovascular morbidity (8). Systematic tests to find the optimal time of treatment administration for the individual patient, to be sure that benefits from a hypotensive effect are not curtailed by inducing or exacerbating another VVD are a challenge for all those receiving antihypertensive therapy. The percentages involved are estimated in Figure 4, involving very many millions of people currently diagnosed or misdiagnosed as «hypertensive». The further dividends from monitoring the sun by the data collected for stroke prevention are another story (6, 7), also in the spirit of Vasily Vasilyevich Dokuchaev, Vladimir Ivanovich Vernadsky and Alexander Leonidovich Chizhevsky (9), with special focus upon the frequencies that can be resolved (7, 10). The chronobiologic path depends on its being learned in education broadly, not only in universities but also in secondary schools. Eventually, monitoring of BP and HR will be started most effectively in pregnancy and continued for a lifetime, starting at birth (4).

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ГЕНОМНЫЕ ИССЛЕДОВАНИЯ ВАРИАБЕЛЬНОСТИ СОСУДИСТОГО КРОВООБРАЩЕНИЯ (ВСК), ВКЛЮЧАЯ МЕЗОР-ГИПЕРТОНИЮ, С ПЕРСОНАЛИЗИРОВАННЫМ ВРЕМЕННЫМ СТРУКТУРИРОВАНИЕМ (ХРОНОМОМ)

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Компьютеризированное, автоматическое, статистически выверенное, самосовершенствующееся профилактическое здравоохранение улучшается и удешевляется, если личные наблюдения осуществляются через безопасное Интернет-соединение, без привлечения врача. Внедрение подобной системы на медицинских факультетах, а затем и в масштабах университета, и дальнейшее внедрение в среднее образование, может привести к всеобщей научной грамотности населения, создавая в то же время условия для успешных научних исследований в области космической погоды, в духе Александра Леонидовича Чижевского, которые были не осуществимы в до-компьютерную эпоху.

Ключевые слова: временное структурирование, хроном, мониторинг артериального давления, вариабельность сосудистого кровообращения (ВСК).