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100 or 30 years after Janeway or Bartter, Healthwatch helps avoid 'flying blind'

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Abstract

Longitudinal records of blood pressure (BP) and heart rate (HR) around the clock for days, weeks, months, years, and even decades assessed by self-measurements (during waking) and/or automatically by ambulatory monitoring reveal, in addition to well-known wide within-day variation, considerable day-to-day variability in most people, whether normotensive or hypertensive. As a first step, the circadian variation is considered along with gender differences and changes as a function of age to derive time-specified reference values (chronodesms), while reference values accumulate to also account for the circaseptan variation. Chronodesms serve for the interpretation of single measurements and of circadian and other rhythm parameters. Refined diagnoses can thus be obtained, namely MESOR hypertension when the chronome-adjusted mean value (MESOR) of BP is above the upper limit of acceptability, excessive pulse pressure (EPP) when the difference in MESOR between the systolic (S) and diastolic (D) BP is too large, CHAT (circadian hyper-amplitude tension) when the circadian BP amplitude is excessive, DHRV (decreased heart rate variability when the standard deviation [SD] of HR is below the acceptable range), and/or ecphasia when the overall high values recurring each day occur at an odd time (a condition also contributing to the risk associated with 'non-dipping'). A non-parametric approach consisting of a computer comparison of the subject's profile with the time-varying limits of acceptability further serves as a guide to optimize the efficacy of any needed treatment by timing its administration (chronotherapy) and selecting a treatment schedule best suited to normalize abnormal patterns in BP and/or HR. The merit of the proposed chronobiological approach to BP screening, diagnosis and therapy is assessed in the light of outcome studies. Elevated risk associated with abnormal patterns of BP and/or HR variability, even when most if not all measurements lie within the range of acceptable values, becomes amenable to treatment as a critical step toward prevention (prehabilitation) to reduce the need for rehabilitation (the latter often after costly surgical intervention).

Keywords: Blood pressure; Heart rate; MESOR; Chronbiology

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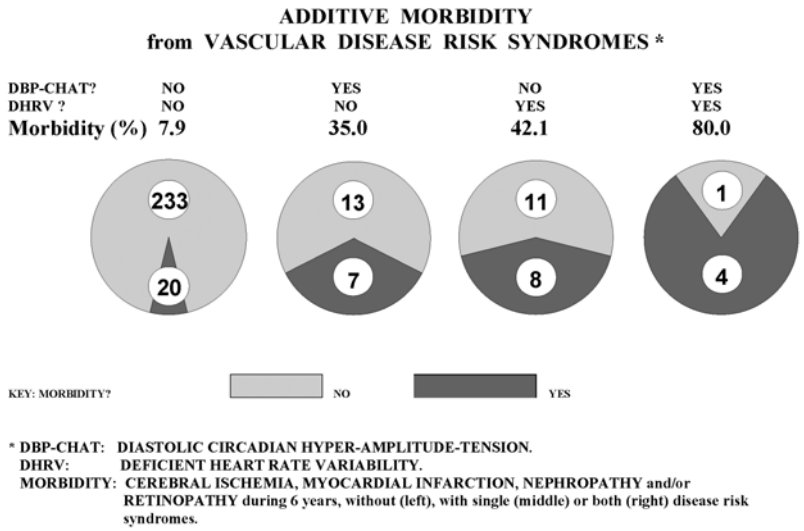


Fig. 1. Seven-day/24-hour monitoring can detect in the neglected normal range abnormality in variabilities of BP and HR that make the difference between <8% and 80% morbidity within 6 years of the initial record. Data of K Otsuka. © Halberg.

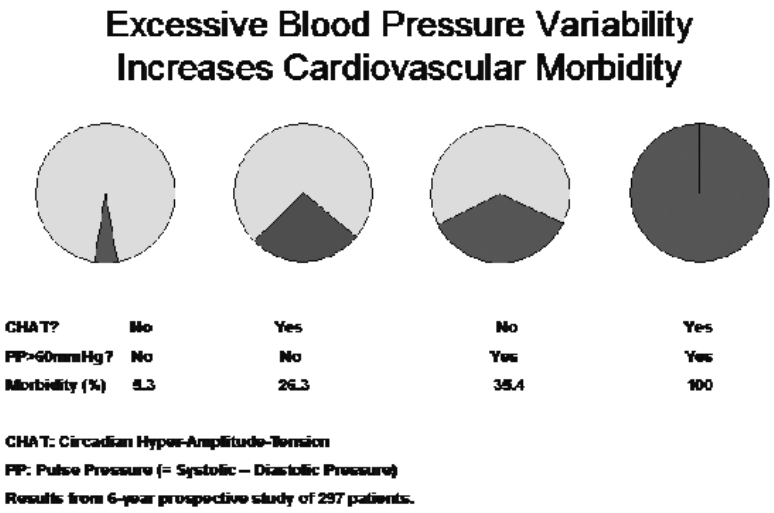


Fig. 2. Around the clock monitoring can detect in the neglected normal range excessive BP variability along the scales of the cardiac cycle and the 24-hour day that make the difference between <6% and 100% within 6 years of diagnosis in this study of 297 patients. Data of K Otsuka. © Halberg.

1. Introduction

The merit of treating elevated blood pressure (BP) is no longer disputed and is widely viewed as a critical way of reducing morbidity and mortality associated with cardiovascular disease. In this study, evidence is provided that abnormal patterns of BP and heart rate variability (HRV) are also associated with a significant increase in cardiovascular disease risk, whether or not BP is elevated. Most if not all BP measurements collected during a 7-day/24-hour profile can be within the range of acceptable values, but if the daily variation in BP is excessive, the risk of cerebral ischemia is increased by 72%, an increase in risk larger than that associated with elevated BP! Similarly, the risk of coronary artery disease is increased by 55% when HR variability is below a critical threshold. Considering all morbid events occurring within 6 years among 297 (121 normotensive and 176 treated hypertensive) patients, the risks associated with too large a daily BP swing and a decreased HR variability are found to be additive, suggesting that these two risk factors are mostly independent (Fig. 1). As shown in Fig. 2, the risk associated with an excessive daily BP variation is also separate from the known risk of elevated pulse pressure, which can be viewed as an excessive BP variation within the cardiac cycle. The case is made herein of the merit of treating abnormal BP and/or HR patterns as a step toward prehabilitation, a cost-effective alternative to waiting until eventual debilitating target organ damage occurs, before initiating a then too often expensive treatment.

2. Comment

In 1904, Theodore C. Janeway wrote "**…**it is essential that a record of the pressure be made at frequent intervals at some time previous [presumably to an examination], to establish the normal level and the extent of the periodic variations. When this is done, it may be possible to demonstrate changes of small extent, which, lacking this standard for comparison, would be considered within the limits of normal variation" [1]. In a patient whose blood pressure was diagnosed differently by two physicians who saw him at different[1] times of day in 1974, Frederic C. Bartter added the need for (time-structured) cosinor analysis: "By conventional standards, this patient is clearly normotensive every morning. But 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 [data curves compiled under differing circumstances, such as 24 hours a day/7 days a week] become a *routine minimal amount* of information accepted for the description of a patient's blood pressure. *The analysis of this information by COSINOR[1] should become a routine practice.* It is essential that enough information be collected to allow objective characterization of a periodic phenomenon, i.e. an estimate of M (MESOR1)… an estimate of (the amplitude of) A itself, and finally an estimate of acrophase, ϕ. In this manner, the patient can be compared with him or herself at another point in time, or under another treatment, and can be compared with a normal or with another patient [2]. In 2004, what Janeway wanted in terms of data collection and Bartter required in terms of data analysis can be achieved within the BIOCOS project [3]. Accordingly, there is no need to 'fly blind' [4]. The 'why' and 'how' have been succinctly summarized for the lay person and for health-care providers.

3. Terminology

The cosinor provides a statistical summary with a display on rectangular and/or polar coordinates of rhythm characteristics. The single cosinor adjusts, by least squares, a rhythmic function with a presumed period (anticipated on the basis of prior experience) to a data series, thus providing point-and-interval estimates of MESOR, amplitude and acrophase. The statistical significance of the fitted curve is checked by means of a zero-amplitude (no rhythm) test. The population-mean cosinor derives inferences for the population from parametric estimates obtained from three or more individuals or from three or more time series obtained from the same individual [5,6].

The MESOR (acronym for Midline-Estimating Statistic of Rhythm) is a rhythm-adjusted mean, defined as the average value of the rhythmic function fitted to the data. The MESOR differs from the arithmetic mean whenever the data are nonequidistant and/or cover a non-integral number of cycles, in which case the MESOR is usually more accurate (i.e. associated with less bias from sampling). When the data are equidistant, the MESOR is also usually more precise (i.e. it is associated with a smaller standard error if the time series undergoes a rhythmic change). The double amplitude is a measure of the extent of predictable change within a cycle, and the acrophase is a measure of the timing of overall high values recurring in each cycle, expressed in (negative) degrees, with 360° equated to the period length and 0° set to the chosen reference time (e.g. midnight between Saturday and Sunday preceding the start of data collection) [7].

1. See terminology.

4. Diagnosis of hypertension

By necessity rather than choice, hypertension is currently diagnosed by means of single casual measurements in the physician's office. These measurements are repeated only when they are interpreted as being abnormal in the light of fixed limits that are specified neither by time, age or gender. Current guidelines [8] were prepared on the assumption that blood pressure is mostly constant and that it can be measured accurately at almost any time. When a blood pressure measurement is acceptable, a return visit in two years is advocated. When the blood pressure is repeatedly found to be elevated, treatment with anti-hypertensive medication is started. To some extent, this approach has been successful in decreasing the number of heart attacks, strokes and other complications of hypertension [9]. But evidence accumulating from cooperating centers and ourselves suggests that it may be possible to achieve even better results [10–12], while the cost of health care could be reduced by education in self-help [13,14], which includes self-monitoring for a week or longer, as need be, an endeavor also serving basic science [15].

5. Within-day variation of blood pressure

Data obtained automatically around the clock with ambulatory monitors (and by self-measurements or manual staff measurements earlier) have shown that blood pressure is not constant, but rather changes, in part predictably, notably along the 24-hour scale. Fig. 3 shows the variability of blood pressure at any given clock hour in measurements collected by a seemingly healthy neurosurgeon during several weeks and plotted along the scale of a 24-hour day. Usually, pressures are lower during rest/sleep and higher during the active span of the day in subjects with an acceptable week-long average of blood pressure and also in most patients with an elevated blood pressure. The change from night to day is often larger than 20 mmHg. Guidelines have started to consider these daily changes in blood pressure by providing acceptable fixed limits that differ between night-time

and daytime [16]. Several studies have shown that a diagnosis based on a 24-hour profile obtained by ambulatory blood pressure monitoring is more reliable than single casual blood pressure measurements in the physician's office because target organ damage can be better predicted [17].

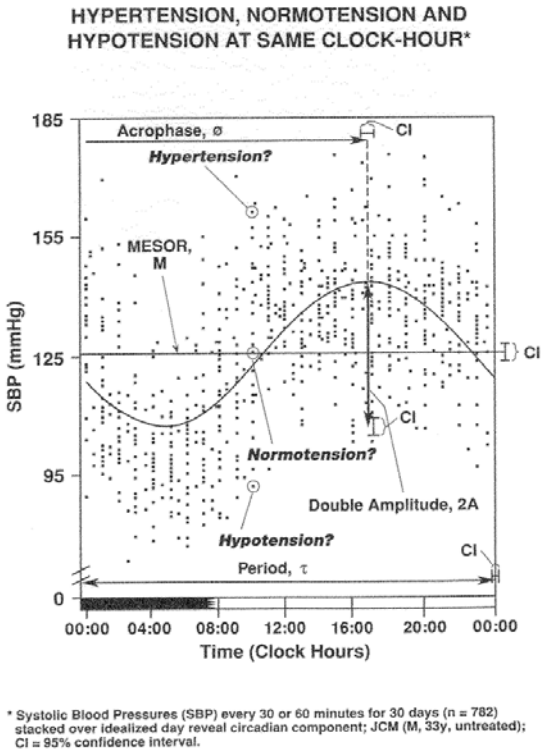


Fig. 3. A 33-year old neurosurgeon diagnosed conventionally as moderately hypertensive monitored his BP around the clock for 30 days. His systolic values are plotted after being stacked over an idealized 24-hour day, revealing a very large variability of BP from moment to moment, as well as within a day and from day to day, as also seen in Fig. 4. This large variability in BP raises the question of the validity of a diagnosis based on single measurements, however accurate they may be. Any single measurements hardly reflect the extent of variation over time. © Halberg.

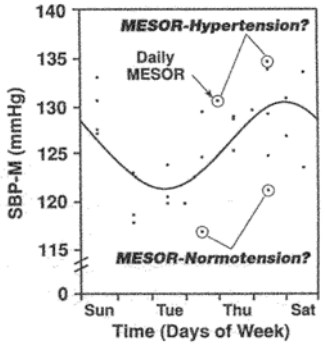


Fig. 4. The day-to-day variability in the circadian characteristics of BP can be so large that the MESOR of SBP (measured at 15–30-min intervals around the clock) can be compatible with the diagnosis of MESOR-hypertension on one day, that of MESOR-normotension on another day, and even that of MESOR-hypotension on yet another day. This result raises the question of whether a 24-hour profile of ambulatory monitoring (today's gold standard) can still be regarded as a reliable diagnostic criterion. © Halberg.

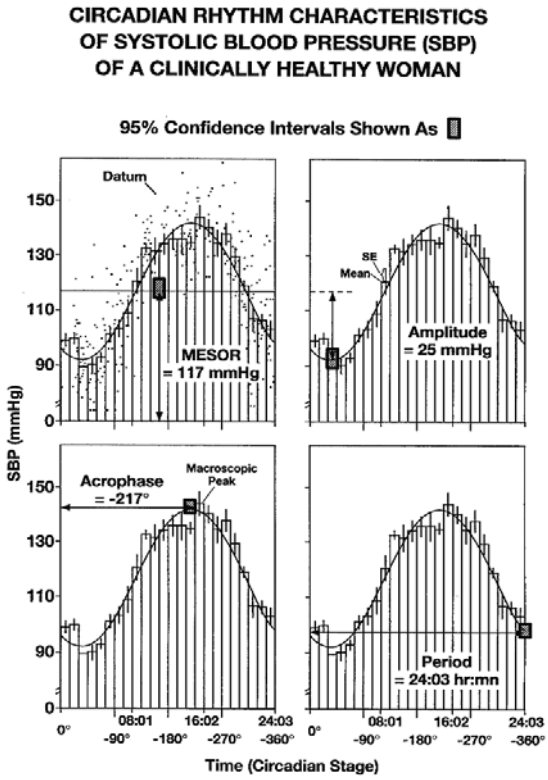


Fig. 5. Illustration of circadian rhythm characteristics for the case of a series of SBP values collected over several weeks by a clinically healthy woman. Data are shown as dots (top left), plotted after stacking over an idealized circadian cycle. The data have been analyzed by linear-nonlinear rhythmometry, consisting of the linear least squares fit of cosine curves with different trial periods, followed by the nonlinear analysis. The latter allows the period to be estimated as a parameter in the model, together with other parameters, each with a measure of uncertainty, the 95% confidence interval (shown as a dark rectangle). The four parameters are illustrated separately for the same data series: 1) The MESOR (Midline Estimating Statistic Of Rhythm), a time structure (chronome)-adjusted mean value (top left). 2) The circadian amplitude, half the extent of predictable change within a day (top right). 3) The circadian acrophase, a measure of the timing of overall high values recurring in each cycle (bottom left). 4) The period, the duration of one cycle (bottom right). © Halberg.

New studies have also suggested that a target blood pressure of 120 mm Hg on the average is better than a higher upper limit of acceptability used earlier [8]. But whether hypertension is diagnosed by ambulatory monitoring or by single measurements in the physician's office, treatment is usually initiated using a fixed daily dose often administered as a single 24-hour formulation. All these practices can be improved upon.

6. Day-to-day variability in blood pressure

We are all born with natural variations in blood pressure, such as the within-day changes reviewed above. Variations can also occur in relation to physical exercise, excitement, anxiety or other loads that may be present one day but not another day [18]. The large extent of day-to-day variability

in blood pressure has become increasingly apparent from long-term around-the-clock monitoring over many weeks, months or years [19]. These long series have been analyzed for a time-structure-adjusted mean, or MESOR. It was seen that blood pressure can be compatible with (MESOR-)normotension one day, but (MESOR-)hypertension may be diagnosed on another day (Fig. 4). Blood pressure can also be abnormal for five consecutive days at the start of monitoring but remain mostly acceptable for several years thereafter, except for occasional deviations associated with grief, conflict or other emotional 'tension' [20].

7. Chronobiology offers an alternative approach

In order to account for the daily rhythm in blood pressure and for day-to-day variations in its characteristics, a new approach is proposed. This approach differs from the conventional way of diagnosing hypertension in the following aspects.

1) Blood pressure is measured around the clock (e.g. half-hourly by ambulatory monitoring or by as dense as possible self-measurements).

2) Measurements can be analyzed if they cover 24 hours but are instead continued for at least 7 and preferably for 17 days (the time it takes to fill the memory of the monitor by taking measurements every 30 minutes).

3) Automatic ambulatory monitoring is advocated for everybody rather than restricted to special cases, as the method of choice for which international reference standards qualified by gender, age and ethnicity accumulate and

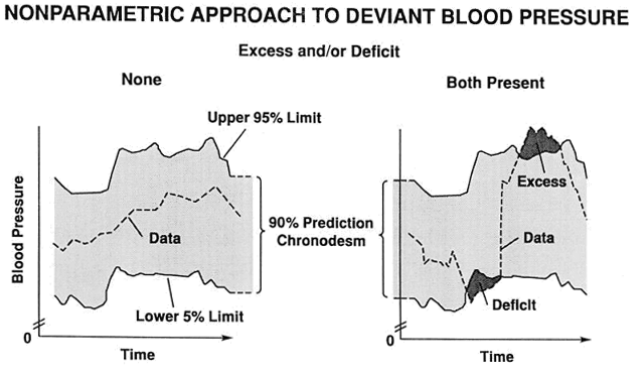


Fig. 6. Nonparametric assessment of a BP profile. The actual data are stacked over an idealized 24-hour day (dashed curve) for comparison with time-specified 90% prediction limits (solid curves) derived from clinically healthy subjects matched by gender and age (and whenever possible also by ethnicity, geographic/geomagnetic location and social class). Deviations are shown as darker areas below the lower 5% and above the upper 95% prediction limits, representing blood pressure deficit and excess, respectively. These abnormalities are assessed non-parametrically as the percent time deficit or elevation and as the area delineated by the profile when it is outside acceptable limits and the limit itself (hypobaric or hyperbaric index, respectively). An indication of the timing when most of the excess (or deficit) occurs is also provided as a guide for timing any needed intervention. © Halberg.

are to be extended to consider other factors such as geographic (and/or geomagnetic) location and social class.

4) The data are analyzed initially in two ways. First, the daily variation is assessed in terms of the MESOR, the extent of predictable change within a day (the double amplitude), and the timing of overall high values recurring each day (the acrophase) (Fig. 5). These characteristics are compared with reference standards obtained from clinically healthy peers matched by gender and age (and whenever possible by ethnicity, geography, and social class). Second, the subject's average 24-hour pattern is compared by computer with time-specified reference limits from the appropriate gender- and age-matched healthy peer group. Estimates are thus obtained of the percentage time elevation, the amount of excess (as the area under the curve, delineated by the subject's profile when it is excessive and the limit itself), and the time when the excess is most likely to occur (Figs 6 and 7). Results are summarized in an easily understood form, the sphygmochron (Fig. 8) [11,12,21]. As the time series length increases, the period (Fig. 5, bottom right) can also be estimated as an important characteristic in its own right.

8. Advantages of the chronobiological approach

While the conventional approach is likely to correctly diagnose patients with either low normal blood pressures or severely elevated blood pressures, it is associated with a larger probability of error in the case of patients with high normal blood pressures, borderline hypertension or mildly elevated blood pressures [19]. These groups, however, could represent as much as 60% of the population, which is hardly negligible.

Because measurements taken occasionally can be unusually high or low, false positive and false negative diagnoses can occur. This means that some individuals who receive unneeded treatment may suffer unnecessary concern, expense, and side effects from medications. People who actually need treatment can be lulled into a false sense of well-being (notably since hypertension may not be accompanied by symptoms) and bear the high risk of complications related to untreated greatly elevated risk of cardiovascular disease, including hypertension [11,12].

9. Detection of abnormalities in blood pressure variability

A blood pressure profile can reveal abnormalities other than an elevated MESOR. Too large a daily variation in blood pressure (a condition known as overswinging or CHAT, short for Circadian Hyper-Amplitude-Tension; see scheme in Fig. 9) is also a very great risk of stroke and kidney disease (top rightmost two columns in Figs 10 and 11) [10], even when all measurements lie in the range of accep-

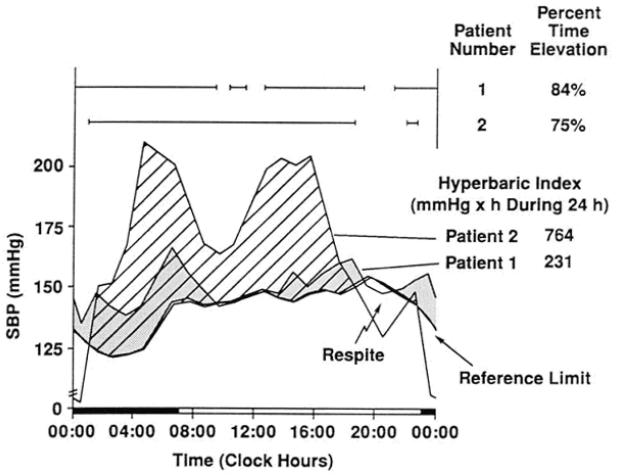


Fig. 7. The need to assess the hyperbaric index as a complement to the percent time elevation is illustrated by a comparison of profiles from two patients with a similar number of deviant readings. Patient 1 has a numerically slightly larger percent time elevation but a much smaller excess. The very large difference in hyperbaric index between the two patients likely reflects the difference in their prognosis. © Halberg.

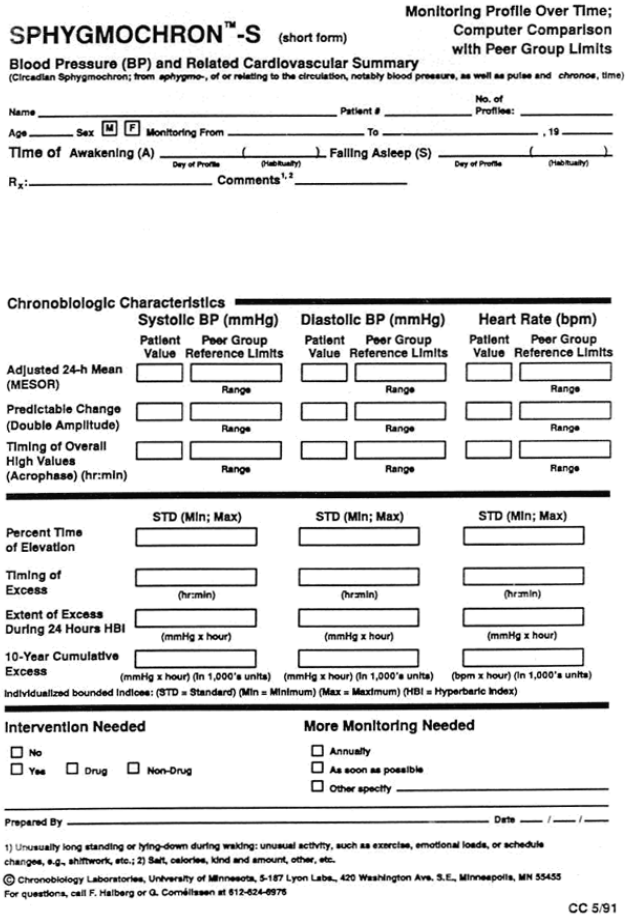


Fig. 8. Sphygmochron, the computer-generated form used to summarize results from the combined parametric and nonparametric assessment of a BP and HR profile. Results from both approaches are compared with reference values specified by gender and age, given in boxes next to the subject's estimates for the rhythm characteristics. © Halberg.

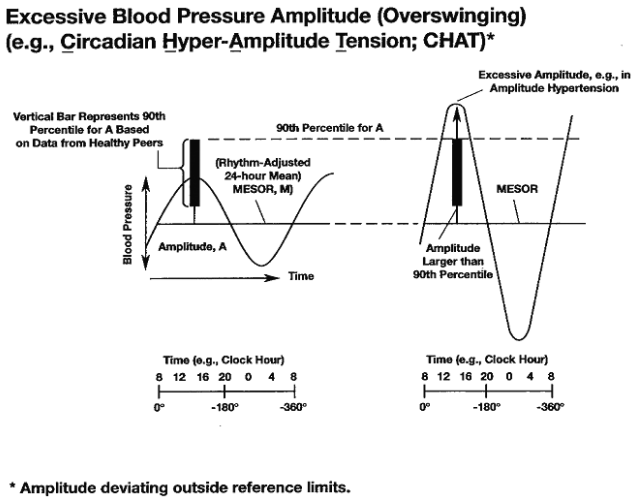


Fig. 9. Definition of CHAT (circadian hyper-amplitude-tension), a condition characterized by an excessive circadian amplitude of BP and found to be associated with a very large increase in vascular disease risk. The reference circadian variation in BP is shown on the left, with an estimate of the 90% prediction limits for the circadian amplitude (dark vertical bar). CHAT is diagnosed when the circadian variation has an amplitude that exceeds the upper 95% prediction limit (right). © Halberg.

table values (leftmost two columns in Fig. 12) [22,23]. Even when diagnosed on the basis of self- or manual measurements carried out by staff, CHAT has been related to increased mortality (Fig. 13; see [24]) and in the perspective of 28 years (Fig. 14; see [25]). Together with an excessive pulse pressure (difference between systolic and diastolic blood pressure, when the heart contracts and relaxes) and with a reduced heart rate variability, CHAT accounts for 100% morbidity occurring within 6 years among 297 patients with no prior vascular disease, as compared to less than 4% in the absence of these risk factors (Fig. 15). An odd timing of high blood pressure values is also found in some diabetic patients with autonomic nervous dysfunction [26,27].

The percentage of morbid outcomes (such as a stroke) among subjects testing positive (e.g. for CHAT or for MESOR-hypertension) is known as the sensitivity of the test (e.g. circadian amplitude or MESOR of blood pressure) [28]. CHAT has a sensitivity of 28.2%, as compared to 92.3% for the case of MESOR-hypertension. The specificity of a given test is the percentage of subjects with no adverse outcome among those testing negative. CHAT has a specificity of 94.6%, as compared to 45.7% for the case of MESOR-hypertension. The efficiency coefficient is the percentage of correct diagnoses in the light of outcomes. For CHAT it is 85.9%, as compared to 51.9% for MESOR-hypertension. These values strongly suggest the merit of assessing the blood pressure variability, notably the circadian amplitude of blood pressure, since the diagnosis of CHAT is not meant to be used as a substitute, but rather as a complement to the diagnosis of MESOR-hypertension. The

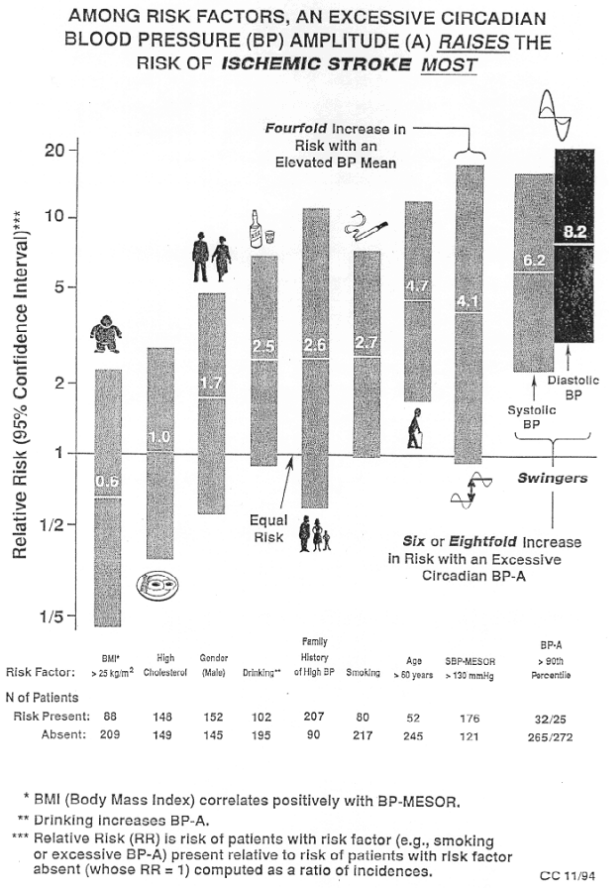


Fig. 10. Relative risk of cerebral ischemic event for various factors, computed as the ratio of the incidence of morbidity that occurred among patients presenting with the tested factor by comparison with that among patients not presenting with the tested factor. Results of a 6-year prospective study on 297 patients indicate that the risk associated with CHAT is larger than that of all other risk factors considered (obesity, high cholesterol, male gender, alcohol consumption, presence of familial antecedents, smoking, age above 60 years, and an elevated mean value of BP). As compared to patients with an acceptable circadian BP amplitude, patients with diastolic CHAT have a risk 8.2 times larger (i.e. they have a 720% increase in risk) of having a cerebral ischemic event within 6 years of monitoring. © *Halberg.*

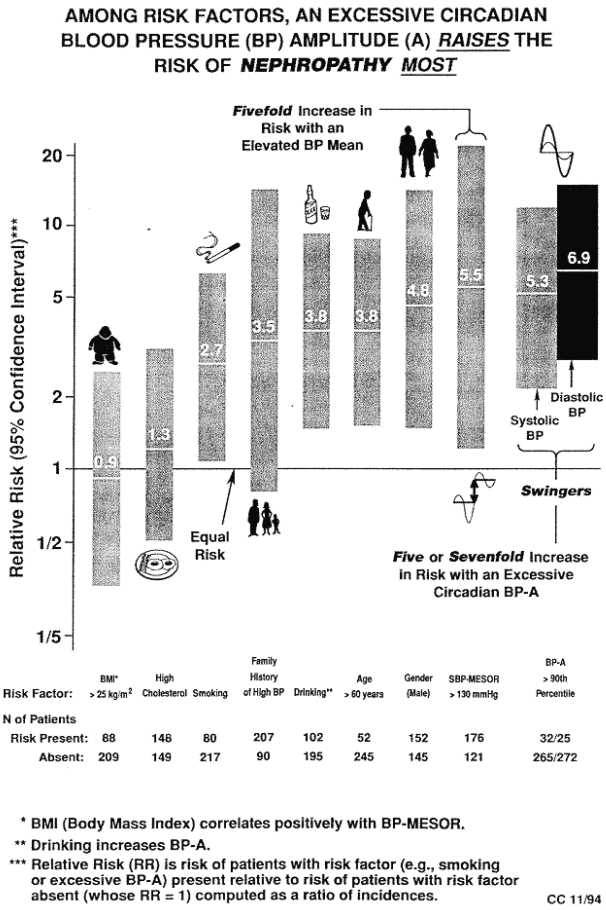


Fig. 11. CHAT is also associated with a large increase in the risk of nephropathy (see legend to Fig. 10). © Halberg.

same comment applies to the assessment of heart rate variability, gauged by the standard deviation (sensitivity: 25.6%; specificity: 95.7%; coefficient of efficiency: 86.5%), and to that of an elevated pulse pressure (sensitivity: 56.4%; specificity: 94.6%; coefficient of efficiency: 84.5%).

10. Who is to benefit from a chronobiological approach?

Whereas patients with borderline hypertension are the most likely to benefit from the higher accuracy of a diagnosis of MESOR-hypertension (or MESOR-normotension), everyone is to benefit from a chronobiological screening of blood pressure, since abnormalities in blood pressure variability (such as CHAT) cannot be diagnosed in the physi-

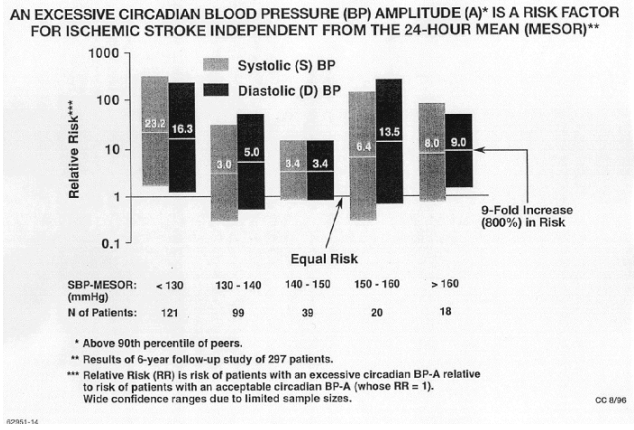


Fig. 12. The risk of a cerebral ischemic event associated with CHAT shown in Figure 10 applies to patients with different values of the MESOR of SBP, including patients who are MESOR-normotensive (left; the 95% confidence interval for relative risk, shown as the vertical dark bar, does not overlap one, representing a risk equal to that of patients with an acceptable circadian amplitude of BP). This result suggests the need to extend the monitoring to everybody since the diagnosis of CHAT cannot be made on the basis of single measurements. © Halberg.

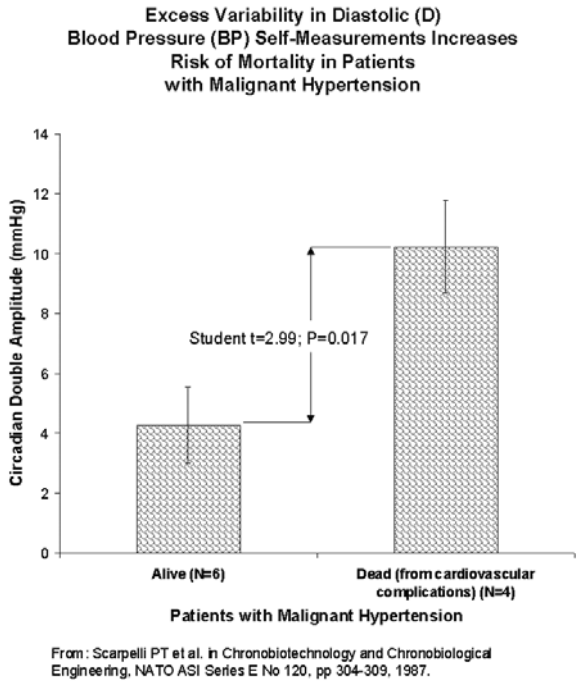


Fig. 13. When ambulatory monitors are not available, self-measurements can also be obtained at intervals (e.g. of 3 hours) during waking for analysis by cosinor to estimate the circadian characteristics. In keeping with the risk of CHAT shown in Figures 10-12, the circadian amplitude of self-measured DBP by patients with malignant hypertension was larger among those who died than among those who survived. © Halberg.

cian's office on the basis of single measurements. Blood pressure can also be elevated at odd times (such as during the night) not covered by office hours. This may happen spontaneously or because of long-acting blood pressure-lowering medications that cease to act sooner than anticipated. Fig. 16 shows the case of a patient with severely and

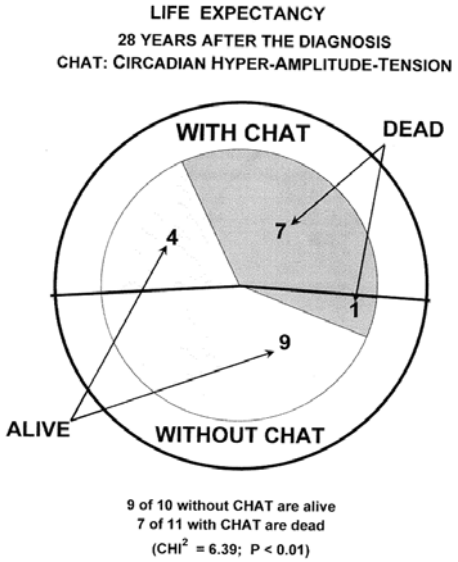


Fig. 14. Manual measurements taken 6 to 7 times daily at 2- to 3-hour intervals during waking for 2 days by staff were also able to distinguish between patients who died and those who survived 28 years later. The incidence of CHAT was statistically significantly larger among those who died than among the survivors. © Halberg.

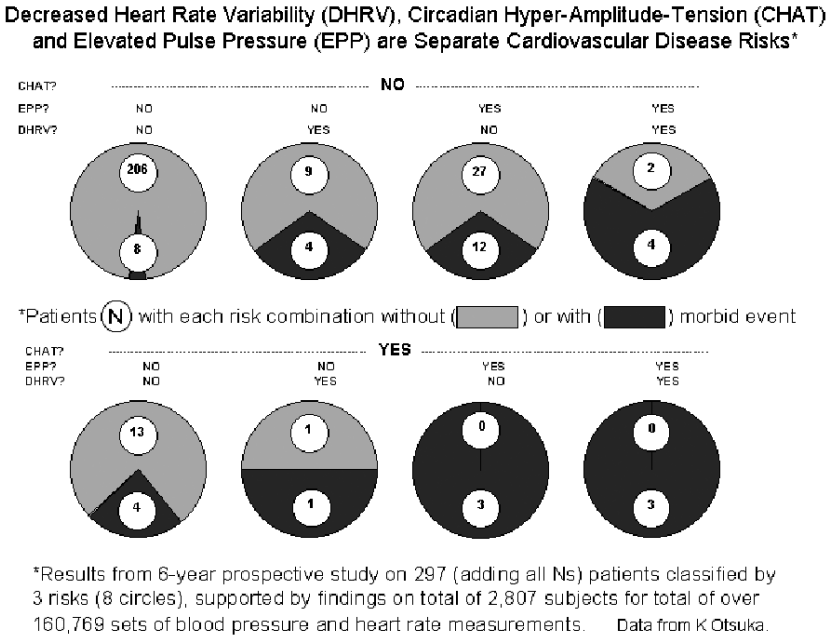


Fig. 15. CHAT is one of several conditions related to the *variability* in BP and/or HR that is associated with an increase in vascular disease risk. Too large a pulse pressure (the difference between SBP and DBP, when the heart contracts or relaxes, or the extent of change in pressure during a cardiac cycle) and a decreased HR variability (defined as the standard deviation of HR) are two other such conditions. Vascular disease risk is elevated in the presence of any one of these three risk factors, and it is elevated further when more than a single risk factor is present, suggesting that these abnormalities in *variability* of BP and HR are mostly independent and additive. © Halberg.

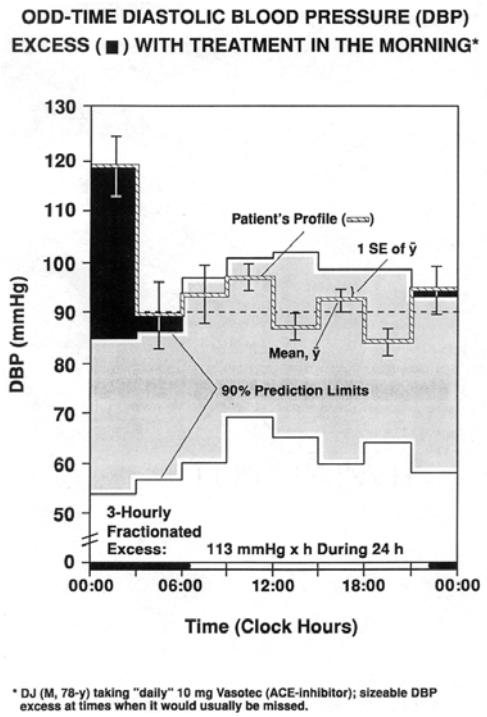


Fig. 16. Around-the-clock monitoring is useful to check on the efficacy of treatment. The DBP values of a 78-year old patient treated daily with an ACE inhibitor, collected over an 11-day span have been stacked over an idealized 24-hour day for comparison with 90% prediction limits from clinically healthy peers matched by gender and age. Whereas he seems to be well treated in the afternoon when he usually sees his physician, between midnight and 03: 00, night after night, DBP is greatly and consistently elevated, suggesting that during part of the night this patient escaped from the desired effect of treatment. © Halberg.

consistently elevated diastolic pressures between midnight and 3:00 a.m. These high readings will not be recognized by measurements taken only during the day, yet they constitute a harbinger of risk. The extent of suffering after a massive stroke is enormous, and the health care costs related to high blood pressure are staggering ($30 billion in 1998 in the USA). To correctly diagnose a larger proportion of the population is likely to further improve the management of blood pressure disorders and to reduce the cost of treating complications such as a heart attack, stroke, kidney disease, retinopathy and other major handicapping and fatal diseases (Fig. 17).

11. Why take blood pressure readings 7 days a week?

Abnormality can occur on some days but not on others. Fewer than 7 days of monitoring mean a greater chance of a false diagnosis. Two features of the chronobiological approach render the monitoring highly effective. First, blood pressure can be automatically monitored without interrupting everyday life. Nothing special needs to be done and the procedure is hardly noticeable. This type of monitoring greatly reduces the likelihood of false readings and

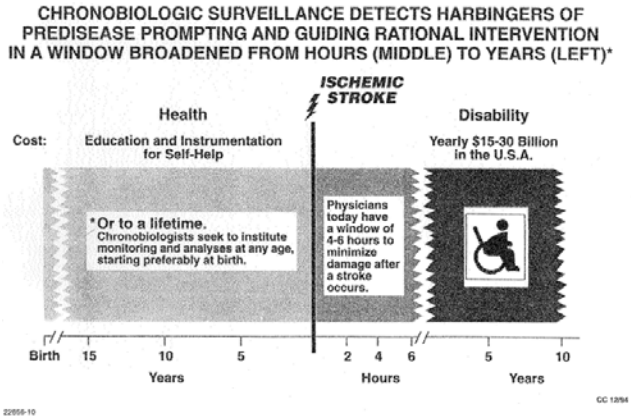


Fig. 17. The detection of an elevated risk before there is overt disease and target organ damage can prompt timely and timed intervention as a means to prehabilitation, with the hope to reduce the need for rehabilitation, that is for the need of after the fact care associated with much suffering and high cost. © Halberg.

helps reaching an informed decision regarding treatment. Second, the data analyzed for rhythms are interpreted in the light of reference standards from gender- and age-matched peers in clinical health. Longer than 7-day profiles become indispensable when some circadian abnormality is detected, some about-half-weekly or about-weekly abnormality is sought, and/or the response to a change in treatment needs to be assessed.

The benefits are as follows:

1) The diagnosis of MESOR-hypertension is improved.

2) Abnormalities of blood pressure variability provide warning signs of a heightened vascular disease risk prompting prophylactic action.

3) The decision to treat is facilitated in terms of choosing between non-pharmacologic or pharmacologic treatment and, in the latter case, in terms of selecting the kind of medication, its dosage, and the timing of its administration in an individualized fashion (rather than following guidelines derived from results on inhomogeneous collectives).

4) The response to treatment can be rigorously assessed for each individual patient.

12. Treatment considerations

Two kinds of analyses can be performed to determine the efficacy of a given intervention for the given patient. When data are collected before and after the start of treatment, parameter tests [29] can be applied to test the equality of the MESOR, of the double (circadian) amplitude and of the acrophase, considered singly or in combination (Fig. 18). A lowering of the MESOR can thus be ascertained in the case of a MESOR-hypertensive patient, or the restoration of an oddly timed acrophase, or the elimination of an excessive circadian amplitude (CHAT). Control charts [30,31] can also be used as a sequential test capable of detecting a change in MESOR, acrophase or amplitude and also of esti-

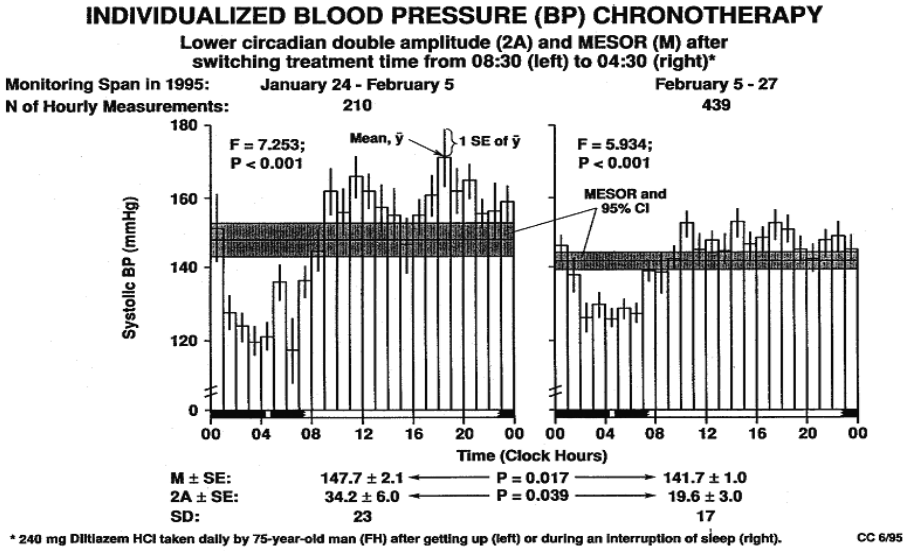


Fig. 18. Techniques are available to test on an individualized basis the efficacy of treatment. One such method consists of testing the equality of rhythm parameters before and after the start of treatment. In the case of this 75-year old man, the same dose (240 mg) of the same drug (Diltiazem HCl) was given either upon awakening (left) or during an interruption of sleep (right). The change in timing of medication was associated with both a further decrease in the MESOR of SBP and with a decrease in the circadian amplitude of this variable. Timing treatment (chronotherapy) can hence be useful to treat CHAT as well as MESOR-hypertension. © Halberg.

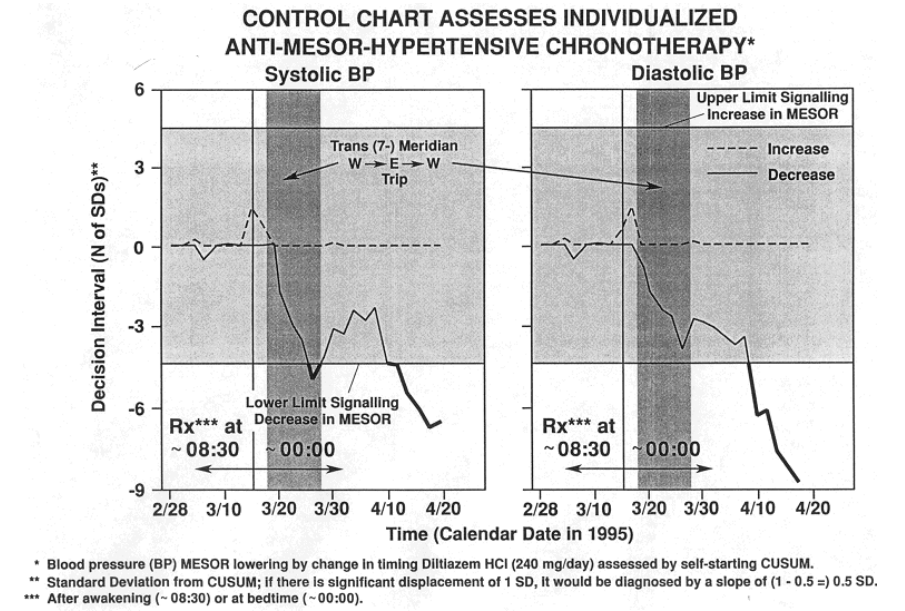


Fig. 19. Control charts of daily MESORs of SBP (left) and DBP (right) of a 75-year old man treated with 240 mg of Diltiazem HCl when the timing of this medication was changed from awakening to bedtime. While the series of daily MESORs is proceeding 'in control' (i.e., before the change in timing of medication), the cumulative sum (CUSUM) comprises two line graphs that generally stay within the limits of the 'decision interval' (shaded area). The two curves signal increase and decrease in mean, respectively. When one curve breaks out of the (shaded) decision interval boundary, it provides the rigorous validation of the decrease (in this case) in daily BP MESOR. The time at which the MESOR changed is estimated by tracking the line segment leading to the breakout back to the last occasion on which it lay on the horizontal axis. In this case, the breakout occurs around April 10 and the decrease in BP is estimated to have occurred shortly after the change in timing of medication. © Halberg.

mating when the change first took place (Fig. 19; see [32]). When this time is closely related to the start of treatment (or treatment modification), the test result is as close to causality as any statistical test can be.

Studies on individual patients as well as investigations on groups have shown that it is possible to treat CHAT. This can be done non-pharmacologically with relaxation techniques of interest to MESOR-normotensive patients [33], but continued monitoring is essential in order to detect silent

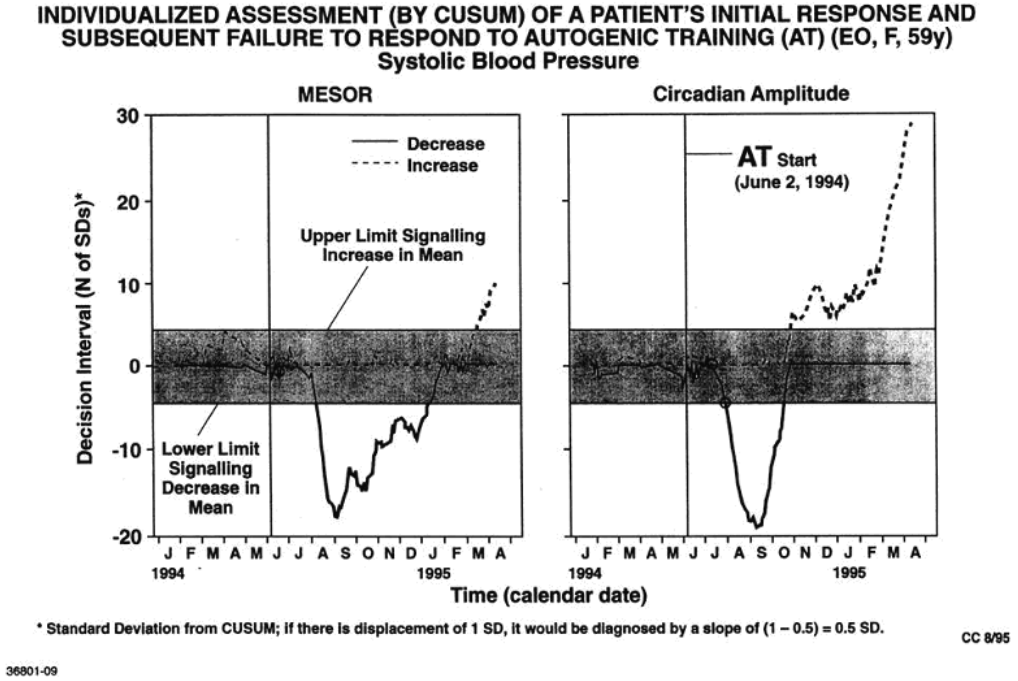


Fig. 20. Control charts of the MESOR (left) and circadian amplitude (right) of SBP of a 59-year old woman starting non-pharmacological treatment with autogenic training. Whereas treatment was effective for the first 3 months, an emotional upset was associated with the subsequent failure of autogenic training in this case. This result suggests the need for continued monitoring to check on the continued efficacy of treatment, usually administered for a lifetime. © Halberg.

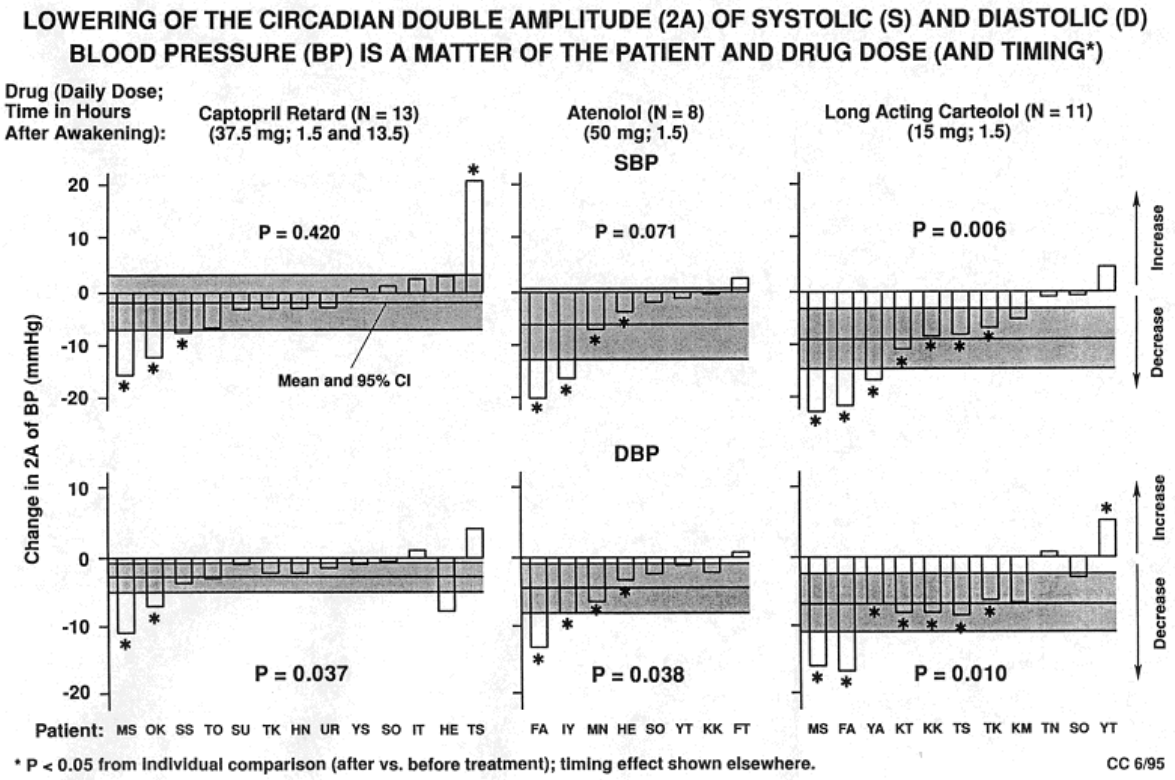


Fig. 21. Whereas anti-hypertensive drugs are administered to decrease an elevated BP mean, their effect on the circadian amplitude of BP can be very different. For instance, on the average, long-acting carteolol but not captopril can decrease the circadian amplitude of BP of most patients participating in the study. This difference should be considered when CHAT is diagnosed. Long-acting carteolol was also shown to decrease the amplitude of the about 7-day and of several about-yearly components in BP (not shown). © Halberg.

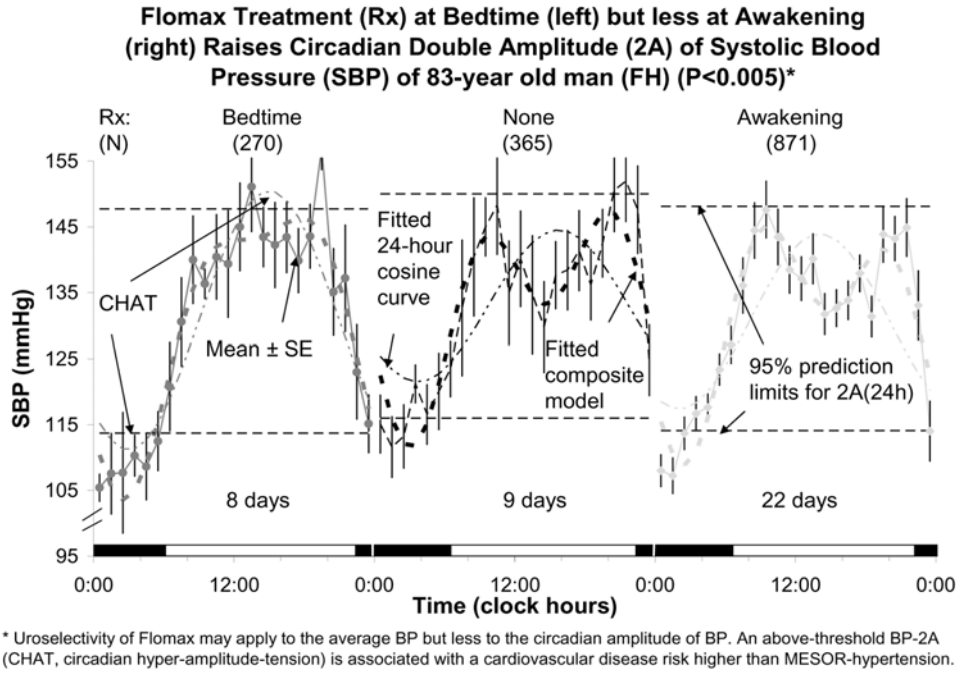


Fig. 22. CHAT can be iatrogenously associated with the taking of a medication such as flomax, an α_{1A}-adrenoceptor antagonist, useful for treating benign prastatic enlargement. Changing the dosing and/or timing of medication may restore an acceptable circadian pattern of BP. © Halberg.

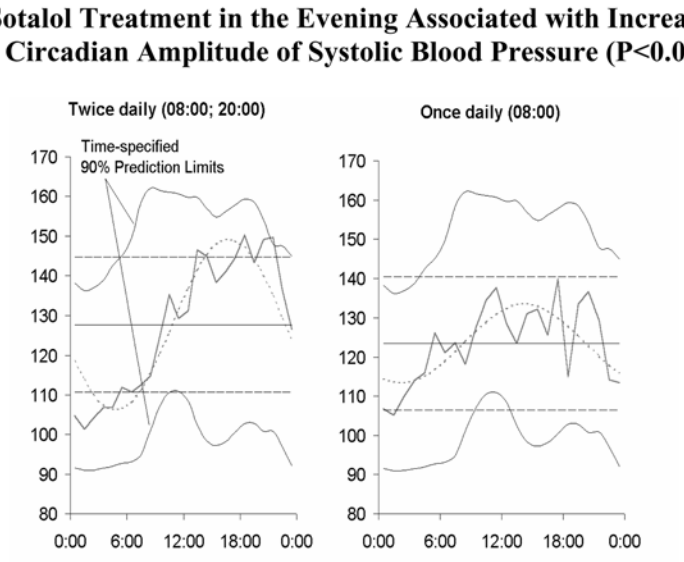


Fig. 23. CHAT can be iatrogenously associated with the taking of a medication such as sotalol, a β-adrenoceptor blocker with class III anti-arrhythmic properties. Removing the dose taken at the wrong time (in the evening) can eliminate CHAT and restore an acceptable circadian pattern of BP. © Halberg.

escapes from any treatment that is only transiently effective, as in the case shown in Fig. 20 when treatment was effective for three months but not thereafter [34]. For patients with MESOR-hypertension complicated by CHAT, some antihypertensive drugs are more effective than others in reducing an excessive blood pressure swing, while also lowering the blood pressure MESOR [35,36]. For instance, long-acting carteolol, a β-adrenoceptor antagonist with intrinsic sympathomimetic activity, compares favorably with other drugs with the doses tested (Fig. 21). This drug reduces not

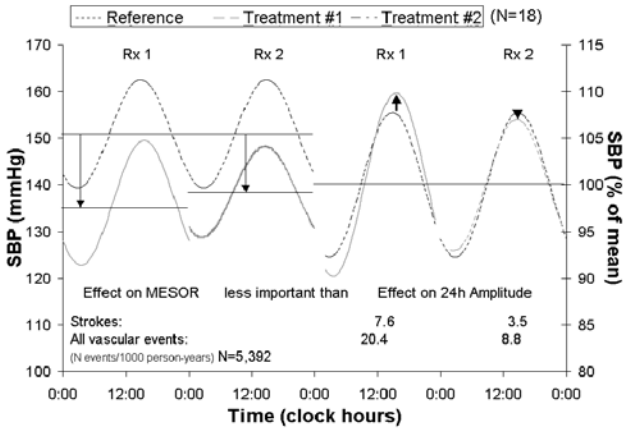
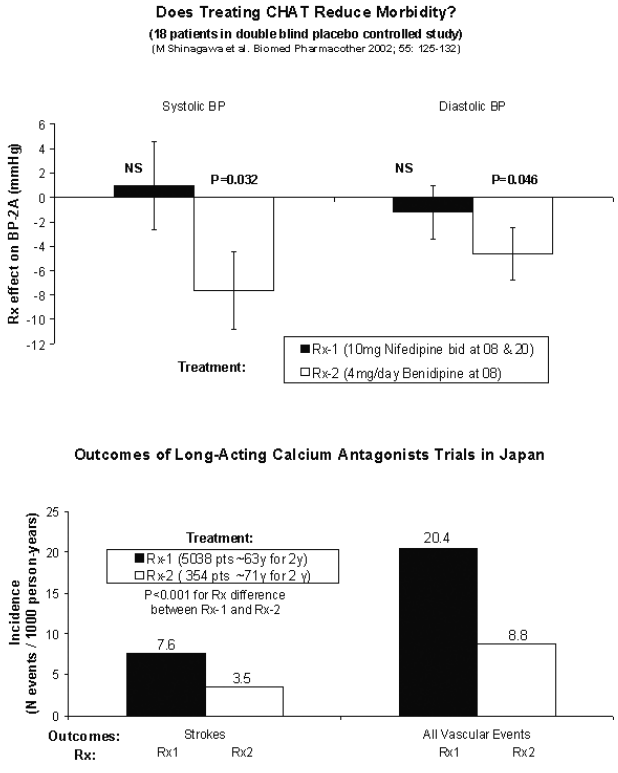


Fig. 24 A cross-over study investigates the effect of two different treatments on the circadian pattern of BP. Whereas nifedipine (taken twice a day, in the morning and in the evening, Rx1) is associated with a slightly more pronounced decrease in the MESOR of SBP as compared to benidipine (taken once a day upon awakening, Rx2), it is also associated with a numerical increase rather than with a decrease in the circadian amplitude of SBP. © Halberg.



CHAT: Circadian Hyper-Amplitude-Tension, condition defined by circadian double amplitude (2A) of blood pressure (BP) above 95% prediction limit of healthy peers matched by gender and age.
Outcomes of 2-year calcium antagonist trials on 5392 patients.
Over 50% reduction of strokes (left) and of all severe vascular events (right) by treatment (Rx) that reduces (Rx2, white bars) vs. one that does not reduce (Rx1, black bars) BP-2A. Rx1 vs Rx2 comparison: P<0.001.

Fig. 25. Benidipine (taken once a day upon awakening, Rx2) was found in large Asian clinical trials to be associated with better outcomes than nifedipine (taken twice a day, in the morning and in the evening, Rx1). Reducing the incidence of CHAT may be the reason accounting for the difference (almost by a factor 2) in outcomes, whether strokes or all cardiovascular events are considered. © Halberg.

only the circadian amplitude but also the amplitudes of the about-weekly, the about-yearly and trans-yearly components [37].

By optimizing (changing) the time to administer the medication (Fig. 18) or by omitting a dose given at the wrong time for the given patient (treated as ascertained by blood pressure monitoring; see Fig. 22), the desired effects can be obtained. The MESOR can be lowered (Fig. 18) or an acceptable circadian amplitude of blood pressure can be restored (Fig. 22). The elimination of dosing at the wrong time can also eliminate CHAT (Fig. 23). Optimal medication time is best determined for each individual patient while blood pressure continues to be monitored around the clock. Results from studies on groups have further shown that the reduction of an excessive blood pressure swing is associated with a much reduced risk (by over 50%) of later morbidity when of two presumably similar treatments one reduced the circadian amplitude of blood pressure, but not the other (Figs 24 and 25; see [38]).

Individualization of treatment includes the consideration of a given drug's effects on the variabilities of BP and HR in addition to its BP lowering action. Any differential effects of anti-hypertensive agents should by targeted to the patient's chronodiagnosis. For instance, Fig. 26 summarizes results from a study comparing the effect of lercanidipine and felodipine on Chinese patients with primary hypertension [39]. Whereas both drugs lower the BP MESOR and reduce the pulse pressure, only lercanidipine increases the standard deviation of HR, while felodipine but not lercanidipine may decrease the circadian BP amplitude. Lercanidipine may thus be the preferred treatment for patients with a decreased HR variability, whereas felodipine may be the preferred treatment for patients with CHAT.

The need to individualize the treatment of high BP has been emphasized by John Laragh [40]. He commented on the need for guidelines based on science rather than politics. For the treatment of risk elevation (pre-habilitation), drugs available to restore abnormalities in BP and HR patterns should be chosen as a function of the chronodiagnosis specifying the kind of abnormal variability encountered. As a first step, Fig. 26 shows the kind of questions to be raised and how they may be answered with specific molecules (as no more than illustrative examples). The individualized therapy of risk elevation will eventually have to become a bootstrap operation as-one-goes.

13. Future outlook

With the increased awareness of the circadian variation in blood pressure, a 24-hour blood pressure profile is occasionally recommended to reach a decision for the patient's treatment plan. Whereas the 24-hour profile is much better than single casual measurements, it falls short of providing a reliable diagnosis, as now documented in many hundreds of 7-day/24-hour monitoring series obtained within the

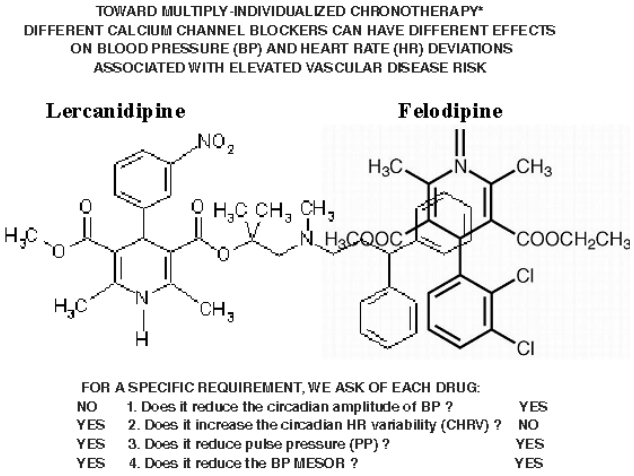


Fig. 26. Differential effects of lercanidipine and felodipine on the variabilities of BP and HR may be used for the individualization of treatment in the light of a chronodiagnosis established on the basis of around the clock monitoring of BP and HR, analyzed chronobiologically, with results interpreted in the light of time-specified reference values of gender- and age-matched healthy peers. © Halberg.

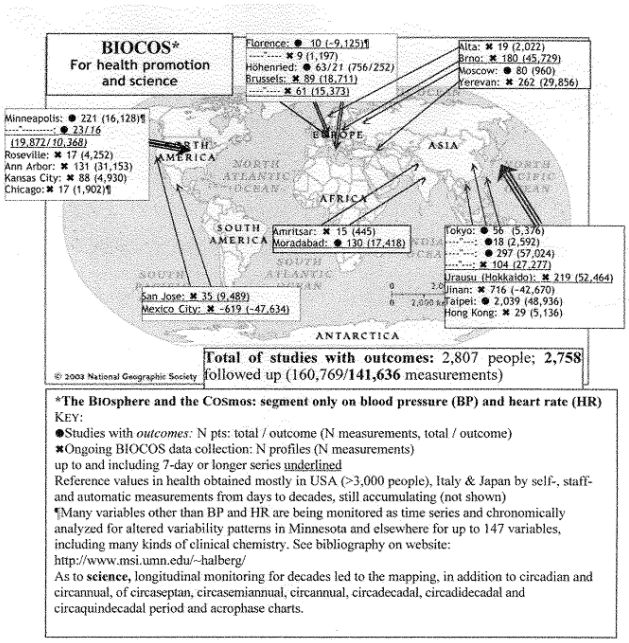


Fig. 27. Map of participation in the project on the biosphere and the cosmos (BIOCOS) aimed at mapping broad time structures (chronomes) and deriving reference values therefrom. © Halberg.

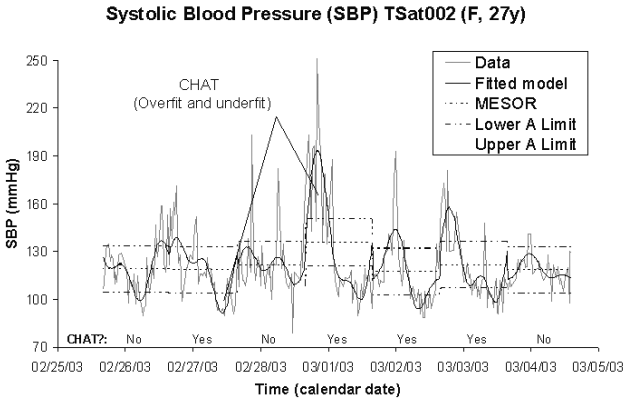


Fig. 28. The need for continuous monitoring is supported by the very large day-to-day variability in circadian characteristics of BP observed in some people, including this seemingly healthy young woman (TS) who monitored herself for several months (illustrative 7-day profile shown here). © Halberg.

ongoing BIOCOS project worldwide (Fig. 27). The day-to-day variability can be so large in some cases that a perfectly acceptable profile observed on one day may reveal on another day MESOR-hypertension complicated by CHAT. Intermittent MESOR-hypertension and intermittent CHAT have been observed both in untreated asymptomatic subjects (Figs 28 and 29; see [41]) as well as in treated MESOR-hypertensive patients (Fig. 30; see [42]), the diagnoses being made on different 2-day or week-long monitoring spans.

The conclusions drawn from the new information are first and foremost the desirability of continued monitoring for self-surveillance, what opinion leaders with blood pressure disorders have done for themselves for a lifetime after diagnosis [2,43]. Second, but not less important, the wisdom of current treatment modalities is also questioned. Since blood pressure is highly variable, should the treatment remain the same every day, in keeping with emphasis now placed on the development of 24-hour formulations? It is proposed to develop a new system of continued monitoring of blood pressure, perhaps by means of an implanted sensor, linked to a drug delivery device capable of programmed patterned delivery of fast-acting anti-hypertensive medication by means of telemetry relaying the information from the sensor to the pump as a means of closing the loop (abstract, Fig. 31). The short half-life of novel gene therapy based for instance on encapsulated h-ANP-producing cells [44,45] may actually constitute an advantage in such a closed-loop system.

Arguments against the implantation of a blood pressure sensor in patients with no immediately obvious life-threatening condition are not necessarily warranted, since cases such as that in Figure 16 are presumably at a very high risk. A compromise consists of initiating the procedure in patients with overt disease who already require the implantation of a pacemaker or a defibrillator. Outcomes in this selected group of patients may provide the evidence needed to render the procedure more generally acceptable.

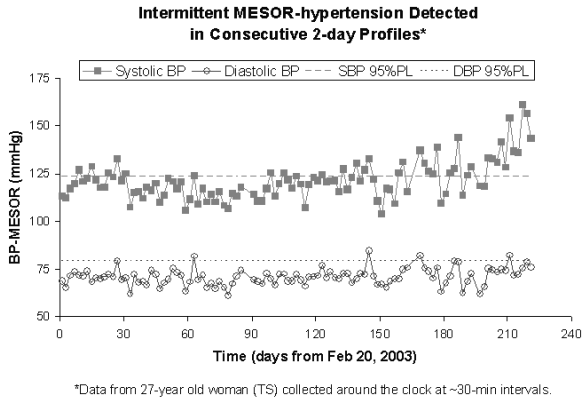


Fig. 29a. Time course of MESORs of SBP and DBP of 28-year old woman (TS), assessed for consecutive 2-day spans over 8 months, shows that MESOR-hypertension can be diagnosed consistently for a week or longer and alternate with month-long spans of MESOR-normotension. Additional data collected at the end of 2003 and beginning of 2004 are mostly within acceptable limits (not shown) © Halberg.

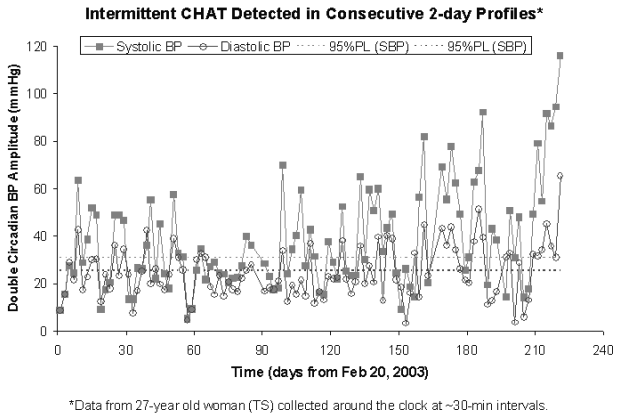


Fig. 29b. Time course of circadian double amplitudes of SBP and DBP of 28-year old woman (TS), assessed for consecutive 2-day spans over 8 months, shows that CHAT can be diagnosed consistently for a week or longer and alternate with week-long spans of an acceptable circadian amplitude of BP. Additional data collected at the end of 2003 and beginning of 2004 are mostly within acceptable limits (not shown) © Halberg.

14. Conclusions

14.1. For now

In keeping with the evidence presented herein, it is proposed to radically change the approach to diagnose and to treat blood pressure disorders, in the following ways:

1) To extend the 7-day/24-hour blood pressure screening to everyone rather than to limit the monitoring to a single 24-hour profile to be obtained only in special cases.

2) Thereby, to identify individuals at risk because of abnormalities in their blood pressure (and heart rate) variability that single measurements cannot detect.

3) To institute continued longitudinal monitoring for self-surveillance when a high risk condition is diagnosed, so as

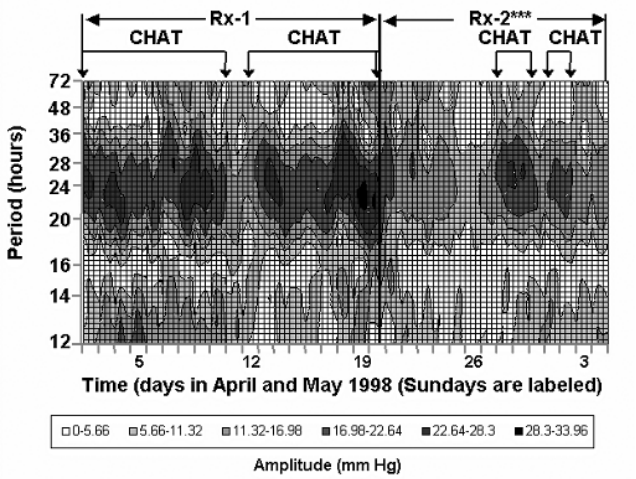


Fig. 30. CHAT can be intermittent in treated MESOR-hypertensive patients such as this 72-year old man. Although the change in medication (vertical line) is associated with a decrease in the (excessive) circadian amplitude of SBP (shown as a reduction of the dark area in a gliding spectrum), CHAT reappears transiently a few days after the change in medication. This result supports the recommendation of continuous monitoring, so that treatment can be adjusted as need be. © Halberg.

to rigorously assess the efficacy of treatment by using statistical methods applicable to the given individual.

4) While guarding confidentiality of the data, to include them into an accumulating database, preferably with follow-up in terms of outcomes. The cross-sectional database thus originating can serve both basic science and public benefit with returns for the individual patient as new knowledge is acquired from the extending data pool.

For the future, once the loop between sensing of pressure and treatment is closed, research is needed:

1) To arrive at the best compromise between selecting an anti-hypertensive medication that continuously adjusts the dose so that treatment is administered when it is needed but not when it is not needed and may only lead to undesirable side effects, while also restoring a healthy circadian pattern when needed.

2) To find out whether fast-acting formulations are more flexible to address the need of the moment without interfering with circadian and other patterns.

The lessons to be derived today are first the desirability of obtaining a 7-day/24-hour profile of BP and HR for everybody and second to realize that abnormalities of BP and/or HR patterns may be compatible with having most if not all data within the range of acceptable values. For instance, all systolic readings can be below a target value such as 130 mmHg, but if the circadian amplitude of BP is excessive within the normal range, it still indicates an elevation in cardiovascular disease risk, which should be treated before the onset of complications such as a stroke or a myocardial infarction. Single measurements may be better than none, but serial measurements are an improvement, notably when they are strategically placed to detect and treat elevated risks, even when they occur in a fictional normal range, an important issue for hospital, office and home measurement alike, whether automatic or manual.

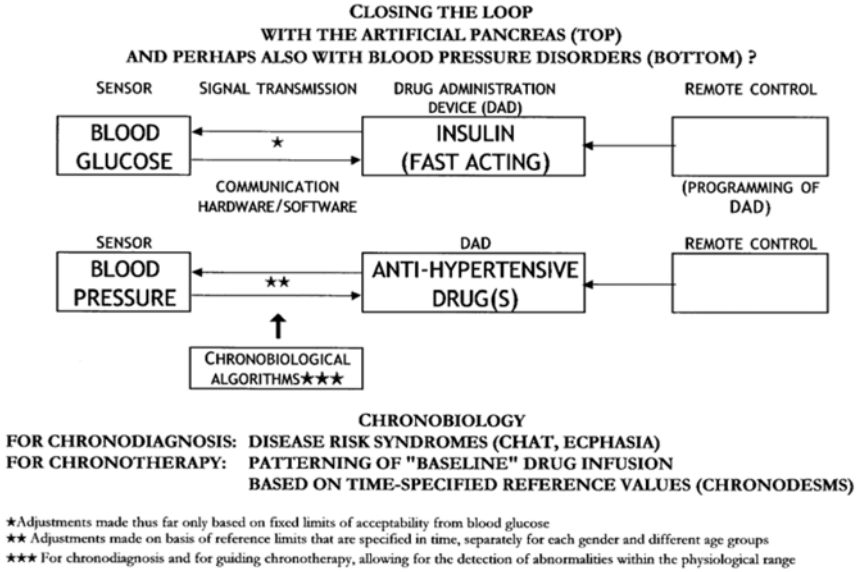


Fig. 31. Task for the future. To facilitate the continuous adjustment of treatment in the light of large within-day and day-to-day changes in BP, new devices could be designed to close the loop between the monitoring of BP and the administration of anti-hypertensive medication. The merit of switching from 24-hour formulations to fast-acting drugs should be further evaluated to achieve optimal control. But self-monitoring and self-adjustment of an educated public remains the task that can be cost-effectively implemented today, with ambulatory monitors available with a 90% reduction in price by participation in BIO-COS (contact: corne001@umn.edu). © Halberg.

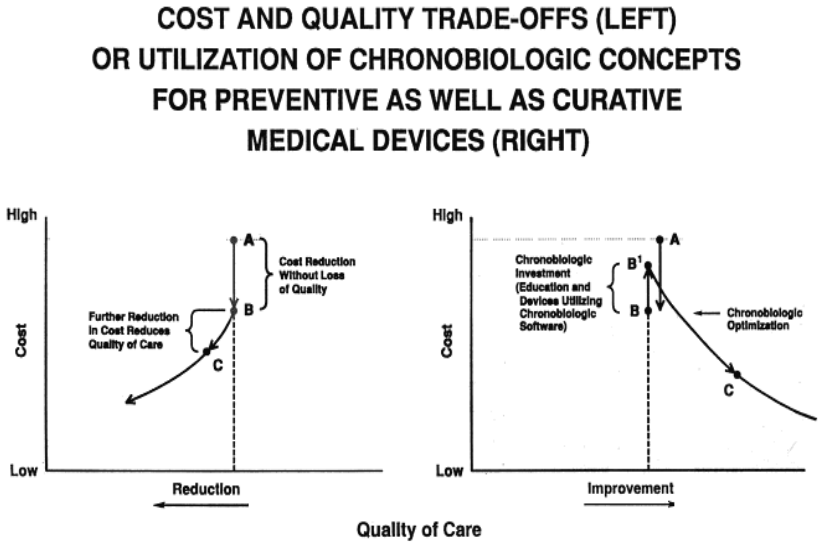


Fig. 32. Even with tools available today, self-measurements and/or ambulatory monitoring can be very useful when the data are analyzed by the methods of Chronobiology. It is thus possible to diagnose not only MESOR-hypertension but also abnormalities of the *variability* in BP and HR. The best decision can thus be taken to treat preventively each individual patient and restore an acceptable circadian pattern of BP and HR. Toward this goal, education at all ages is recommended. Emphasis on prehabilitation in preference to rehabilitation only could lead to a large decrease in medical costs without compromising and actually improving on the quality of care. © Halberg.

15. Ten amendments (to guidelines for blood pressure management)

The following amendments are based on the formulated and experimentally validated demonstration that in the pursuit of happiness an education in chronobiology is an immediate fundamental channel in health promotion and universal health care.

1) Self-surveillance and self-experimentation [15] analyzed for and guided by time structures (chronomics) can be started at all ages, continuing throughout life, providing returns for health care and science.

2) Self-surveillance is best implemented by collecting time series focusing upon endpoints of *variability* as well as upon averages in manual and preferably automatic blood pressure and heart rate measurements, among other variables pertinent to the care of patients and their environmental health.

2) Chronomics, the mapping of broad time structures (chronomes), detects in a timely fashion *risks greater than hypertension* as a basis for countermeasures that are possible by relaxation methods and/or medications.

4) Chronomics also detects, more reliably than by conventional spotchecks, actual disease such as MESOR-hypertension, and is best continued to validate effects of treatment.

5) *Clinical significance,* gauged by return to reference values of the individual and/or of gender- and age-matched peers in clinical health, is an indispensable complement to the required, but in itself not sufficient, *statistical significance* of treatment effects.

6) Chronomics can establish whether treatment is beneficial, undesirable, or indifferent by as-one-goes sequential analysis available for the individual patient to observe treatment effects and eventually to validate the beneficial effect, all in continued monitored and sequentially time-structure analyzed serial data (such as by cumulative sums control charts [30-32]).

7) Literacy in chronomics [13,14,46] should be built into an integrated comprehensive curriculum.

8) Such literacy is best started from scratch in developing areas as a model for the developed world, where modification of existing programs is more difficult to achieve.

9) Literacy in chronomes and self-help is likely to lead to higher-quality care, focusing on prevention, at less cost (Fig. 32; [11–14]).

10) Research standards of hypothesis testing (*P*-values) and parameter estimation (95% confidence intervals) may thus enter routine health care practice for the first time in the service of the individual patient. They serve for diagnosing and treating risk elevations as well as for diagnosing and treating actual disease, in a timely and timed way, and in continuing to validate the effectiveness of treatment.

References

[1] Janeway TC. The clinical study of blood pressure. New York: Appleton & Co.; 1904. 300 pp.

[2] Bartter FC. Periodicity and medicine. In: Scheving LE, Halberg F, Pauly JE, Eds. Chronobiology. Tokyo: Igaku Shoin Ltd.; 1974. p. 6–13.

[3] Halberg F, Cornélissen G, Otsuka K, et al. International BIOCOS Study Group. Cross-spectrally coherent ~10.5- and 21-year biological and physical cycles, magnetic storms and myocardial infarctions. Neuroendocrinol Lett 2000;21:233–58.
Analyses of 7-day/24-hour profiles collected within the BIOCOS project are provided free of charge from a centralized facility; ambulatory blood pressure monitors from the A&D company can also be obtained at a cost reduced by 85% for BIOCOS participants who wish to contribute to an accumulating international data base; for details, contact corne001@umn.edu.

[4] Fossel M. Editor's note. J Anti-Aging Med 1998;1:239.

[5] Halberg F. Chronobiology. Annu Rev Physiol 1969;31:675–725.

[6] Cornélissen G, Halberg F. Chronomedicine, vol. 1. In: Armitage p, Colton T, Eds. Encyclopedia of Biostatistics. J Wiley, Chichester, UK, 1998, pp. 642–9.

[7] Halberg F, Carandente F, Cornélissen G, Katinas GS: Glossary of chronobiology. Chronobiologia 1977;4(Suppl. 1):189 pp.

[8] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. J Am Med Assoc 2003;289:2560–72.

[9] Lenfant C. Reflections on hypertension control rates: a message from the director of the National Heart, Lung, and Blood Institute [Editorial]. Arch Intern Med 2002;162:131–2..

[10] Cornélissen G, Schwartzkopff O, Halberg F, Otsuka K, Watanabe Y. 7-day ambulatory monitoring for adults with hypertension and diabetes. Am J Kidney Dis 2001;37:878.

[11] Halberg F, Cornélissen G, Wall D, et al. Engineering and governmental challenge: 7-day/24-hour chronobiological blood pressure and heart rate screening. Biomed Instrument Technol 2002;36(Part I):89–122.

[12] Halberg F, Cornélissen G, Wall D, et al. Engineering and governmental challenge: 7-day/24-hour chronobiologic blood pressure and heart rate screening. Biomed Instrument Technol 2002;36:(Part II):183–97.

[13] Halberg F, Cornélissen G, Carandente A, Bakken E, Young E. Chronobiologic perspectives of international health care reform for the future of children. Chronobiologia 1993;20:269–75.

[14] Cornélissen G, Delmore P, Bingham C, et al. A response to the health care crisis: a 'health start' from 'womb to tomb'. Chronobiologia 1993;20:277–91.

[15] Halberg F, Cornélissen G, Schack B. Self-experimentation on chronomes, time structures; chronomics for health surveillance and science: also transdisciplinary civic duty? Behav Brain Sci. http: // www.bbsonline.org/Preprints/Roberts/Commentators/Halberg.html

[16] Mallion JM, Baguet JP, Siche JP, Tremel F, De Gaudemaris R. Clinical value of ambulatory blood pressure monitoring. J Hypertens 1999;17:585–95.

[17] Veerman DP, de Blok K, Delemarre BJ, van Montfrans GA. Office, nurse, basal and ambulatory blood pressure as predictors of hypertensive target organ damage in male and female patients. J Hum Hypertens 1996;10:9–15.

[18] Frazier L. Factors influencing blood pressure: development of a risk model. J Cardiovasc Nursing 2000;15 62–79.

[19] Cornélissen G, Halberg F. Impeachment of casual blood pressure measurements and the Þxed limits for their interpretation and chronobiologic recommendations. Ann NY Acad Sci 1996;783:24–46.

[20] Halberg F, Cornélissen G, Otsuka K, et al. Chronomics detects altered vascular variabilities constituting risks greater than hypertension: with an illustrative case report. In: Mitro P, Pella D, Rybar R, Valocik G, Eds. Proceedings, 2nd congress on cardiovascular diseases, Kosice, Slovakia, 25–27 April, 2002. Bologna: Monduzzi; 2002. p. 223–58.

[21] Cornélissen G, Otsuka K, Halberg F. Blood pressure and heart rate chronome mapping: a complement to the human genome initiative. In: Otsuka K, Cornélissen G, Halberg F, Eds. Chronocardiology and chronomedicine: humans in time and cosmos. Tokyo: Life Science Publishing; 1993. p. 16–48.

[22] Otsuka K, Cornélissen G, Halberg F. Predictive value of blood pressure dipping and swinging with regard to vascular disease risk. Clin Drug Invest 1996;11:20–31.

[23] Otsuka K, Cornélissen G, Halberg F, Oehlert G. Excessive circadian amplitude of blood pressure increases risk of ischemic stroke and nephropathy. J Med Eng Technol 1997;21:23–30.

[24] Scarpelli PT, Romano S, Livi R, et al. Instrumentation for human blood pressure rhythm assessment by self- measurement In: Scheving LE, Halberg F, Ehret CF, Eds. Chronobiotechnology and chronobiological engineering. The Netherlands: Martinus Nijhoff; 1987. p. 304–9.

[25] Müller-Bohn T, Cornélissen G, Halhuber M, et al. CHAT und Schlagfall. Dtsche Apothek Z 2002;142:366–70.

[26] Nakano S, Fukuda M, Hotta F, et al. Reversed circadian blood pressure rhythm is associated with occurrence of both fatal and nonfatal vascular events in NIDDM subjects. Diabetes 1998;47:1501–6.

[27] Sanchez de la Peña S, Gonzalez C, Cornélissen G, Halberg F. Chronomics: time structure (chronome) of blood pressure and heart rate in health and diabetes. Abstr. 27, 2nd Int Symp: workshop on chronoastrobiology and chronotherapy, Tokyo, Japan, Nov. 17, 2001.

[28] Takagi Y, Gomi K. Sensitivity, specificity and predictive value in laboratory tests. Nippon Rinsho 1997;55(Suppl. 1):5–10.

[29] Bingham C, Arbogast B, Cornélissen G, Lee JK, Halberg F. Inferential statistical methods for estimating and comparing cosinor parameters. Chronobiologia 1982;9:397–439.

[30] Hawkins DM. Self-starting cusum charts for location and scale. Statistician 1987;36:299–315.

[31] Cornélissen G, Halberg F, Hawkins D, Otsuka K, Henke W. Individual assessment of antihypertensive response by self-starting cumulative sums. J Med Eng Technol 1997;21:111–20.

[32] Halberg F, Cornélissen G, International Womb-to-Tomb Chronome Initiative Group: resolution from a meeting of the International Society for Research on Civilization Diseases and the Environment (new SIRMCE confederation), Brussels, Belgium, March 17–18, 1995: fairy tale or reality? Medtronic chronobiology seminar no. 8, April 1995. http: //www.msi.umn.edu/~halberg/

[33] Watanabe Y, Cornelissen G, Halberg F, et al. Chronobiometric assessment of autogenic training effects upon blood pressure and heart rate. Percept Motor Skills 1996;83:1395–410.

[34] Watanabe Y, Cornelissen G, Halberg F, et al. Method and need for continued assessment of autogenic training effect upon blood pressure: case report. New Trends Exp Clin Psychiatry 1996;12:45–50.

[35] Tamura K, Kohno I, Saito Y, Wakasugi K, Achiwa S, Imanishi Y, et al. Antihypertensive individualized therapeutic strategy. Dif Soc 1991;6:109–24.

[36] Watanabe Y, Cornélissen G, Watanabe M, et al. Effects of autogenic training and antihypertensive agents on circadian and circaseptan variation of blood pressure. Clin Exp Hypertens 2003;25:405–12.

[37] Watanabe Y, Cornélissen G, Katinas G, et al. Case report: a drug for damping circannual and transannual amplitudes of blood pressure and heart rate. Abstract, 2nd Int. Symp., Problems of rhythms in natural sciences. Moscow, March 1–3, 2004. p. 18–20.

[38] Shinagawa M, Kubo Y, Otsuka K, Ohkawa S, Cornélissen G, Halberg F. Impact of circadian amplitude and chronotherapy: relevance to prevention and treatment of stroke. Biomed Pharmacother 2001;55(Suppl. 1):125–32.

[39] Fok BSP, Cornélissen G, Halberg F, Chu TTW, Thomas GN, Tomlinson B. Different effects of lercanidipine and felodipine on circadian blood pressure and heart rate among hypertensive patients. J Hong Kong Coll Cardiol 2004;12(Abstr. 15):33.

[40] Rosch PJ. Why treating hypertension has become a dismal fiasco. Health Stress 2003;10:1–12.

[41] Halberg F, Cornélissen G, Schwartzkopff O, et al. Health promotion beyond Bohumil Fiser's 60th birthday. In: Halberg F, Kenner T, Siegelova J, Eds. Proc. Symp. Chronobiological analysis in the pathophysiology of the cardiovascular system. Brno: Masaryk Univ; 2003; p. 9–73.

[42] Katinas G, Halberg F, Cornélissen G, et al. Transient circadian hyper-amplitude-tension (CHAT) may be intermittent: case reports illustrating gliding spectral windows. Biomed Pharmacother 2003;57(Suppl. 1):S104–109.

[43] Levine H, Halberg F. Clinical aspects of blood pressure autorhythmometry. In: Scheving LE, Halberg F, Pauly JE, Eds. Chronobiology. Proc. Int. Soc. for the study of biological rhythms, Little Rock, AK, USA. Stuttgart: Georg Thieme; Tokyo: Igaku Shoin; 1974. p. 406–14.

[44] Wang ZR, Chen LG, Wan CM, Qu Y, Cornélissen G, Halberg F. In vitro circadian ANP secretion by gene transferring cells encapsulated in polycaprolactone tubes. Peptides (in press).

[45] Chen LG, Wang ZR, Wan CM, Xiao J, Guo L, Guo HL, et al. Circadian renal rhythms influenced by implanted encapsulated hANP-producing cells in Goldblatt hypertensive rats. Gene Ther (in press).

[46] Halberg F. More on educative chronobiology, health and the computer. Int J Chronobiol 1974;2:87–105.