

HEALTHWATCH

Why 7-Day Blood Pressure Monitoring?

3



What everyone should know about blood pressure

Health Watch 3

Dedicated, on his 80th birthday,
to Earl E. Bakken, the developer of the
implantable cardiac pacemaker for long-term
use (and founder of Medtronic Inc., the
company manufacturing many devices for
rehabilitation) to be better known in the
future for *pre*-habilitation

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HEALTHWATCH 3

Diagnosis of Hypertension

By necessity rather than choice, hypertension is currently diagnosed by means of single casual measurements in the physician's office. These 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 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. But evidence accumulating from cooperating centers and ourselves suggests that it may be possible to achieve even better results, while the cost of health care could be reduced by education in self-help, which includes self-monitoring for a week or longer, as need be, an endeavor also serving basic science.

Within-day variation of blood pressure

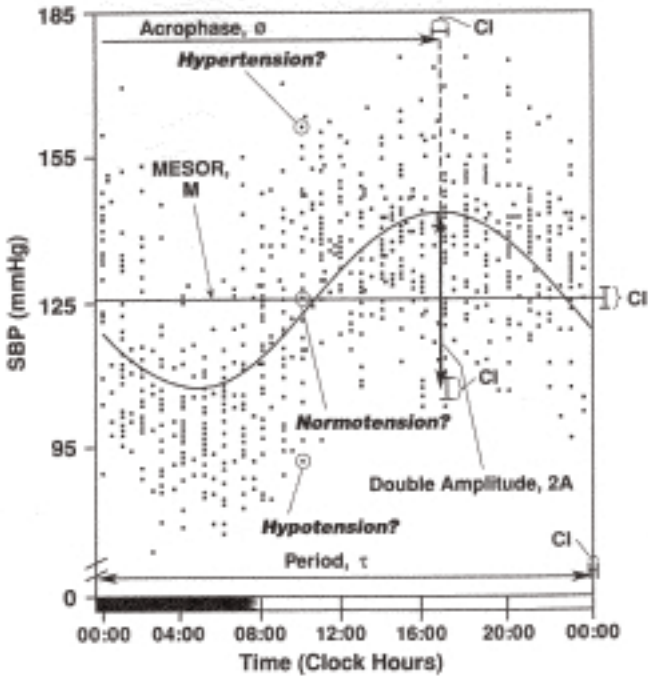
Data obtained automatically around the clock with ambulatory monitors (and by self-measurements or manual staff measurements earlier) have shown that blood pressure is not constant, but rather changes, in part predictably, notably along the 24-hour scale. Figure 1 shows the variability of blood pressure 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 mm Hg. Guidelines have started to consider these daily changes in blood pressure by providing acceptable fixed limits that differ between nighttime and daytime. 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. 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. 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.

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. 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. 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, Figure 2. 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".

HYPERTENSION, NORMOTENSION AND HYPOTENSION AT SAME CLOCK-HOUR*



* Systolic Blood Pressures (SBP) every 30 or 60 minutes for 30 days ($n = 782$) stacked over idealized day reveal circadian component; JCM (M, 33y, untreated); CI = 95% confidence interval.

Figure 1: A 33-year old neurosurgeon diagnosed conventionally as moderately hypertensive monitored his blood pressure 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 blood pressure from moment to moment, as well as within a day and from day to day, as seen also in Figure 2. This large variability in blood pressure 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.

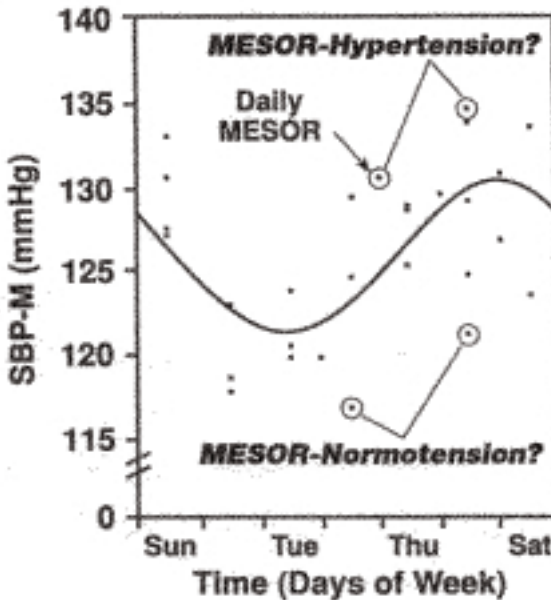


Figure 2: The day-to-day variability in the circadian characteristics of blood pressure can be so large that the MESOR of systolic blood pressure (measured at 15-30 min intervals around the clock) can be compatible with the diagnosis of MESOR-hypertension on one day, that of MESOR-normotension on another 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.

Chronobiology offers an alternative approach

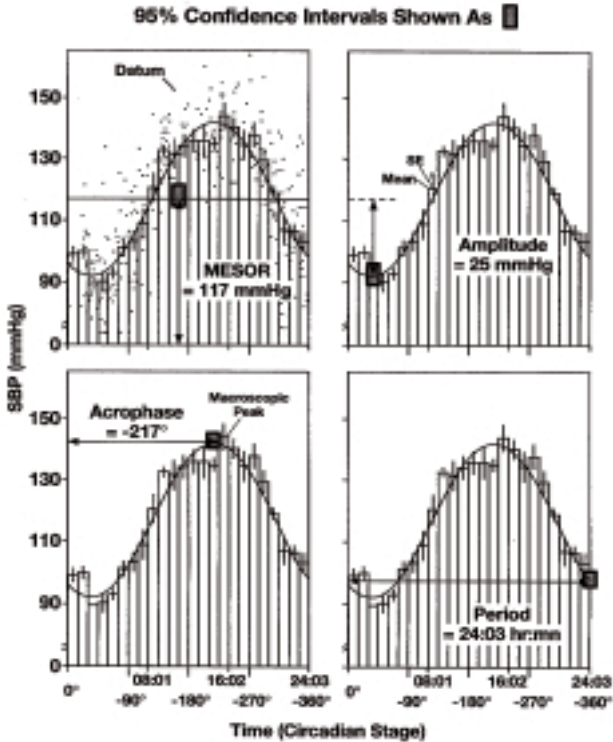
In order to account for the daily rhythm in blood pressure and for day-to-day variations in its characteristics, a new approach is proposed. This approach differs from the conventional way of diagnosing hypertension in the following aspects.

- a. Blood pressure is measured around the clock (e.g., half-hourly by ambulatory monitoring or by as dense as possible self-measurements).
- b. Measurements can be analyzed if they cover 24 hours but are instead continued for at least 7 and preferably for 17 days.

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

- d. 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), Figure 3. 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, Figures 4 and 5. Results are summarized in an easily understood form, the sphygmochron, Figure 6. As the time series length increases, the period (Figure 3, bottom right) can also be estimated as an important characteristic in its own right.

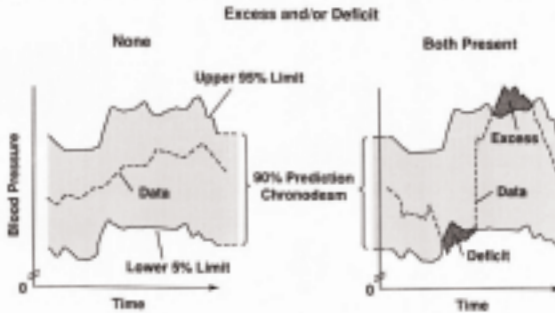
CIRCADIAN RHYTHM CHARACTERISTICS OF SYSTOLIC BLOOD PRESSURE (SBP) OF A CLINICALLY HEALTHY WOMAN



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Figure 3: Illustration of circadian rhythm characteristics for the case of a series of systolic blood pressures 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).

NONPARAMETRIC APPROACH TO DEVIANT BLOOD PRESSURE



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Figure 4: Nonparametric assessment of a blood pressure 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.

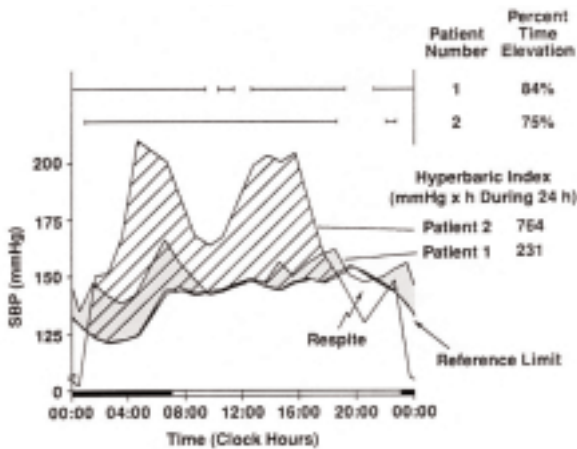


Figure 5: The need to assess the hyperbaric index as a complement to the percent time elevation is illustrated by a comparison of profiles from two patients with a similar number of deviant readings. Patient 1 has a numerically slightly larger percent time elevation but a much smaller excess. The very large difference in hyperbaric index between the two patients likely reflects the difference in their prognosis.

Monitoring Profile Over Time;
Computer Comparison
with Peer Group Limits

SPHYGMOCHRON™-S (short form)
Blood Pressure (BP) and Related Cardiovascular Summary
(Chronobiologic Sphygmochron, or in relation to the circadian, circadian blood pressure, as well as pulse and volume time)

Name _____ Patient # _____ No. of Profiles _____
Age _____ Sex Monitoring from _____ To _____
Time of Awakening (K) _____ 3. Falling Asleep (S) _____
E₂₄ _____ Comments ^{1,2} _____

Chronobiologic Characteristics

	Systolic BP (mmHg)		Diastolic BP (mmHg)		Heart Rate (bpm)	
	Patient Value	Peer Group Reference Limits	Patient Value	Peer Group Reference Limits	Patient Value	Peer Group Reference Limits
Adjusted 24-h Mean (MESOR)	<input type="text"/>	Range <input type="text"/>	<input type="text"/>	Range <input type="text"/>	<input type="text"/>	Range <input type="text"/>
Predictable Change (Double Amplitude)	<input type="text"/>	Range <input type="text"/>	<input type="text"/>	Range <input type="text"/>	<input type="text"/>	Range <input type="text"/>
Timing of Overall High Values (Acrophase) (hr:min)	<input type="text"/>	Range <input type="text"/>	<input type="text"/>	Range <input type="text"/>	<input type="text"/>	Range <input type="text"/>

	STD (Min, Max)	STD (Min, Max)	STD (Min, Max)
Percent Time of Elevated	<input type="text"/>	<input type="text"/>	<input type="text"/>
Timing of Excess (hr:min)	<input type="text"/>	<input type="text"/>	<input type="text"/>
Extent of Excess During 24 Hours Hill (hr:min x hour)	<input type="text"/>	<input type="text"/>	<input type="text"/>
10-Year Cumulative Excess (hr:min x hour) (in 1,000's units)	<input type="text"/>	<input type="text"/>	<input type="text"/>

Substituted Standard Deviations (STD = Standard Deviation) (Min = Minimum) (Max = Maximum) (HR = Heart Rate Index)

Intervention Needed **More Monitoring Needed**

No Annually
 Yes Drug Non-Drug As soon as possible
 Other specify _____

Prepared by _____ Date _____

1) Unusually long standing or lying-down-during-waking unusual activity, such as exercise, emotional tasks, or schedule changes, e.g., shiftwork, etc.; 2) Nat, tobacco, alcohol and/or other, etc.

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Figure 6: Sphygmochron, the computer-generated form used to summarize results from the combined parametric and nonparametric assessment of a blood pressure and heart rate 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.

Advantages of the chronobiologic 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. 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.

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**; scheme in Figure 7) is also a very great risk of stroke and kidney disease (highest rightmost two columns in Figures 8 and 9), even when all measurements lie in the range of acceptable values (leftmost two columns in Figure 10). Even when diagnosed on the basis of self- or manual measurements by staff, CHAT has been related to increased mortality, Figures 11 and in the perspective of 28 years, Figure 12. 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, Figure 13. An odd timing of high blood pressure values is also found in some diabetic patients with autonomic nervous dysfunction.

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). 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 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%).

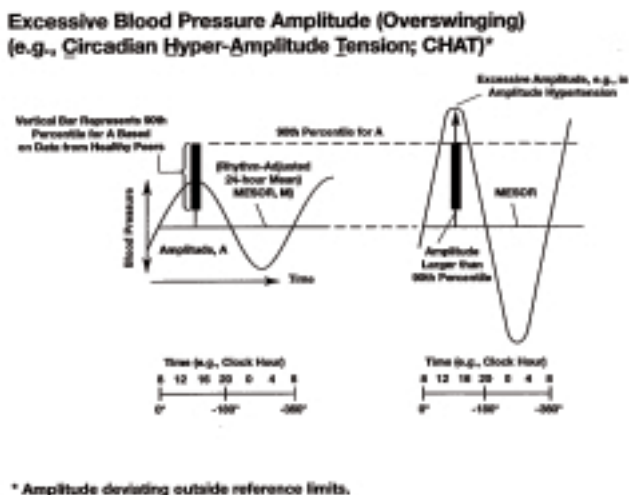


Figure 7: Definition of CHAT (circadian hyper-amplitude-tension), a condition characterized by an excessive circadian amplitude of blood pressure and found to be associated with a very large increase in vascular disease risk. The reference circadian variation in blood pressure is shown on the left, with 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).

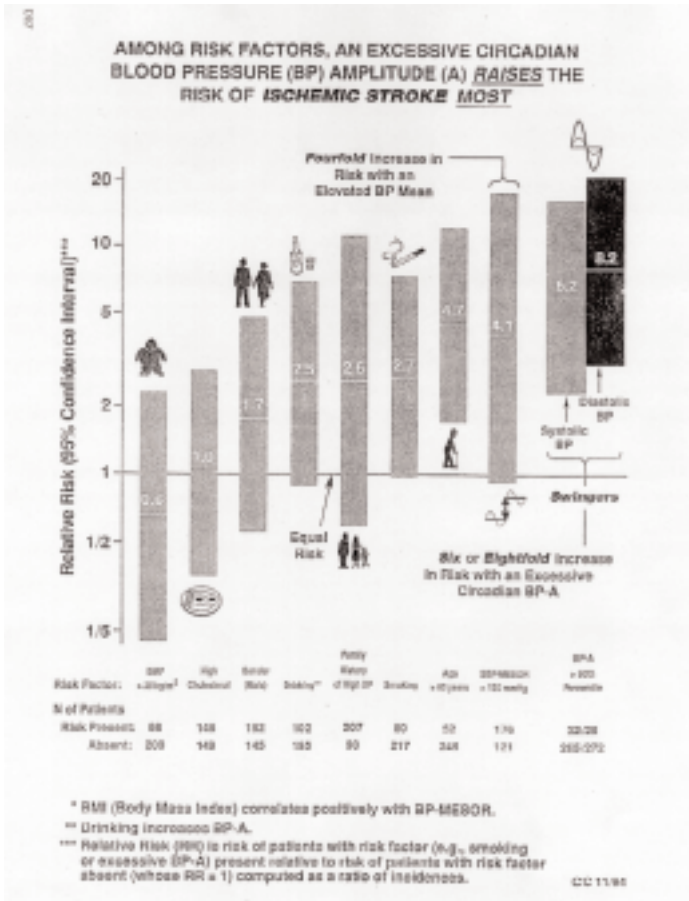
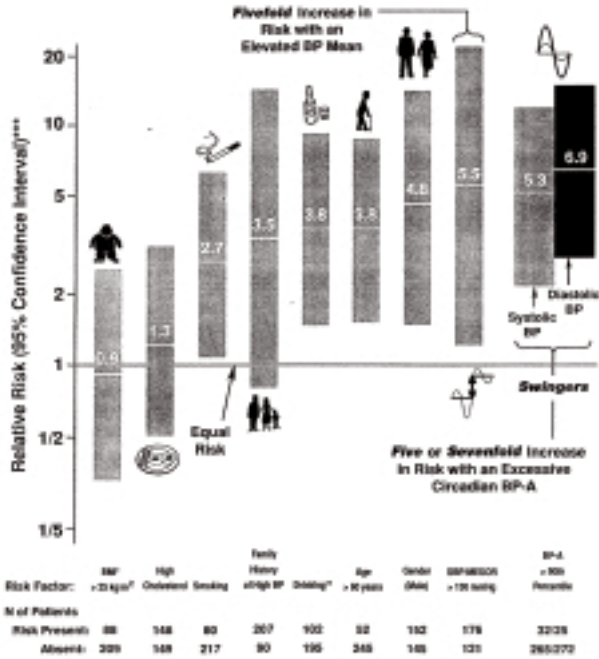


Figure 8: Relative risk of cerebral ischemic event for various factors, computed as the ratio of the incidence of morbidity that occurred among patients presenting with the tested factor by comparison with that among patients not presenting with the tested factor. Results of a 6-year prospective study on 297 patients indicate that the risk associated with CHA2DS2-VASc 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 blood pressure). As compared to patients with an acceptable circadian blood pressure amplitude, patients with diastolic CHA2DS2-VASc 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.

AMONG RISK FACTORS, AN EXCESSIVE CIRCADIAN BLOOD PRESSURE (BP) AMPLITUDE (A) RAISES THE RISK OF NEPHROPATHY MOST



* BMI (Body Mass Index) correlates positively with BP-MESOR.

** Drinking increases BP-A.

*** Relative Risk (RR) is risk of patients with risk factor (e.g., smoking or excessive BP-A) present relative to risk of patients with risk factor absent (whose RR = 1) computed as a ratio of incidences.

Figure 9: CHAT is also associated with a large increase in the risk of nephropathy (see legend of Figure 8).

AN EXCESSIVE CIRCADIAN BLOOD PRESSURE (BP) AMPLITUDE [A]* IS A RISK FACTOR FOR ISCHEMIC STROKE INDEPENDENT FROM THE 24-HOUR MEAN (MESOR)**

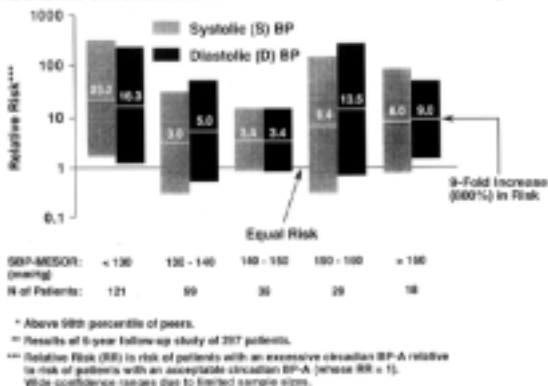
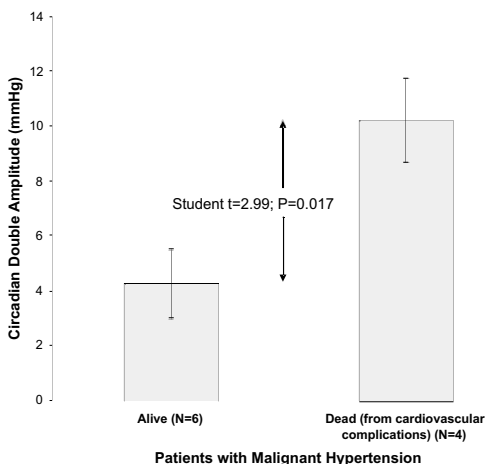


Figure 10: The risk of a cerebral ischemic event associated with CHAT shown in Figure 8 applies to patients with different values of the MESOR of systolic blood pressure, including patients who are MESOR-normotensive (left; the 95% confidence interval for relative risk, shown as the vertical dark bar, does not overlap one, representing a risk equal to that of patients with an acceptable circadian amplitude of blood pressure). 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.

Excess Variability in Diastolic (D) Blood Pressure (BP) Self-Measurements Increases Risk of Mortality in Patients with Malignant Hypertension



From: Scarpelli PT et al. in Chronobiotechnology and Chronobiological Engineering, NATO ASI Series E No 120, pp 304-309, 1987.

Figure 11: 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 8-10, the circadian amplitude of self-measured diastolic blood pressure by patients with malignant hypertension was larger among those who died than among those who survived.

LIFE EXPECTANCY
28 YEARS AFTER THE DIAGNOSIS
CHAT: CIRCADIAN HYPER-AMPLITUDE-TENSION

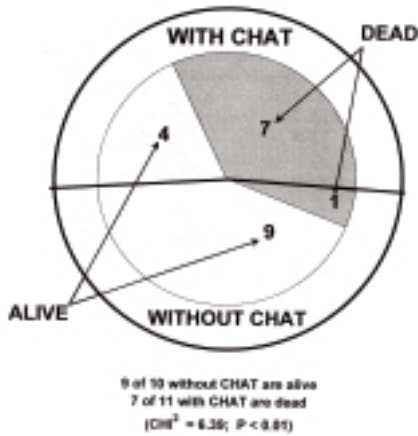


Figure 12: Manual measurements taken 6 to 7 times daily at 2- to 3-hour intervals during waking for 2 days by staff were also able to distinguish between patients who died and those who survived 28 years later. The incidence of CHAT was statistically significantly larger among those who died than among the survivors.

Decreased Heart Rate Variability (DHRV), Circadian Hyper-Amplitude-Tension (CHAT) and Elevated Pulse Pressure (EPP) are Separate Cardiovascular Disease Risks*

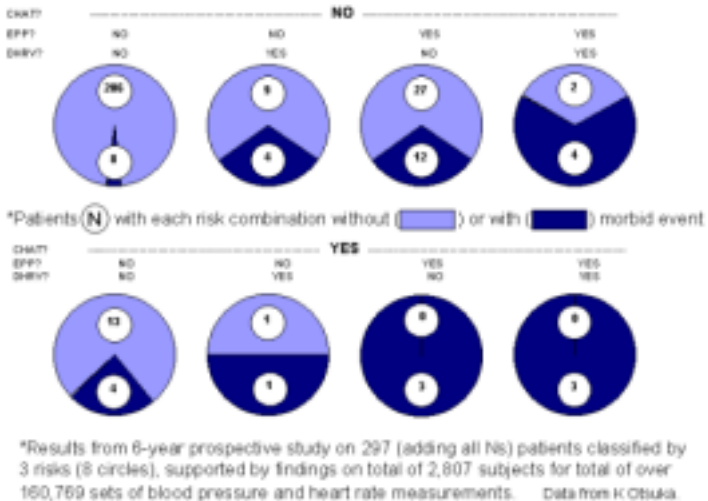
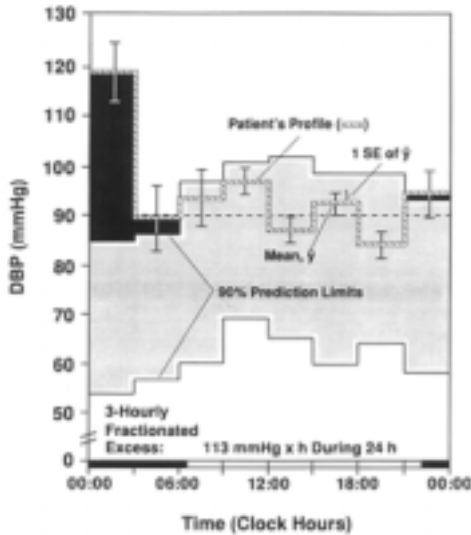


Figure 13: CHAT is one of several conditions related to the **variability** in blood pressure and/or heart rate that is associated with an increase in vascular disease risk. Too large a pulse pressure (the difference between systolic and diastolic blood pressure, when the heart contracts or relaxes, or the extent of change in pressure during a cardiac cycle) and a decreased heart rate variability (defined as the standard deviation of heart rate) 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 blood pressure and heart rate are mostly independent and additive.

Who is to benefit from a chronobiologic 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 chronobiologic screening of blood pressure, since abnormalities in blood pressure variability (such as CHAT) cannot be diagnosed in the physician'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. Figure 14 shows the case of a patient with severely and consistently elevated diastolic pressures between midnight and 03:00. 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, Figure 15.

ODD-TIME DIASTOLIC BLOOD PRESSURE (DBP) EXCESS (■) WITH TREATMENT IN THE MORNING*



* DJ (M, 78-y) taking "daily" 10 mg Vasotec (ACE-inhibitor); sizable DBP excess at times when it would usually be missed.

Figure 14: Around the clock monitoring is useful to check on the efficacy of treatment. The diastolic blood pressures 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, diastolic blood pressure is greatly and consistently elevated, suggesting that during part of the night this patient escaped from the desired effect of treatment.

CHRONOBIOLOGIC SURVEILLANCE DETECTS HARBINGERS OF PREDISSEASE PROMPTING AND GUIDING RATIONAL INTERVENTION IN A WINDOW BROADENED FROM HOURS (MIDDLE) TO YEARS (LEFT)*

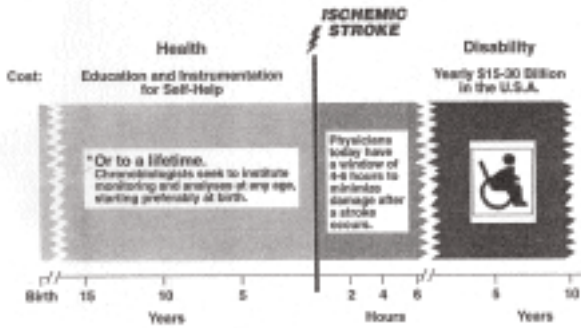


Figure 15: The detection of an elevated risk before there is overt disease and target organ damage can prompt timely and timed intervention as a means to pre-habilitation, with the hope to reduce the need for re-habilitation, that is for the need of after the fact care associated with much suffering and high cost.

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 chronobiologic 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 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.

Benefits are:

- a. The diagnosis of MESOR-hypertension is improved.
- b. Abnormalities of blood pressure variability provide warning signs of a heightened vascular disease risk prompting prophylactic action.
- c. 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).
- d. The response to treatment can be rigorously assessed for each individual patient.

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 can be applied to test the equality of the MESOR, of the double (circadian) amplitude and of the acrophase, considered singly or in combination, Figure 16. 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 can also be used as a sequential test capable of detecting a change in MESOR, acrophase or amplitude and also of estimating when the change first took place, Figure 17. 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.

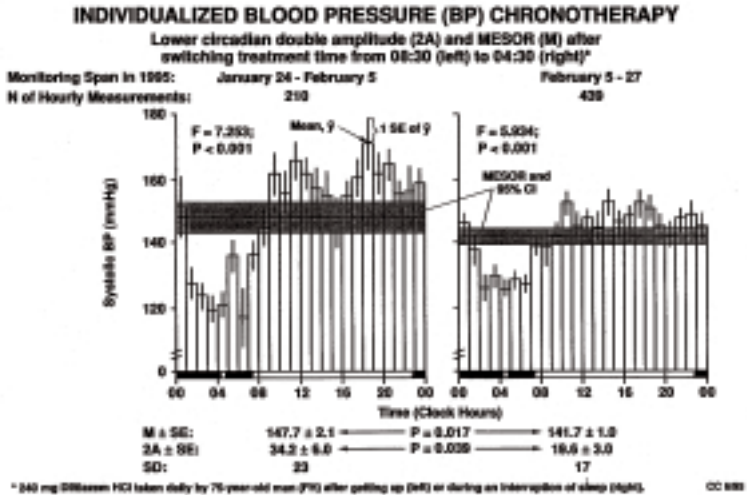


Figure 16: Techniques are available to test on an individualized basis the efficacy of treatment. One such method consists of testing the equality of rhythm parameters before and after the start of treatment. In the case of this 75-year old man, the same dose (240 mg) of the same drug (Diltiazem HCl) 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 systolic blood pressure 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.

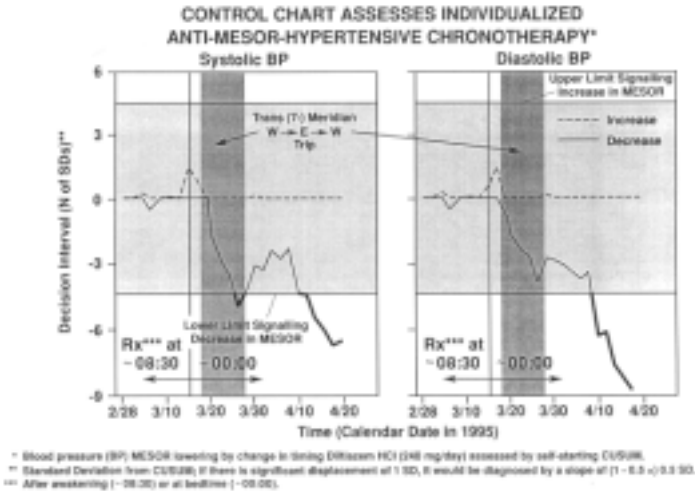


Figure 17: Control charts of daily MESORs of systolic (left) and diastolic (right) blood pressure of a 75-year old man treated with 240 mg of Diltiazem HCl when the timing of this medication was changed from awakening to bedtime. While the series of daily MESORs is proceeding 'in control' (i.e., before 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 blood pressure 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 blood pressure is estimated to have occurred shortly after the change in timing of medication.

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, but continued monitoring is essential in order to detect silent escapes from any treatment that is only transiently effective, as in the case shown in Figure 18 when treatment was effective for three months but not thereafter. For patients with MESOR-hypertension complicated by CHAT, some anti-hypertensive drugs are more effective than others in reducing an excessive blood pressure swing, while also lowering the blood pressure MESOR. For instance, long-acting carteolol, a β -adrenoceptor antagonist with intrinsic sympathomimetic activity, compares favorably with other drugs with the doses tested, Figure 19. This drug reduces not only the circadian amplitude but also the amplitudes of the about-weekly, the about-yearly and trans-yearly components.

INDIVIDUALIZED ASSESSMENT (BY CUSUM) OF A PATIENT'S INITIAL RESPONSE AND SUBSEQUENT FAILURE TO RESPOND TO AUTOGENIC TRAINING (AT) (EO, F, 59y)
Systolic Blood Pressure

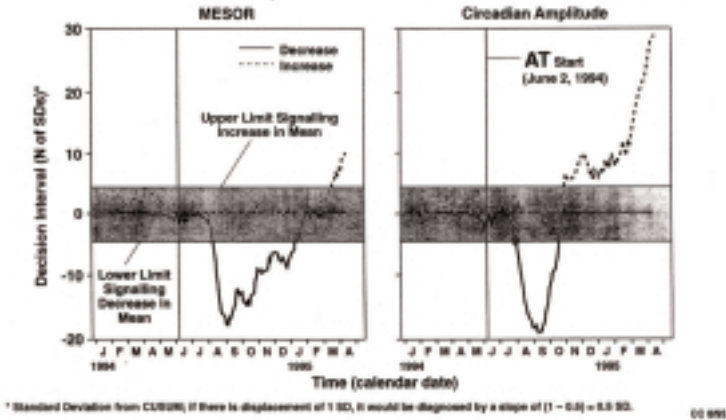


Figure 18: Control charts of the MESOR (left) and circadian amplitude (right) of systolic blood pressure of a 59-year old woman starting non-pharmacological treatment with autogenic training. Whereas treatment was effective for the first 3 months, an emotional upset was associated with the subsequent 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.

LOWERING OF THE CIRCADIAN DOUBLE AMPLITUDE (2A) OF SYSTOLIC (S) AND DIASTOLIC (D) BLOOD PRESSURE (BP) IS A MATTER OF THE PATIENT AND DRUG DOSE (AND TIMING)*

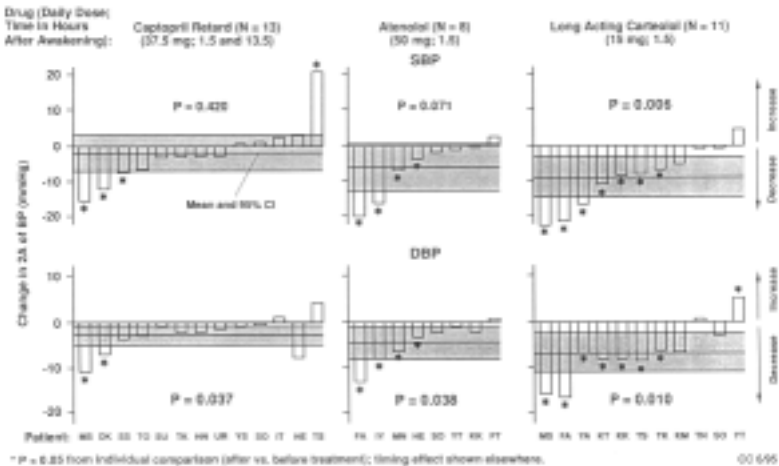
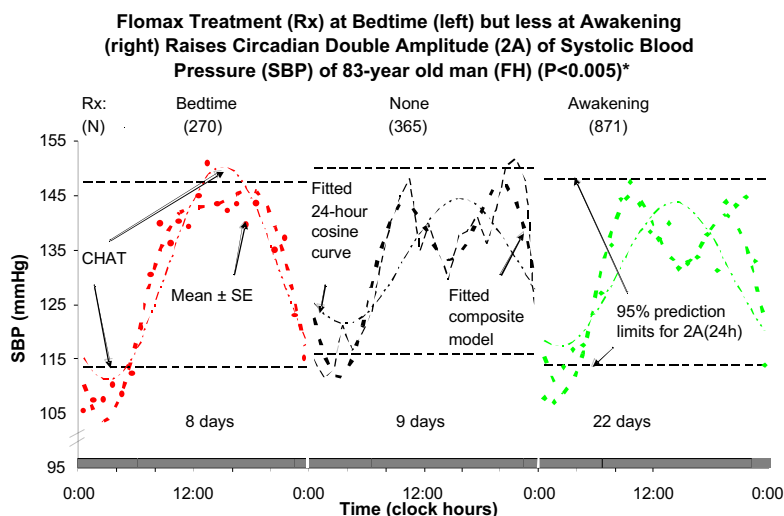


Figure 19: Whereas anti-hypertensive drugs are administered to decrease an elevated blood pressure mean, their effect on the circadian amplitude of blood pressure can be very different. For instance, on the average, long-acting carteolol but not captopril can decrease the circadian amplitude of blood pressure 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 blood pressure (not shown).

By optimizing (changing) the time to administer the medication (Figure 16) or by omitting a dose given at the wrong time for the given patient (treated as ascertained by blood pressure monitoring, Figure 20), the desired effects can be obtained. The MESOR can be lowered (Figure 16) or an acceptable circadian amplitude of blood pressure can be restored (Figure 20). The elimination of dosing at the wrong time can also eliminate CHAT, Figure 21. 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, Figures 22 and 23.



* Uroselectivity of Flomax may apply to the average BP but less to the circadian amplitude of BP. An above-threshold BP-2A (CHAT, circadian hyper-amplitude-tension) is associated with a cardiovascular disease risk higher than MESOR-hypertension.

Figure 20: CHAT can be iatrogenously associated with the taking of a medication such as flomax, an $\alpha 1A$ -adrenoceptor antagonist, useful for treating benign prastatic enlargement. Changing the dosing and/or timing of medication may restore an acceptable circadian pattern of blood pressure.

Sotalol Treatment in the Evening Associated with Increase in Circadian Amplitude of Systolic Blood Pressure ($P < 0.001$)

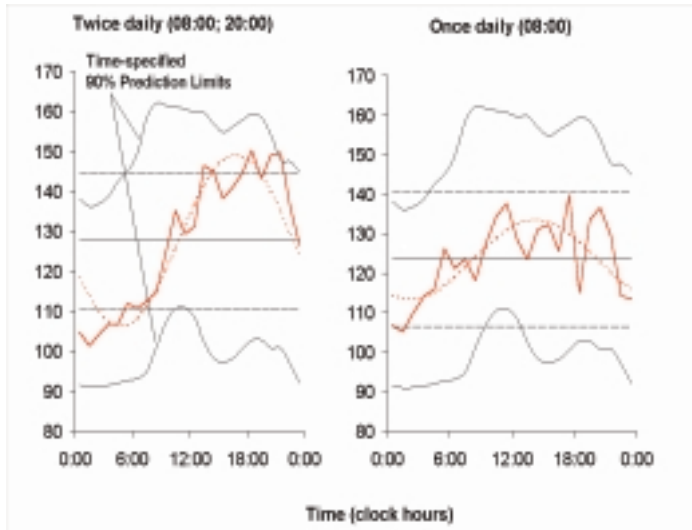


Figure 21: CHAT can be iatrogenously associated with the taking of a medication such as sotalol, a β -adrenoceptor blocker with class III anti-arrhythmic properties. Removing the dose taken at the wrong time (in the evening) can eliminate CHAT and restore an acceptable circadian pattern of blood pressure.

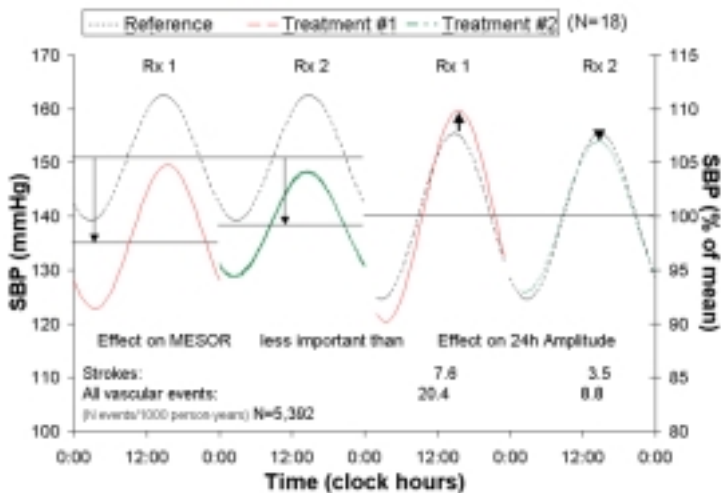
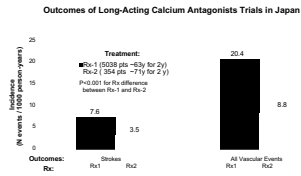
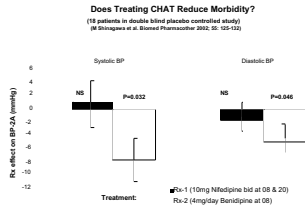


Figure 22: A cross-over study investigates the effect of two different treatments on the circadian pattern of blood pressure. Whereas nifedipine (taken twice a day, in the morning and in the evening, Rx1) is associated with a slightly more pronounced decrease in the MESOR of systolic blood pressure as 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 systolic blood pressure.



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.
 Outcome of 2-year calcium antagonists trials on 5392 patients.
 Over 50% reduction of strokes (left) and of all severe vascular events (right) by treatment (R2) that reduces (R2), while bars vs. one that does not reduce (R1), black bars) BP-24, R1 vs R2 comparison: P<0.001.

Figure 23: 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.

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 ongoing BIOCOS project worldwide, Figure 24. 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 (Figures 25-27) as well as in treated MESOR-hypertensive patients (Figure 28), the diagnoses being made on different 2-day or week-long monitoring spans.

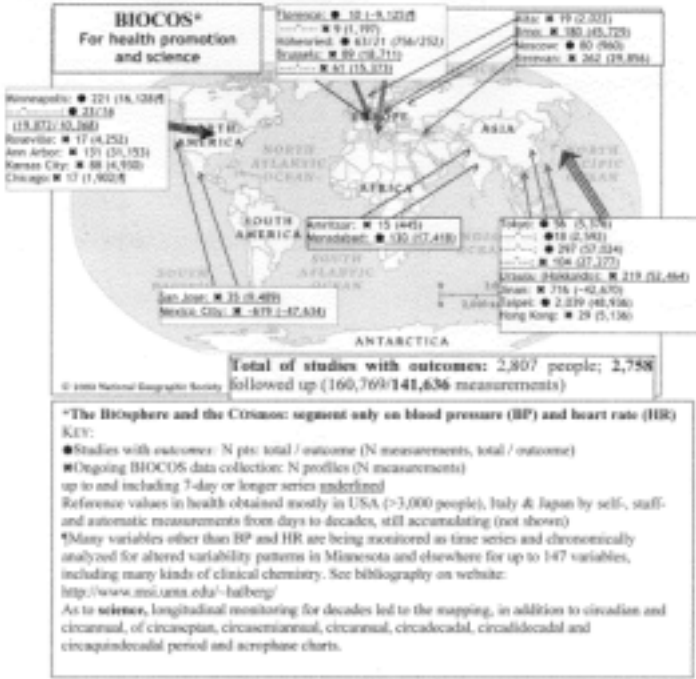


Figure 24: Map of participation in the project on the biosphere and the cosmos (BIOCOS) aimed at mapping broad time structures (chronomes) and deriving reference values therefrom.

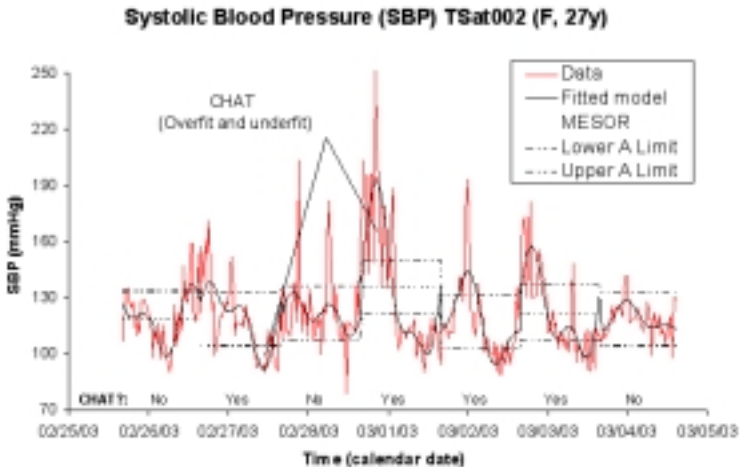


Figure 25: The need for continuous monitoring is supported by the very large day-to-day variability in circadian characteristics of blood pressure observed in some people, including this seemingly healthy young woman (TS) who monitored herself for several months (illustrative 7-day profile shown here).

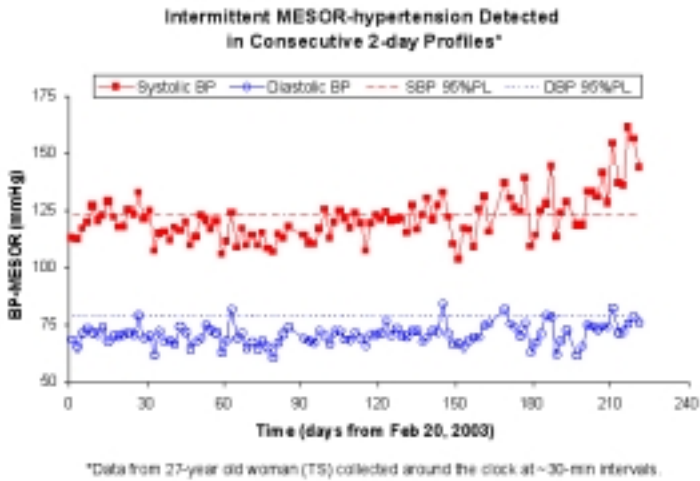


Figure 26: Time course of MESORs of systolic and diastolic blood pressure of 28-year old woman (TS), assessed for consecutive 2-day spans over 8 months, shows that MESOR-hypertension can be diagnosed consistently for a week or longer and alternate with month-long spans of MESOR-normotension.

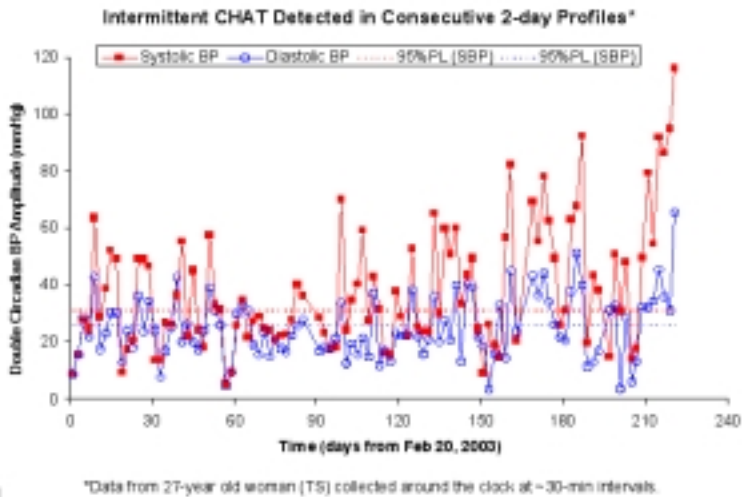


Figure 27: Time course of circadian double amplitudes of systolic and diastolic blood pressure of 28-year old woman (TS), assessed for consecutive 2-day spans over 8 months, shows that CHAT can be diagnosed consistently for a week or longer and alternate with week-long spans of an acceptable circadian amplitude of blood pressure.

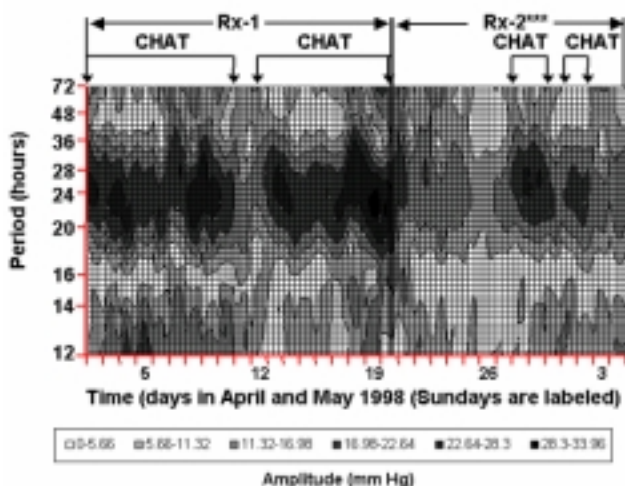


Figure 28: CHAT can be intermittent in treated MESOR-hypertensive patients such as this 72-year old man. Although the change in medication (vertical line) is associated with a decrease in the (excessive) circadian amplitude of systolic blood pressure (shown as a reduction of the dark area in a gliding 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.

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. 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 Figure 29.

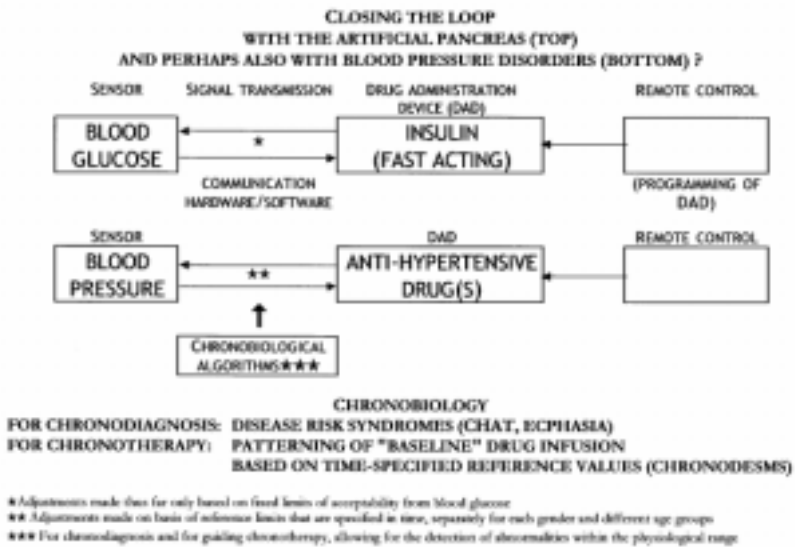


Figure 29: Task for the future. To facilitate the continuous adjustment of treatment in the light of large within-day and day-to-day changes in blood pressure, new devices could be designed to close the loop between the monitoring of blood pressure and the administration of anti-hypertensive medication. 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 BIOCOS (contact: corne001@umn.edu).

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 14 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.

Conclusions

For now

In keeping with the evidence presented herein, it is proposed to radically change the approach to diagnose and 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 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:

5. 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.
6. To find out whether fast-acting formulations are more flexible to address the need of the moment without interfering with circadian and other patterns.

10 AMENDMENTS

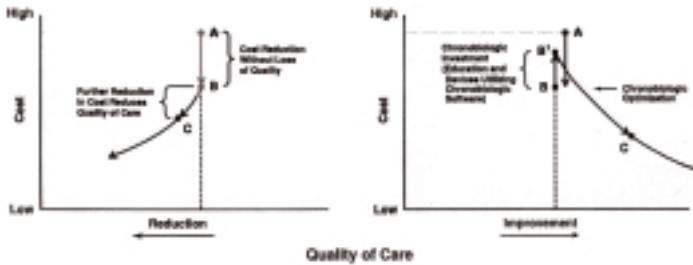
Amendments to Guidelines for Blood Pressure Management

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 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.
3. 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).
7. Literacy in chronomics 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**, Figure 30.
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.

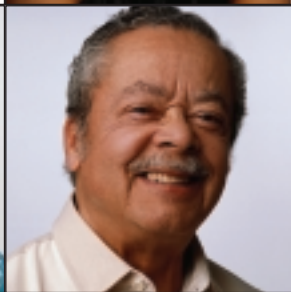
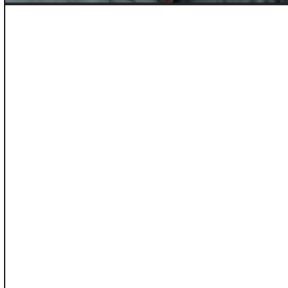
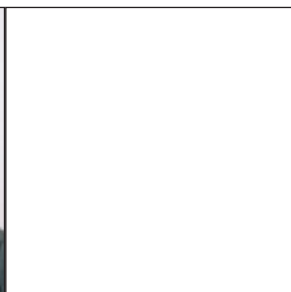
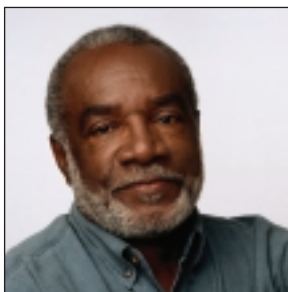
**COST AND QUALITY TRADE-OFFS (LEFT)
OR UTILIZATION OF CHRONOBIOLOGIC CONCEPTS
FOR PREVENTIVE AS WELL AS CURATIVE
MEDICAL DEVICES (RIGHT)**



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Figure 30: 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 blood pressure and heart rate. The best decision can thus be taken to treat preventively each individual patient and restore an acceptable circadian pattern of blood pressure and heart rate. Toward this goal, education at all ages is recommended. Emphasis on pre-habilitation in preference to re-habilitation only could lead to a large decrease in medical costs without compromising and actually improving on the quality of care.



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