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# SEVEN-DAY/24-HOUR CHRONOBIOLOGICALLY INTERPRETED BLOOD PRESSURE MONITORING AND SINGLE MEASUREMENTS BEFORE CATARACT SURGERY

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A b s t r a c t

In an 89-year-old man (FH), who monitored his blood pressure (BP) and heart rate (HR) around-the-clock at half-hour intervals for decades (with interruptions) and continued to do so before, during and after cataract surgery, we seek any alterations in the time structure of BP and/or HR in relation to this intervention (even though FH recognized no anxiety himself). First, we look at BP and HR within the individualized range of the subject at the given time by a sequential test, and second by reference to broader standards derived from clinically healthy peers of the same gender and corresponding age. The sequential test applied to detect any abnormalities used an individualized reference standard and found changes hidden in the normal range of peers, while data remained within that range. In the week following successful mid-week surgery, the circadian amplitude of diastolic BP increased above peer limits, a reason for caution in the interpretation of the results during the week of intervention as possibly related to subconscious anxiety about the surgery. If they were so related at all, these abnormalities were exceeded by the pleasure (in retrospect "tension") associated with preparations of materials for publication at a conference, including this report. Apart from testing for physical or emotional loads (stress), we advocate, for any and all estimations of health more generally, a chronobiologically interpreted ambulatory automatic 7-day/24-hour BP and HR monitoring (C-ABPM) as soon as an appointment for a preoperative or any other health check is made, including cataract surgery.

K e y  w o r d s

Blood pressure monitoring, Seven day monitoring, Chronobiology

## INTRODUCTION

*Background.* Concern about BP variability was emphasized in a doctoral thesis in 1880 (1; cf. 2), by Theodore C. Janeway (*3*) in 1904, by Frederic C. Bartter, head of the Hypertension-Endocrine Branch of the National Institutes of Health (NIH)

in the 1970s (*4*), and subsequently by others (*5*). In 2008, we have tools to assess this variability (*6*), which has not yet been accounted for by official guidelines (*7*). Chronobiologic evidence in *Table 1* (8) and *Figs. 1 and 2* (*6, 8–10*) has led to vascular variability disorders, VVDs. Several coexisting VVDs constitute vascular variability syndromes, VVSs, which cannot be detected without C-ABPM, *Fig. 2*.

Opinion leaders already discourage in their recommendations (*11*) – albeit not (yet) in official guidelines (*7*) – reliance upon office BP measurements, as is now practiced for any health check. Consensus meetings (*10*) recommend a **c**hronobiologically interpreted 7-day/24-hour profile obtained by **a**utomatic ambulatory **BP m**onitoring (C-ABPM), which can detect prehypertension (*8, 9*), prediabetes (*12, 13*) and elevations of the circadian amplitude and MESOR of BP associated with minimal change retinopathy (*14*), another reason for monitoring BP in ophthalmology.

Outcomes in a 7-year follow-up could be predicted from 9 days of half-hourly around-the-clock ambulatory automatic monitoring, but not from 2-, 3- or 4-day profiles (*15*). The same study showed that the response to surgery detected an increase in BP and HR in the morning and a decrease in the afternoon (*15;* figure on lower inside cover of 10). Conceivably, a "white-coat hypertension" in the morning will be a "white-coat hypotension" in the afternoon. Terms such as "white-coat effect" or "masked hypertension", originating from justified concern to account for variability, prompt much investigation (*16–38*) to account for plain false-positive and false-negative diagnoses due to variability, but are no substitute for C-ABPM 7/24 for ruling out abnormality (*8, 9, 12, 13*) and much longer C-ABPM to evaluate VVDs and VVSs (*Figs. 1 and 2*), that carry a risk larger than a high BP, and/or to study the development of high BP, also one of the VVDs.

*Table 1*
Outcomes of chronobiological screens of blood pressure and heart rate*

| N of patients | N at follow-up | Sampling | N measurements: Total (outcomes) | Finding |
|---|---|---|---|---|
| 10 | 10 (up to 5y) | 5/day daily | Up to 9,125 (only partially analyzed) | Among P. Scarpelli's patients, the 4 who died with malignant hypertension had a larger circadian BP amplitude than the 6 who were still alive (SBP: t=1.84; P=0.103; DBP: t=2.99; P=0.017) |
| 63 | 21 after 28y | every 4h for 2 days | 756 (252) | 9 of 10 subjects without CHAT are alive while 7 of 11 subjects with CHAT are dead 28 years later (chi-square=6.390; P<0.01) |
| 56 | 56 Concomitant LVMI | every 15min for 24h | 5,376 (5,376) | Classification by Y. Kumagai of patients by LVMI (<100; 100–130; >130 g/m$^2$) reveals elevation of circadian amplitude at LVMI in 100–130 range whereas MESOR elevation occurs only at LVMI >130. |

| | | | | |
|---|---|---|---|---|
| 221 | 221 (time of delivery) | every 1h/48h in each trimester of pregnancy (336 profiles) | 16,128 (16,128) | In addition to an 8 mmHg difference in mean value between women who will or will not develop complications (gestational hypertension, preeclampsia) already observed during the first trimester of pregnancy, the occurrence of complications is also associated with BP profiles characterized by an elevated circadian BP amplitude. In particular, one case (JK) of CHAT where warning was not heeded, was followed 8 weeks later by severe preeclampsia, premature delivery and 26 months of hospitalization of offspring at a cost of about $1 million |
| 297 | 297 after 6y | every 15min for 48h | 57,024 (57,024) | CHAT or a reduced circadian standard deviation of heart rate, or an excessive pulse pressure (>60 mm Hg) are large risk factors (larger than hypertension) for cerebral ischemic events, nephropathy and coronary artery disease, even when the blood pressure is within acceptable limits. |
| 2039 | 2039 Concomitant LVMI | Hourly averages for 24h | 48,936 (48,936) | LVMI is increased in patients with CHAT, a reduced circadian standard deviation of heart rate, or an elevated pulse pressure. The relation between LVMI and the circadian endpoints is nonlinear. |
| 23 | 12 after 7y | every 15min for 9 days | 19,872 (10,368) | 10 of 20 patients with no consistent BP abnormality are alive and well; 2 of 3 patients with consistent BP abnormality reported an adverse vascular event (P=0.015 by Fisher's Exact Test). |
| 80 | 80 Response to treatment administered 2 h before daily BP peak vs. control group treated 3 times a day | every 4h for 24h before and on treatment | 960 (960) | With smaller doses of medications, BP was lowered by R. Zaslavskaya to a larger extent and treatment was accompanied by fewer complications.<br>Treatment: propranolol, clonidine, or alpha-methyldopa (P<0.05 for each effect) |
| 18 | 18 (12 weeks) | every 30min (≥24h) on 3 regimens | ≥2592 (≥2592) | Treating CHAT may prevent adverse vascular events: As compared to placebo, nifedipine (1 mg b.i.d. at 08 & 20) increases and benidipine (4 mg/day at 08) decreases the circadian amplitude of blood pressure. The resulting increase vs. decrease in the incidence of CHAT on nifedipine vs. benidipine may account for the corresponding difference between the number of stroke events of 7.6 vs. 3.5 and the total number of cardiovascular events of 20.4 vs. 8.8 per 1,000 person-years. |
| Totals: | | | | |
| 2,807 | 2,754 | | 160,769 (>141,636) | |

work completed thus far is likely to be larger, and confounding by inter-subject variability smaller. *SBP and DBP: Systolic and Diastolic blood pressure; HR: heart rate; CHAT: Circadian Hyper-Amplitude-Tension, a condition defined by a circadian amplitude exceeding the upper 95% prediction limit of acceptability (for healthy peers matched by gender and age). CHAT is a VVD, as is, among others, an excessive pulse pressure (PP), a deficient (below-threshold) HR variability (DHRV), an odd timing of the circadian BP but not of the HR rhythm (BP ecphasia), and a reliably diagnosed high BP, MESOR-hypertension or MH. LVMI: left ventricular mass index. By comparison with some classical studies, the number of measurements in chronobiological

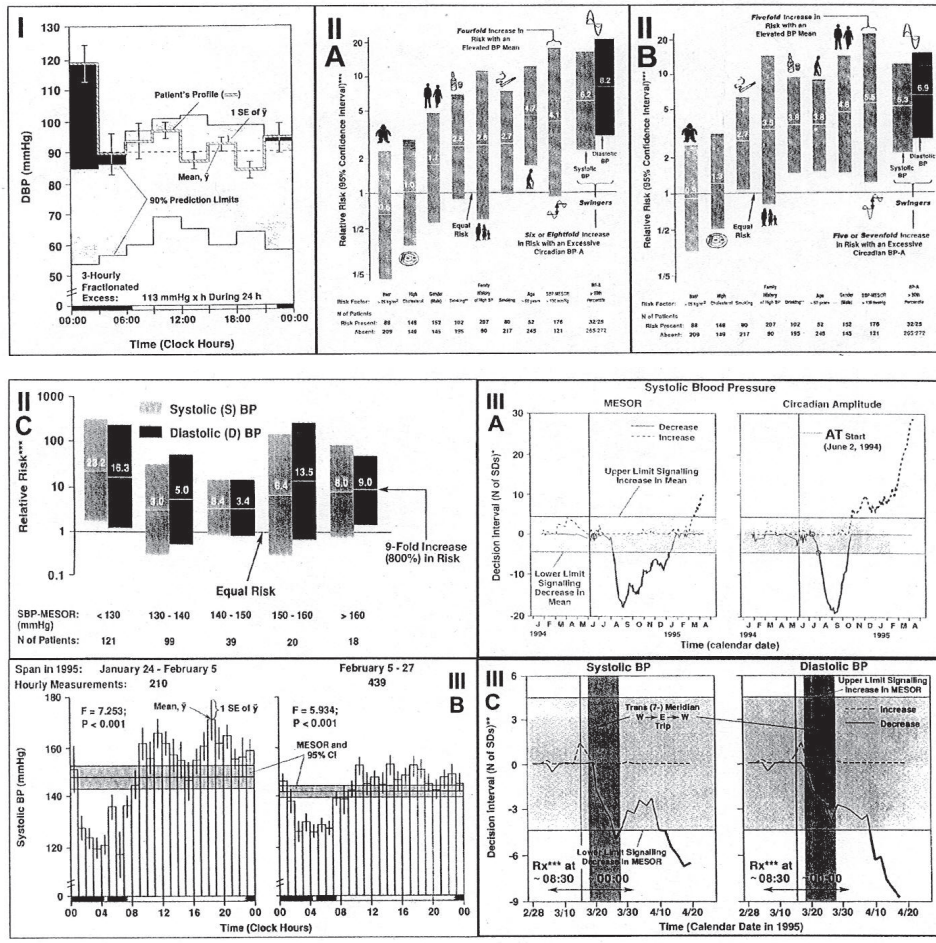


*Fig. 1*

Illustrative results supporting the need for continued surveillance, and for a chronomic analysis of blood pressure series.

I: Nocturnal hypertension: data stacked from 11 days of around-the-clock monitoring. Office spotchecks cannot detect nocturnal pathology. II A: Among risk factors, an excessive circadian blood pressure (BP) amplitude (A) raises the risk of ischemic stroke most. II B: Among risk factors, an excessive circadian blood pressure (BP) amplitude (A) raises the risk of nephropathy most. II C: An excessive circadian BP A is a risk factor for ischemic stroke independent from the 24-hour mean (MESOR). III A: Individualized assessment (by CUSUM) of a patient's initial response and subsequent failure to respond to autogenic training (AT) (EO, F, 59 y). III B: Individualized BP chronotherapy. Lower circadian double A (2A) and MESOR (M) after switching treatment time from 08:30 (left) to 04:30 (right)*. III C – Control chart assesses individualized anti-MESOR-hypertensive chronotherapy.

Chronomics detects nocturnal escape from hypotensive treatment taken in the morning (I above); a circadian overswing, CHAT; a risk of stroke and nephropathy, greater than hypertension (IIA-B),

even in MESOR-normotension (IIC) and monitors transient and/or lasting success of treatment (IIIA-C). Merits are:

• Detection of abnormality during the night when the dose of medication taken in the morning may no longer be effective in certain patients, facts not seen during office visits in the afternoon but revealed as consistent abnormality by around-the-clock monitoring;

• Detection of abnormal circadian pattern of blood pressure (CHAT, "overswinging") associated with a risk of cerebral ischemia and nephropathy larger than other risks (including "hypertension") assessed concomitantly (IIA and B);

• Finding that CHAT carries a very high risk even among MESOR-normotensives who do not need anti-hypertensive drugs (IIC);

• Availability of statistical procedures such as a self-starting cumulative sum (CUSUM) applicable to the individual patient to determine whether an intervention such as autogenic training is effective and if so for how long it remains effective (IIIA);

• N-of-1 designs for the optimization of treatment timing: the same dose of the same medication can further lower the same subject's blood pressure MESOR and circadian amplitude when the timing of daily administration is changed (IIIB and C), as ascertained by as-one-goes (sequential) testing and parameter tests, procedures applicable to the given individual. © Halberg.

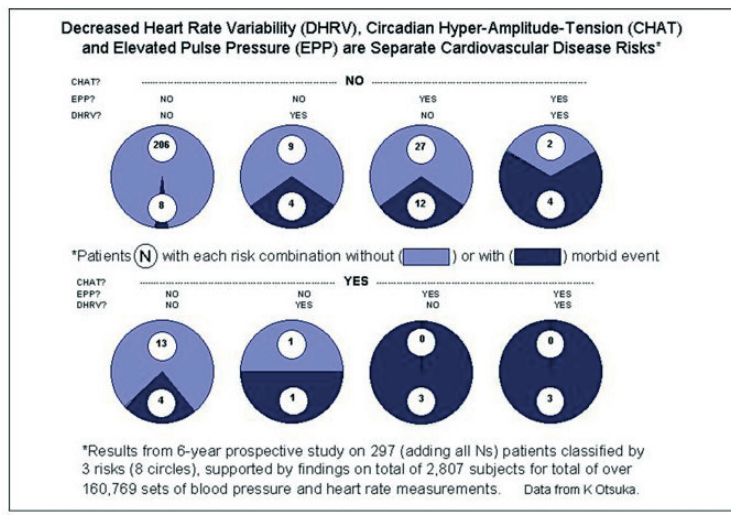


*Fig. 2*

Based on C-ABPM 7/24, a **d**ecreased **h**eart **r**ate **v**ariability (DHRV), gauged by the standard deviation of HR, in relation to a threshold, preferably eventually assessed by reference to data from clinically healthy gender- and age-matched peers, a **c**ircadian **h**yper-**a**mplitude-**t**ension (CHAT) and an **e**levated **p**ulse **p**ressure (EPP) (the difference between systolic [S] and diastolic [D] blood pressure [BP], i.e., between the heart's contraction or relaxation, or the extent of change in pressure during a cardiac cycle) are separate **v**ascular **v**ariability **d**isorders (VVDs) that may coexist to form **v**ascular **v**ariability **s**yndromes (VVSs), along with other risk conditions such as an abnormal circadian timing of BP but not of HR, not shown, and of course with or without an abnormal, e.g., elevated BP average (MESOR), i.e., MESOR-hypertension. Vascular disease risk is elevated in the presence of any one of these VVDs and is elevated further when more than a single VVD or other risk factor is present, suggesting that these abnormalities in variability of BP and HR are mostly independent and additive. Abnormalities in the variability of BP and HR, impossible to find in a conventional office visit

(the latter aiming at the fiction of a "true" blood pressure), can raise cardiovascular disease risk (gauged by the occurrence of a morbid event like a stroke in the next six years) from 4% to 100%. By comparison to subjects with acceptable BP and HR variability, the relative cardiovascular disease risk associated with a DHRV, an EPP and/or CHAT is greatly and statistically significantly increased. These VVDs and VVSs, silent to the person involved and to the care provider, notably the risk of CHAT, can usually be reversed by chronobiologic self-monitoring and thus self-help, also with a non-pharmacologic approach in the absence of MESOR-hypertension. © Halberg.

## MATERIALS AND METHODS

FH, an 89-year-old man planning to have cataract surgery on his right eye, was informed that his use of Flomax® (tamsulosin hydrochloride), an $\alpha$-1 blocker for benign prostatic hypertrophy, may cause a condition known as intraoperative floppy iris syndrome (IFIS). IFIS results in prolapse of a billowing, floppy iris, causing progressive intraoperative miosis which increases the risk of intraoperative complications. Because of these increased surgical risks, the package insert for Flomax states that "If you are contemplating cataract surgery, make certain to advise your eye surgeon that you have taken Flomax".

On the day of surgery, FH was brought into the preoperative holding area, where a retrobulbar anesthetic was administered. The anesthetic consisted of a 50% mixture of 2% lidocaine and 50% mixture of 0.75% bupivicaine. After approximately 15 minutes, FH was transported to the operating room. He was given $O_2$ by nasal cannula while his BP, HR, respiratory rate and blood oxygenation were monitored by anesthesia personnel. FH was prepped and draped in a sterile fashion, after which the surgery commenced. The iris demonstrated poor dilation, which was likely to be secondary to the use of Flomax. A Malyugin ring was placed to expand the pupil and stabilize the iris. The remainder of the cataract surgery progressed in a standard fashion. Upon completion, FH's operated eye was patched closed and he was taken to the recovery room.

FH had monitored his BP around-the-clock at half-hourly intervals for decades (with interruptions) with a TM-2421 monitor from A&D (Tokyo, Japan). He provided data for analyses by cosine fitting (top) and by stacking (bottom), summarized in a sphygmochron (*39*) in *Figs. 3 and 4.* Cosinors were prepared on a daily basis (not shown) to examine characteristics of BP and HR variability on the day of surgery and during the days and weeks preceding and following the operation. Comparisons were made by parameter tests (40; cf. 39) and sequential testing (cusums) (*41*).

## RESULTS

The sphygmochron in *Fig. 3* summarizes the chronobiologically interpreted monitoring profile for the week bracketing surgery. On top, the upper half of parametric analyses yields measures of predictable extent of change, or double amplitude, 2A, and of timing of change, or acrophase, $\phi$, as well as a midline-estimating statistic of rhythm, or MESOR, M, that are listed with reference ranges of acceptable values from clinically healthy peers matched by gender and age. The HR-M is below an age- and gender-matched peer-threshold HR-M; the timing of the circadian HR rhythm is odd, but these alterations were noted for the subject during the preceding years. *Fig. 4,* another sphygmochron, summarizes results for the subsequent week.

## SPHYGMOCHRON-TM

Monitoring Profile over Time;
Computer Comparison with Peer Group Limits

Blood Pressure (BP) and Related Cardiovascular Summary.

Name:----------  Patient #: FHal389
Age: 89  Sex: M
Monitoring From: 8/2/2008 16:30  To: 8/9/2008 11:32
Comments:

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) | 137.9 | 109.3-141.6 Range | 83.2 | 69.6-86.8 Range | *60.6* | 65.9-87.9 Range |
| PREDICTABLE CHANGE (DOUBLE AMPLITUDE) | 28.09 | 3.41-34.00 Range | 23.34 | 0.00-27.55 Range | 3.70 | 0.00-33.40 Range |
| TIMING OF OVERALL HIGH VALUES (ACROPHASE) (hr:min) | 14:38 | 8:30-18:27 Range | 14:41 | 8:54-16.58 Range | 23:47 | 9:39-18:57 Range |

| | STD (MIN; MAX)* | STD (MIN; MAX)* | STD (MIN; MAX)* |
|---|---|---|---|
| PERCENT TIME OF ELEVATION | 7.8% | 7.4% | 0.0% |
| TIMING OF EXCESS | 20:55 (hr:min) | 20:04 (hr:min) | 0:00 (hr:min) |
| EXTENT OF EXCESS DURING 24 HOURS HBI* | 22 (mmHg x hour) | 3 (mmHg x hour) | 0 (mmHg x hour) |
| 10-YEAR CUMULATIVE EXCESS | 79 (mmHg x hour)(in 1,000's units) | 11 (mmHg x hour)(in 1,000's units) | 0 (mmHg x hour)(in 1,000's units) |

Individualized bounded indices: (STD = Standard)(Min = Minimum)(Max = Maximum)(HBI = Hyperbanic Index)

INTERVENTION NEEDED
No
Yes Drug Non-Drug

MORE MONITORING NEEDED
Annually
As soon as possible
Other specify_____

Prepared By_____ Date____/____/_____

1) Unusually long standing or lying down during waking: unusual activity, such as exercise, emotional loads, or schedule changes, e.g. shiftwork; etc.; 2) Salt, calories, kind and amount, other, etc.



*Fig. 3*
Sphygmochron of the data during the week bracketing the operation. Abnormality such as that for HR was present during prior years and does not seem pertinent to cataract surgery. Other abnormality in *Fig. 10* needs a personalized reference standard provided by cusums for FH on the basis of his accumulating data. © Halberg.

## SPHYGMOCHRON-TM

Monitoring Profile over Time;
Computer Comparison with Peer Group Limits

Blood Pressure (BP) and Related Cardiovascular Summary.

Name:----------  Patient #: FHal390
Age: 89  Sex: M
Monitoring From: 8/9/2008 13:00  To: 8/16/2008 15:00
Comments:

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) | 135.1 | 109.3-141.6 Range | 82.5 | 69.6-86.8 Range | *61.1* | 65.9-87.9 Range |
| PREDICTABLE CHANGE (DOUBLE AMPLITUDE) | 27.84 | 3.41-34.00 Range | 27.95 | 0.00-27.55 Range | 2.83 | 0.00-33.40 Range |
| TIMING OF OVERALL HIGH VALUES (ACROPHASE) (hr:min) | 14:54 | 8:30-18:27 Range | 15:12 | 8:54-16.58 Range | 20:43 | 9:39-18:57 Range |

| | STD (MIN; MAX)* | STD (MIN; MAX)* | STD (MIN; MAX)* |
|---|---|---|---|
| PERCENT TIME OF ELEVATION | 9.9% | 7.4% | 0.0% |
| TIMING OF EXCESS | 21:10 (hr:min) | 20:52 (hr:min) | 0:00 (hr:min) |
| EXTENT OF EXCESS DURING 24 HOURS HBI* | 16 (mmHg x hour) | 6 (mmHg x hour) | 0 (mmHg x hour) |
| 10-YEAR CUMULATIVE EXCESS | 60 (mmHg x hour)(in 1,000's units) | 22 (mmHg x hour)(in 1,000's units) | 0 (mmHg x hour)(in 1,000's units) |

Individualized bounded indices: (STD = Standard)(Min = Minimum)(Max = Maximum)(HBI = Hyperbanic 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 loads, or schedule changes, e.g. shiftwork; etc.; 2) Salt, calories, kind and amount, other, etc.



*Fig. 4*

Sphygmochron revealing (in bold) a diastolic circadian overswing, called **c**ircadian **h**yper-**a**mplitude-**t**ension, CHAT, associated, when persistent, with a risk of severe disease greater than a high blood pressure, but reversible in FH by relaxation or drugs (found on the basis of years of prior monitoring to be transient and amenable to treatment). The appearance of CHAT in the week following surgery,

rather than in that of the intervention, prompts one to compare the lesser association with surgery of the breakout from the decision interval of the sequential test of the circadian DBP amplitude in *Fig. 10* with the appearance in *Fig. 4* of CHAT, the latter perhaps as a response to the pleasure of completing scientific papers. © Halberg.

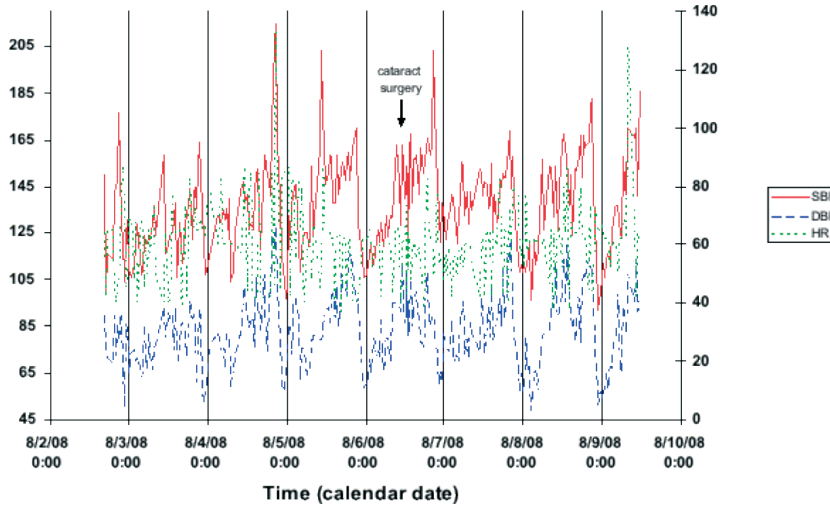


*Fig. 5a*
Data bracketing cataract surgery on August 6, 2008, scheduled for 1:30 pm. The unaided eye sees an elevation of SBP and DBP on 2 days before surgery, but also sees elevations after surgery. Sequential tests in *Fig. 10* are more objective. © Halberg.

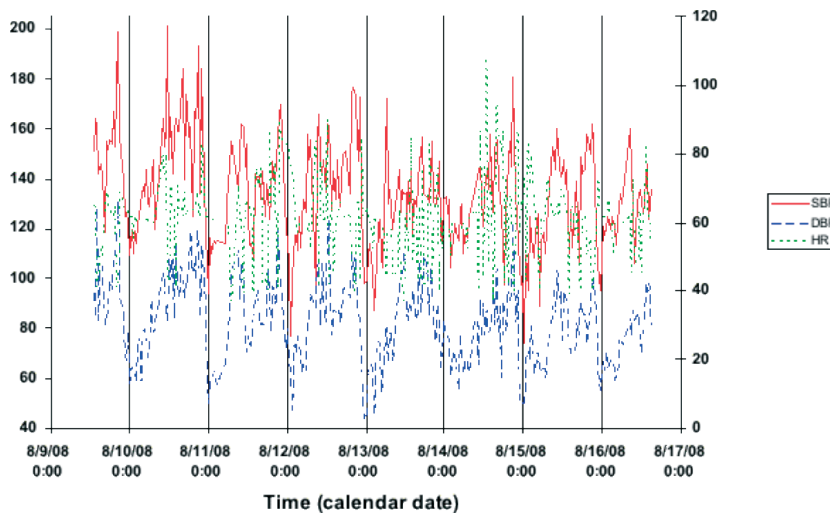


*Fig. 5b*
Data from the week following that of mid-week surgery. © Halberg.

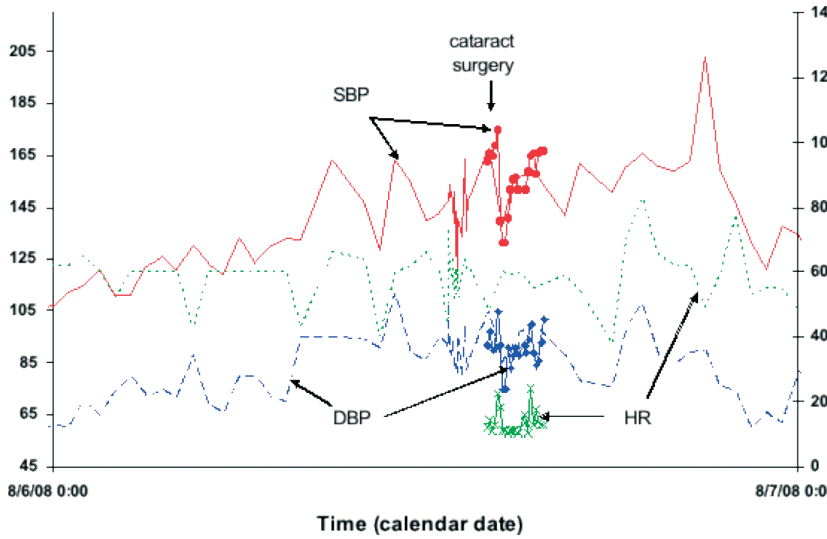


*Fig. 6*
Original C-ABPM data of FH connected by lines on the day of monitoring with data of FH from the institute where surgery was performed, added as dots. © Halberg.

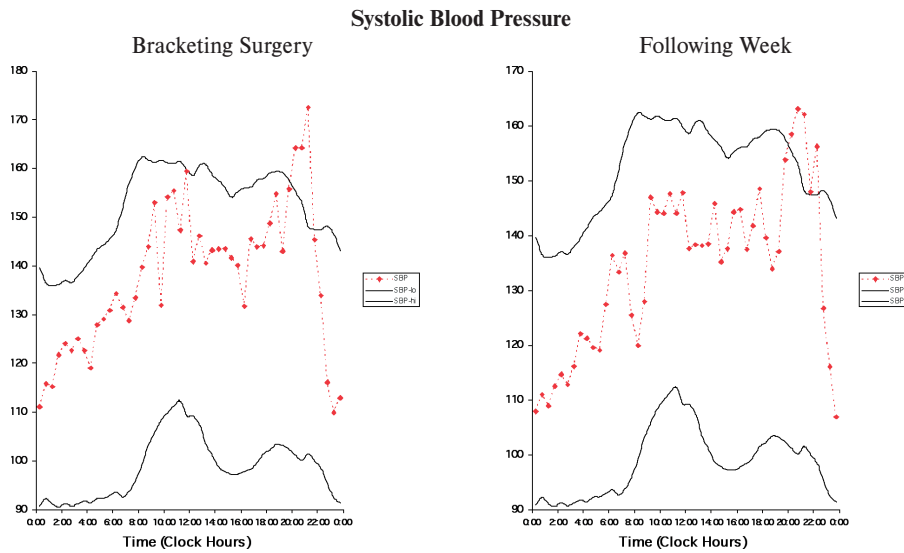


*Fig. 7*
Systolic blood pressure plexogram of FH: data during the week bracketing surgery (left) and the following week (right), stacked along an idealized day at half-hour intervals, framed by time-varying reference limits from clinically healthy peers matched by gender and age. © Halberg.

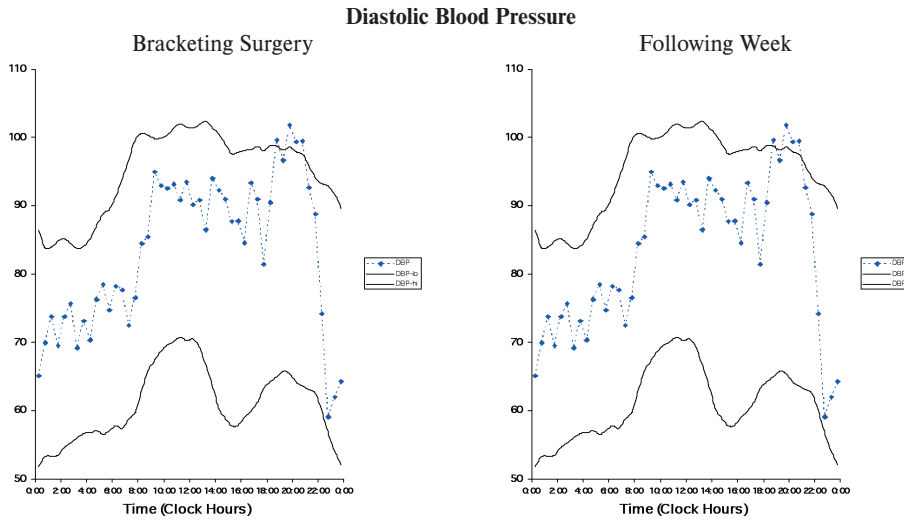


*Fig. 8*

Diastolic blood pressure plexogram of data of FH during the week bracketing surgery (left) and the following week (right), stacked along an idealized day at half-hour intervals, framed by time-varying reference limits from clinically healthy peers matched by gender and age. © Halberg.

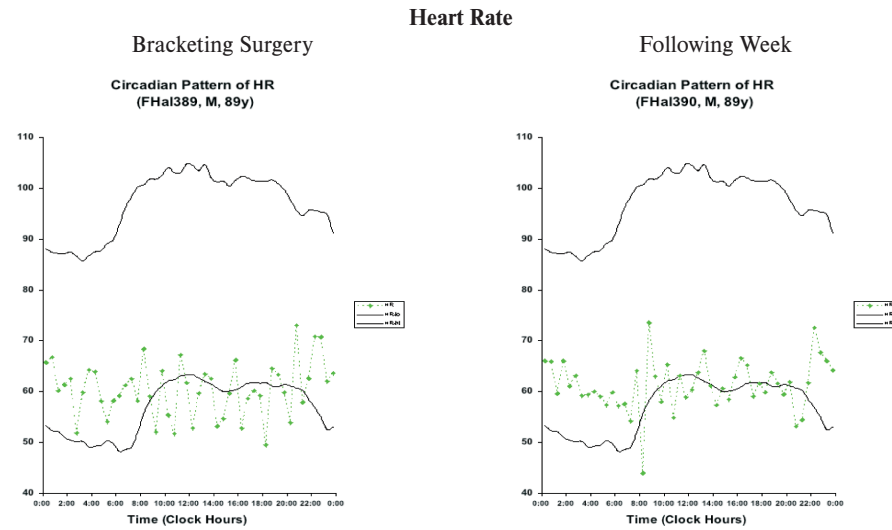


*Fig. 9*

Heart rate plexogram of data of FH during the week bracketing surgery (left) and the following week (right), stacked along an idealized day at half-hour intervals, framed by time-varying reference limits from peers matched by gender and age. © Halberg.

| Date | SBP-M | DBP-M | HR-M | PP | SBP-2A | DBP-2A | HR-2A |
|---|---|---|---|---|---|---|---|
| 19-Jul-08 | 112.1 | 67.7 | 62.1 | 44.4 | 21.40 | 5.23 | 7.64 |
| 20-Jul-08 | 119.3 | 70.1 | 60.2 | 49.2 | 20.51 | 17.21 | 10.89 |
| 21-Jul-08 | 129.7 | 73.6 | 64.2 | 56.1 | 33.12 | 8.35 | 3.97 |
| 22-Jul-08 | 115.8 | 69.4 | 65.7 | 46.4 | 13.90 | 11.56 | 27.55 |
| 23-Jul-08 | 125.7 | 72.4 | 60.9 | 53.3 | 6.27 | 11.03 | 5.66 |
| 24-Jul-08 | 122.2 | 69.5 | 61.4 | 52.7 | 27.76 | 20.07 | 6.51 |
| 2-Aug-08 | 125.8 | 77.6 | 58.5 | 48.2 | 11.05 | 12.23 | 2.15 |
| 3-Aug-08 | 131.0 | 79.3 | 63.4 | 51.7 | 11.99 | 20.93 | 9.60 |
| 4-Aug-08 | 143.6 | 84.9 | 64.1 | 58.7 | 37.29 | 24.73 | 18.20 |
| 5-Aug-08 | 137.4 | 86.3 | 56.2 | 51.1 | 36.62 | 30.04 | 5.49 |
| 6-Aug-08 | 145.6 | 82.5 | 57.5 | 63.1 | 23.79 | 15.08 | 6.46 |
| 7-Aug-08 | 135.3 | 84.1 | 61.0 | 51.2 | 32.80 | 33.27 | 9.01 |
| 8-Aug-08 | 143.5 | 87.0 | 63.9 | 56.5 | 40.83 | 33.04 | 7.82 |

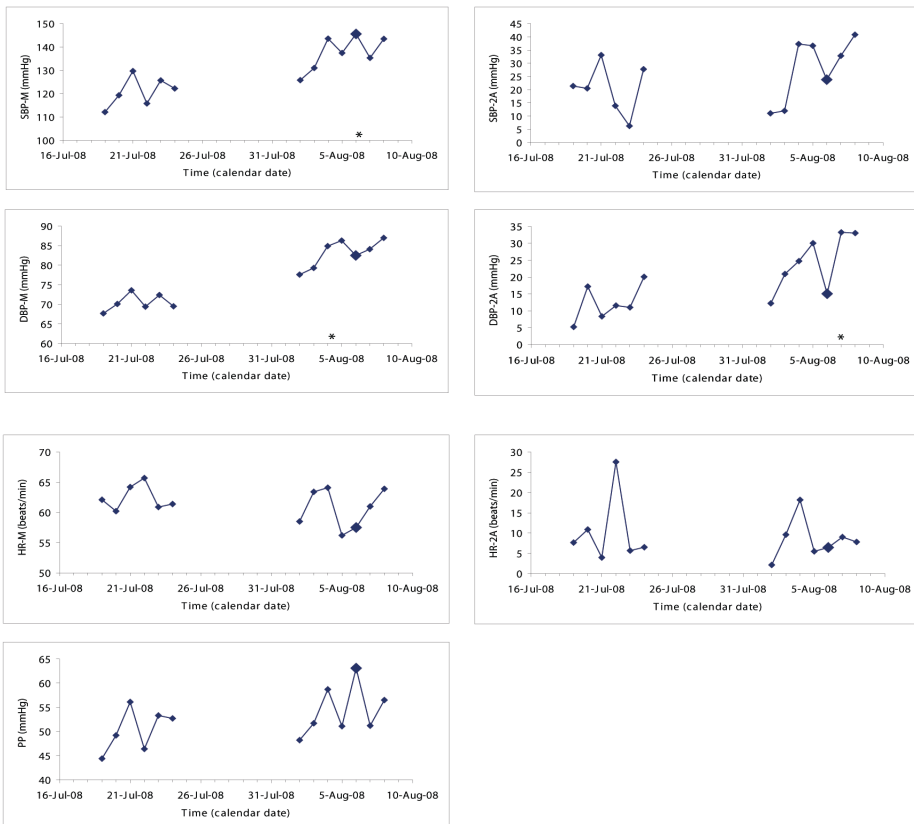


*Fig. 10*

Cumulative sums serve for sequential testing. Asterix on abscissa of rows 1 and 2 (left) and row 2 (right) indicates detection of deviation from norm. © Halberg.

The elderly man here monitored (FH) is professionally active, usually 7 days a week, including the morning before surgery, scheduled for 13:30, and the hours after surgery and the continuance of his endeavors involving reading. Thus, his eyesight is important to him, but he was unaware of any

anxiety and pursued his activities routinely. Hence the detection by cusum of an increase in the circadian DBP-A and of the SBP-M and DBP-M is noteworthy in the absence of conscious concern about the operation. These changes for a relatively brief span are almost certainly a physiologic response. But in other subjects, a CHAT of longer duration can be a useful warning even when the cardiologist's stress test is non-contributory, *Fig. 11* (*46–48*). Monitoring of BP for the week prior to surgery may be part of preoperative screening, yet the restriction of the monitoring span to a week of recording holds only until automatic, unobtrusive and affordable devices become available.

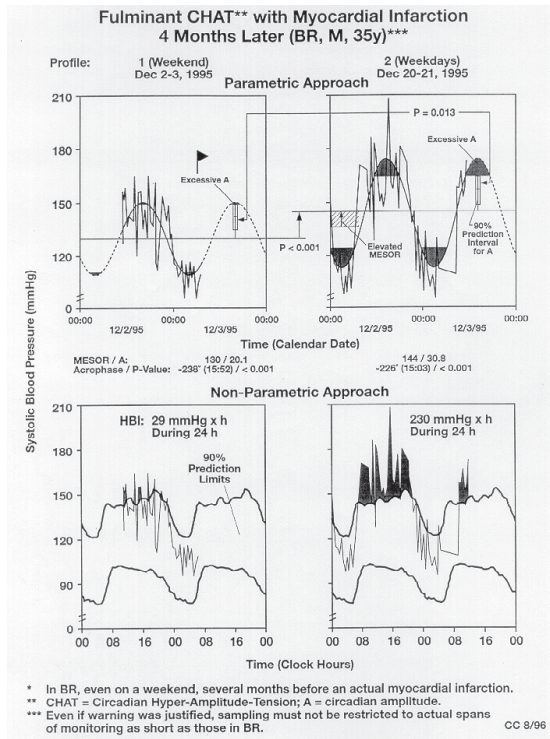


*Fig. 11*

Excessive circadian BP-A is a more sensitive warning (flag) than a conventional "stress test"*. A myocardial infarction (MI) in April 1996, after an ignored chronobiologic warning of a fulminant CHAT, was necessary to convince a 35-year-old man (BR) of the need for C-ABPM. Four months before the MI, BR reluctantly agreed to be monitored for 7 days, but stopped after 1 day (of a weekend; Profile 1: 12/02/1995); 18 days later, he returned for another 7 days, but monitored only for 2 added days (midweek; Profile 2: 12/20–21/1995) 4 months before a myocardial infarction (MI) in April 1996:

A diastolic BP overswing, CHAT, short for circadian hyper-amplitude-tension, is then diagnosed. A finding in the week of surgery of an elevation of the circadian DBP-2A, which was then still in the acceptable range, is exaggerated rather than damped in the week following successful uncomplicated surgery.

*Figs. 5a* and *5b* show the original data in the week bracketing the day of surgery and the following week, while the data of the day of surgery are seen in *Fig. 6,* with dots representing measurements during the procedure and bracketing it by minutes rather than hours. *Figs. 7–9* show stacked data with a large circadian BP swing in the week bracketing surgery (left) and in the following week (right) after successful recovery. *Fig. 10* reveals that the sequential individualized test by cumulative sums led to a breakout from the decision interval for 3 of the 7 endpoints monitored, namely SBP-M and DBP-M and DBP-A, as indicated by an asterix on the abscissa. The sphygmochron in *Fig. 4* shows that this circadian amplitude alteration was more pronounced in the week following successful surgery.

## DISCUSSION

Chronobiologically interpreted ambulatory, automatic BP and HR monitoring has been suggested as a test of the emotional and physical load impinging upon an individual (*42–45*). In FH, unknown to him, changes in BP MESORs and in his diastolic but as yet not in the systolic circadian amplitude were detected in the week bracketing surgery. There were no detectable changes in HR or pulse pressure by cusum (*41*). The finding of an effect of the load (unconscious worry about the operation, if any), within the physiologic range of clinically healthy gender- and age-matched peers, is remarkable if one's attention is restricted to the week bracketing surgery, but is minor if compared to the greater alterations associated with the task of preparing this paper and a number of more complex reports for publication in a forthcoming conference volume.

| Endpoint (units)* | SBP (mmHg) | | DBP (mmHg) | | HR (beats/min) | |
|---|---|---|---|---|---|---|
| Profiles | 1 | 2 | 1 | 2 | 1 | 2 |
| MESOR | 130.3 | **144.0**** | 81.0 | 86.5* | 70.6 | 82.4*** |
| 2A (amplitude) | **40.5** | **57.5*** | 20.0 | **45.8***** | 27.1 | 29.2 |
| ϕ (hr:min) | 15:39 | 15:06 | 16:34 | 14:52 | 15:25 | 15:33 |
| PTE (%) | 17 | 54.8 | 8.5 | 15.8 | 0 | 9.2 |
| tEx (hr:min) | 14:49 | 14:59 | 22:56 | 16:23 | - | 15:57 |
| Index (HBI or TCI) | 29 | **230** | 7 | **92** | 0 | 15 |

PTE: percent time elevation (of BP or HR above time-specified reference limit computed on upper 95% prediction limit); tEx: timing of excess; index: extent of excess measured as area under the

curve delineated by time-specified upper reference limit; for BP; HBI: hyperbaric index in mmHg x h during 24h; for HR; TCI: tachycardic index, in beats/min x h during 24h. Values in **bold** are outside chronodesmic (time-varying and time-specified) reference limits. P: *0.05; **<0.01; ***<0.001. In BR's first profile, only the SBP-2A was deviant; 18 days later, the SBP-MESOR and both the SBP-2A and DBP-2A and HBIs were deviant.

We routinely advocate a 1-week BP and HR profile at the outset, since there are cases where MESOR-hypertension was observed for up to 5 initial days of monitoring but not for a year thereafter, and since there can be large day-to-day differences in MESOR and 2A when monitoring is limited to 24 hours (in addition to any weekend vs. weekday difference, as part of multiseptan variation). With these qualifications, in BR, a **c**ircadian **h**yper-**a**mplitude-**t**ension, CHAT, with MESOR-normotension may have alternated with or preceded (as in the Okamoto rat and in human studies) the MESOR elevation of the second profile (see tabulation above), then associated with an elevated HBI of SBP and DBP. The recommended continued monitoring after the first profile and the urged immediate treatment after the second profile were not acted upon. The subject went to a care provider, who ordered a stress test which was acceptable. He started long-term monitoring 4 months later, after having had an MI.

BR and others could be isolated cases, but not 297 patients followed prospectively for 6 years, established first on a population basis in the hands of *Kuniaki Otsuka* (*47, 48*), the high relative vascular disease risk of CHAT, which can be fleeting or gradual as well as fulminant. With a proxy outcome, the left ventricular mass index, the risk of CHAT involving the heart, as well as the brain, kidney and eye, has been extended to a much larger number of patients, *Table 1.*

An increase of the human BP-2A can precede adverse vascular events at the time when as yet there is no change in other parametric or non-parametric chronobiologic or conventional indices for a deviant BP. Methods here used allow us to extend inferential statistical considerations from groups to the given patient. Preferably with more user-friendly instrumentation, yet with education in chronobiology irrespective of the kind of available tools, the monitoring of BP in time and its chronobiologic interpretation should prompt action for timely vascular disease prevention. © Halberg.

C-ABPM should constitute part of a preoperative screening routine and should further serve in research for a postoperative follow-up, so that the effects in spans bracketing the operation can be compared with those of other loads. Thus, an emotional load is detected by chronobiologically interpreted changes in the circadian amplitude of DBP and of changes in BP-MESORs coincident with cataract-related (or any other) surgery, yet their effect compares unfavorably with that of other loads. In FH, other presumably benetensive tasks (*44*), such as the (to him) pleasure of writing in preparation for a meeting abroad, involve more drastic changes than cataract surgery that exceeded the individualized limits set on the basis of his data prior to surgery but neither did the response exceed the limits of clinically healthy gender- and age-matched peers, nor did it equal changes associated with routine tasks.

## CONCLUSION

The wear and tear of everyday life can be assessed by C-ABPM and is best interpreted on the basis of long-term monitoring of BP and HR. Objective findings that are statistically significant, made, e.g., in the context of cataract surgery, may then be identified as physiological transients and as minor by comparison to changes associated with other routine tasks.

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