Commentary:
Chronomes: Time Structures Within the Physiological Range Identify Early Disease Risk Aiming at Primary Prevention

Franz Halberg and Germaine Cornelissen

Chronobiology Laboratories, University of Minnesota, Minneapolis.

In the preceding article, Prof. Pietro Cugini and his team of chronobiologists (1) describe how the circadian variation of blood pressure (BP) and heart rate (HR) has a much reduced harmonic content in the early stage of Alzheimer's disease (AD). The 12- and 8-hour components usually contributing to the circadian waveform of these variables could not be demonstrated on a population basis for the patients with AD, whereas the circadian rhythm was maintained. This finding is in keeping with another report on the circadian HR variation in AD with James M. Waterhouse, president of the International Society for Chronobiology, as one of the authors (2). Moreover, the loss of ultradian variation (components with frequencies higher than one cycle per day) in plasma 17-OHCS has been reported at a much earlier age for patients with Down syndrome as compared to patients with phenylketonuria or to healthy subjects (3). Specifically, when sampling was limited to 4-hourly values for 24 hours on small groups of 6 or 7 subjects, so that the circadian rhythm was detected by cosinor neither in clinically healthy (p = .498) nor in patients with phenylketonuria (p = .125), it was statistically significant in Down syndrome (p = .014). The timing of overall high values was, however, approximately the same for all three groups (around 08:30). Moreover, the extent of ultradian variation, gauged by the average difference between consecutive values after removal of the circadian variation, was reduced in Down syndrome by comparison with the other two groups (p < .05). Focus upon ultradian variation in AD is warranted, along with circadians and infradians (spectral components with frequencies lower than one cycle per day). Assessing infradians requires, of course, series longer than the 24-hour series which thus far are the rule, with notable exceptions (4). In particular, the study of about 3.5-day (circasemiseptan) and about 7-day (circaseptan) changes is the more important because these infradians are more prominent in elderly people than in young adulthood (5, Figure 1), just as they are also very prominent in early extrauterine life, in humans (6) and other species (7–9).

The slightly elevated BP found in AD by Cugini and colleagues (1) may relate to an early stage of the disease, as other studies have reported lower rather than higher BP values (10) as well as a decrease in systolic BP upon standing (11) in patients with AD compared with age-matched healthy controls. A lower cerebrospinal fluid concentration of endothelin-1 in AD (12), higher concentrations of beta-endorphin for which the circadian rhythm was not detected in AD (13), and abnormalities of the noradrenergic system in AD (14) have also been reported.

The reduced ultradian variation in the BP of the patients with AD is also in keeping with an autonomic dysfunction in AD, as discussed by Vitiello and colleagues (14). The finding is the more noteworthy because in clinically healthy subjects, with increasing age, the chronome [time structure; (15,16)] of BP tends to be characterized not only by an increase in the prominence of both ultradian and infradian variations but is accompanied by a decreased circadian amplitude, as well as by an increase in the overall variability gauged by the standard deviation [SD; (5)]. By comparison with adults 40–60 years of age who have an average circadian double amplitude of systolic/diastolic BP (SBP/DBP) of 24/17 mm Hg, elderly people (>75 years) have a predictable average circadian variation of only 15/12 mm Hg. By contrast, the average amplitude of the 12-hour component is increased by 20/17% (SBP/DBP) and that of the 8-hour component by 6.5/5.9%. Higher-order harmonics tend to increase in prominence to an even larger extent, notably the 6-hour (66/16.5%), the 4.8-hour (62.5/28.5%), and the 3-hour (82/63%) components. Similarly, the circaseptan component increases by 45/26% and the circasemiseptan component by 115/49% (5).

A recent survey of institutionalized and community-dwelling elderly people (17) found that treatable vascular risk factors occurred significantly more often in patients with vascular cognitive impairment (with and without dementia) than in patients with probable AD or normal cognitive function. The study of Cugini and associates (1) is the more important because it illustrates the merits of resolving at least the circadian and some ultradian aspects of the rhythmic element in the chronome of physiological variables such as BP and HR in AD. By so doing, the characteristics of anticipated components such as the circadian and ultradian variation can be compared, well within the physiological range, between AD and clinical health. The same consideration applies to the chaotic element of the chronome and its changes with age (18,19) and health status (20–22). These chronome characteristics provide new endpoints that can serve as additional clinical tools for the early diagnosis (or differential diagnosis) of disease, and sometimes even of predisease, in which case the findings can be used as the basis for the rational development of prophylactic interventions aiming at primary prevention (23).

A case in point relates to the newly discovered disease risk syndrome CHAT (circadian hyper-amplitude-tension) characterized by an excessive circadian BP amplitude (above the upper 95% prediction limit of clinically healthy peers matched by age,
MULTISEPTAN PROMINENCE OF BLOOD PRESSURE (BP) AT EXTREME OF HUMAN LIFESPAN

Systolic BP (mmHg)

Diastolic BP (mmHg)

Circaseptan (Biologic Half-Week)

One Way ANOVA
F Ratio: 11.879
P: 0.0001

N of Patients
Risk Present: 359 149 145 195 90 217 245 121 265/272
Risk Absent: 209 149 145 195 90 217 245 121 265/272

Figure 1. Changing prominence of about-weekly and half-weekly components of systolic and diastolic blood pressure with age, gauged by the double amplitude of a cosine function with a period of 7 or 3.5 days fitted by least squares to data records of at least 7 days obtained in early extrauterine life, in young adulthood, and in elderly adults. Both components are prominently expressed after birth and regain importance in old age, but decrease in extent in young adulthood. (Reprinted with permission.)

ACCOUNTING FOR RHYTHMS PROVIDES ADDITIONAL ENDPOINTS (SUCH AS THE AMPLITUDE) WHICH CAN BE USEFUL IN THEIR OWN RIGHT

The Last Entry on the Right Shows That Among Risk Factors, an Excessive Circadian Blood Pressure (BP) Amplitude (A) RAISES the Risk of ISCHEMIC STROKE MOST

Figure 2. Relative risk of adverse cerebral events for various risk factors. As compared to patients with an acceptable circadian amplitude of blood pressure, patients with an excessive circadian amplitude of diastolic blood pressure (diastolic CHAT) have a risk of cerebral ischemic events 8.2 times larger, that is, they have an increase in risk of 720%. *BMI (body mass index) correlates positively with BP-MESOR; **Drinking alcohol 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. (Reprinted with permission.)

In a 6-year prospective study of 297 patients (24), diastolic CHAT was found to be associated with a 720% increase in the risk of adverse cerebral vascular events. Such a relative risk of 8.2 (95% confidence interval: 3.1, 21.7) is higher than that associated with other known risk factors such as obesity, high cholesterol, (male) gender, age, presence of familial antecedents, alcohol consumption, smoking, and even an elevated 24-hour mean value of BP itself (MESOR-hypertension); see Figure 2. The risk of adverse vascular events associated with CHAT remains statistically significantly elevated in subgroups of patients with 24-hour mean values of BP in different SBP categories (from <130 to >160 mm Hg) and in subgroups of patients not presenting with other known risk factors (i.e., in lean people, in patients with an acceptable cholesterol concentration, in women, in people younger than 60 years of age, in patients with no familial antecedents, in nondrinkers and in nonsmokers (24)). The risk associated with CHAT was recently confirmed in a retrospective study of 424 patients who each contributed, in addition to the 24-hour BP profile, an echocardiogram for the determination of the left ventricular mass index used as a surrogate outcome measure (25).

A timely diagnosis of CHAT before the occurrence of a morbid event should prompt the institution of prophylactic intervention such as autogenic training (23) or antihypertensive drugs acting on the circadian amplitude (26) as well as on the mean value of BP. CHAT, together with the altered time structure of BP and HR reported by Cugini and coworkers (1), could be added to the list of vascular risk factors screened for in patient populations irrespective of vascular cognitive impairment. In view of the availability of ambulatory instruments for the automatic measurement of BP and HR, several international consensus meetings (27,28) have advocated monitoring for a minimum of 7 days at the outset in order to obtain a reliable assessment of the circadian variation and also an estimate of the about-weekly and half-weekly changes that may contribute additional information in their own right (5,29,30). Because CHAT can occur in otherwise MESOR-normotensive individuals, the current practice relying on single measurements once
every 2 years when the spotcheck happens to yield values below 130/85 mm Hg (SBP/DBP) (31) is often equivalent to flipping a coin (27, 28) and has been impeached (32).

The importance of infradian variation in elderly adults (5) is just one reason to suggest 7-day monitoring as a routine start. Moreover, it can be argued that from the viewpoint of assessing an about-daily as well as an about-weekly rhythm, that one day (or one week) covers only a single circadian (or circaseptan) cycle (33,34). Not only is modern technology used for surveillance in supermarkets, parking facilities, and other public places, it is also available for the telemetry of BP and HR of laboratory animals around the clock for a lifetime (35).

Anachronistically, the application of such telemetry for BP and ECG monitoring in humans is only used in special cases and for only 24 hours at a time. The investment in physiological monitoring may be rather modest by comparison to the cost incurred to treat patients after a stroke (35), for which CHAT represents the highest risk factor among those examined [(24,28); Figure 2]. As a dividend, the studies by Cugini and Waterhouse and their groups (1,2) provide differential diagnostic information that relates to AD as well and should prompt the extension of focus upon the chronomes of BP, HR, and other variables contemporarily in patients with different stages of various cognitive disorders, including AD (4,36).

REFERENCES


Commentary