Preserved Blood Pressure and Heart Rate Circadian Rhythm in Early Stage Alzheimer's Disease

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Background. This study investigated the blood pressure (BP) values over the day-night period in 11 noninstitutionalized patients affected by probable Alzheimer's disease (AD) in its early stage. The scientific aim was to detect whether the BP circadian rhythm (CR) was preserved, given the fact that CR disruption was observed in advanced or institutionalized AD patients.

Methods. The BP within-day values were gathered via noninvasive ambulatory monitoring. The BP time series were analyzed according to the chronobiological procedure, called Cosinor method with three harmonic components.

Results. The biometric analysis was able to document that BP changes over the 24-h scale in AD patients as a function of a significant CR. Such a preserved circadian regulation is, however, compromised in the second and third harmonic component, suggesting that the BP within-day variability is desynchronized by the environmental clues that act as synchronizers during the diurnal part of the day.

Conclusions. The preservation of the BP CR in the early stage of AD suggests using such a finding as a clinical tool for confirming the recent onset of the disease. As a matter of fact, it is presumed that the disease is not evolved enough to reach the suprachiasmatic nuclei, wherein is located the BP circadian pacemaker. The abolition of the ultradian components is another precocious sign that, in turn, indicates early-stage AD patients to be particularly compromised in their synchronization to diurnal cues, such as social routines, meal timing schedule, psycho-physical activity, and occupational schemes.

Alzheimer's disease (AD) is said to be associated with consistent disorders in biological rhythms because of the possible involvement of neurological structures having the role of endogenous pacemakers. Among the most important neurological structures with the quality of oscillator, the scientific research includes the suprachiasmatic nuclei (1–3).

There is evidence that AD is characterized by the loss of periodicity in the day–night oscillation of body temperature (4–7), motor–rest activity (7–9), sleep–wake alternation (6,10), and hormone secretion (11–14). Additionally, it has been found that AD is strongly disturbed in the day–night excursion of blood pressure (BP) because of the lack in nocturnal decrease (15–17), causing a condition called "non-dipping phenomenon" as well as cases defined "non-dippers."

This study was aimed at investigating the systolic (S) and diastolic (D) BP circadian rhythm (CR) in Alzheimer's patients (AP), taking into account the following two considerations: (a) the disorders in BP 24-h pattern have been described in AP in advanced stage or institutionalized; (b) the circadian oscillation of BP is not only a monocomponent sinusoidal wave with a 24-h period, because of the fact that the diurnal part of the day is longer than the nocturnal span. As a matter of fact, the BP nychthemoeral oscillation is better described by a plurimodal oscillatory wave, resulting by the approximation of at least two other additional harmonics, with a period of 12-h and 8-h, respectively, that reflect the synchronization to the diurnal routines. Therefore, the present study was performed with two aims: (a) to investigate newly diagnosed AP at the onset of their disease without disturbances in social routines and sleep pattern, who were still integrated with their family at home; and (b) to explore the nychthemoeral oscillation of systolic blood pressure (SBP) and diastolic blood pressure (DBP) by means of a multifrequency periodic regression model, for better deciphering the influence of the diurnal activity and nocturnal rest.

MATERIALS AND METHODS

Subjects and Protocol

Eleven noninstitutionalized patients (5 men and 6 women; mean ± SD age: 65.8 ± 6.5 yrs) with a diagnosis of probable AD were evaluated. The diagnosis was made according to NINCDS-ADRDA criteria (18). All patients had deficits in two or more cognitive areas, a progressive worsening of cognitive deficits, and the absence of systemic disorders or other brain disease that could account for their cognitive deficits. Furthermore, a Modified Hachinski Ischemic (19) score ≤2, and Hamilton Depression Scale (20) score ≤17 were required for enrollment. The severity of dementia was quantified using Mini-Mental State Examination [MMSE; (21)]. The mean (±SD) MMSE score of AD patients was 17.7 ± 3.6 (range 13–24), and the mean (±SD) duration of the disease was 23.3 ± 9.6 months (range: 12–26). None of the AP was affected by hypertension or was under treatment using drugs that could interfere with BP. Patients and/or responsible caregivers gave informed consent to participate in the study.

The control group in this study comprised 30 clinically healthy subjects (CHS), 15 men and 15 women (mean ± SD age: 65 ± 9 years), who gave their informed consent to participate.

Both the AP and CHS underwent a noninvasive ambulatory blood pressure monitoring (ABPM) by means of the device Space Labs (model 90202 Redmond, WA), programmed to take readings at 30-minute intervals from an inflatable cuff attached to the upper nondominant arm. The recorder determines the BP values via an oscillometric technique and stores the readings of
SBP, DBP, and heart rate (HR) into a solid memory. The stored readings were imported into an IBM-compatible microcomputer by interfacing the recorder to the calculator via the asynchronous serial port RS232.

**Data Analysis**

**Analyses**

Each individual BP monitoring was biometrically analyzed by taking into account that the experimental readings constitute a temporal series of discrete values that can be estimated in their variability by means of the conventional descriptive statistical analysis. Additionally, each individual BP monitoring was analyzed by considering that each recorded series constitutes the expression of a CR that can be validated and quantified in its rhythmometric properties by means of the chronobiological analysis.

**Conventional descriptive analysis**—Each individual BP series was estimated in its within-day variability via parametric methods in order to compute the daily (from 0000 to 2400 h), diurnal (0700 to 2300 h), and nocturnal (2300 to 0700 h) means along with their SD. The diurnal and nocturnal means were utilized for calculating their percent difference (PD), in order to detect the subjects who were to be regarded as dippers (PD ≥ 10%) or nondippers (PD < 10%) in their SBP and DBP. Ancillary estimates were the daily peak and daily trough, plus their daily range. The individual conventional estimates were averaged in order to compute their mean value in each investigated group.

**Chronobiological analysis**—Each individual BP series was estimated in its CR by means of the Single Cosinor method (22), in order to validate the statistical significance of the nychtohemeral oscillation, and to quantify the parameters that characterize the circadian periodicity in terms of mesor (M, rhythm-adjusted mean, acronym of midline estimating statistic of rhythm), amplitude (A, oscillatory extent from mesor), and acrophase (θ, timing, in hours and minutes, of the oscillatory crest related to local midnight). The Single Cosinor method computes these parameters as being a procedure of periodic regression analysis that fits a 24-h cosine function to the discrete series of BP values by minimizing the sum of residuals (least-squares method). The best fitting sinusoidal curve is the cosinorgram, whose oscillatory profile describes the BP circadian oscillation as a sinusoidal wave via the variance expressed by the regression. The BP CR is validated, as statistically significant, whether the F ratio, between the variance expressed by the cosinorgram and the variance expressed by the BP raw discrete values, results to be significant at a P level of probability less than 0.05 from the Fisher's test tables.

It must be emphasized that the Single Cosinor method was used for investigating the circadian component of the oscillation, knowing that the BP nychtohemeral oscillation is better fitted by a multiple component harmonic method with at least two periodicities, in order to obtain the optimal variance by the regression. Therefore, each individual BP time series was further estimated via a three-component periodic regression analysis fitting a cosine function with the periods of 24-h, 12-h, and 8-h, respectively. The individual rhythmometric estimates were summarized by means of the Population-Mean Cosinor (23) in order to obtain their average in each investigated group.

**RESULTS**

The BP and HR 24-h values recorded in AP and CHS are displayed in Figure 1 as time-qualified mean and standard deviation. From the interpolated profiles, it can be derived that AD patients show a much more fragmented curve as compared to their controls. This means that their BP within-day variability is in some way less symmetrically structured.

**Conventional descriptive analysis**—The estimates of the conventional descriptive analysis applied to the BP and HR 24-h values in AP and CHS are illustrated in Table 1, along with the statistical contrasts. From the tabulation, it can be inferred that AD patients are characterized by a significantly higher SBP during the day-night time. As a matter of fact, they show a significant increase in SBP daily, diurnal, and nocturnal mean levels. Importantly, it can be seen that AD patients realize a higher SBP even though the diurnal-nocturnal mean difference as well as the daily mean peak, daily mean trough, and daily mean range are not significantly increased. This means that AD patients not only can be classified as dippers, but also can be regarded as normotensives.

**Chronobiological analysis**—The estimates of the chronobiological analysis applied to the BP and HR 24-h values in AP patients and CHS are displayed in Table 2, along with the statistical analysis applied to the BP and HR 24-h values in AD patients and CHS are displayed in Table 2, along with the statistical

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**Figure 1.** Twenty-four-hour mean chronograms of systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR) in clinically healthy controls (A) and newly diagnosed Alzheimer's patients (B).
Table 1. Conventional Descriptive Analysis of Systolic and Diastolic Blood Pressure and Heart Rate Monitored in Clinically Healthy Subjects and Alzheimer Patients

<table>
<thead>
<tr>
<th>Estimates</th>
<th>Variables</th>
<th>CHS</th>
<th>AP</th>
<th>t test (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily mean level</td>
<td>SBP</td>
<td>116 ± 12</td>
<td>128 ± 9</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>DBP</td>
<td>72 ± 8</td>
<td>74 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>73 ± 8</td>
<td>70 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Diurnal mean level</td>
<td>SBP</td>
<td>119 ± 13</td>
<td>131 ± 11</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>DBP</td>
<td>74 ± 9</td>
<td>77 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>76 ± 8</td>
<td>75 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Nocturnal mean level</td>
<td>SBP</td>
<td>110 ± 12</td>
<td>122 ± 14</td>
<td>&lt;.02</td>
</tr>
<tr>
<td></td>
<td>DBP</td>
<td>66 ± 8</td>
<td>66 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>67 ± 9</td>
<td>62 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Diurnal-nocturnal mean difference</td>
<td>SBP</td>
<td>9 ± 10</td>
<td>9 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>DBP</td>
<td>8 ± 7</td>
<td>10 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>8 ± 8</td>
<td>12 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Daily mean peak</td>
<td>SBP</td>
<td>152 ± 20</td>
<td>159 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>DBP</td>
<td>94 ± 9</td>
<td>102 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>105 ± 14</td>
<td>97 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>Daily mean trough</td>
<td>SBP</td>
<td>91 ± 12</td>
<td>95 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>DBP</td>
<td>52 ± 9</td>
<td>48 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>54 ± 9</td>
<td>50 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>Daily mean range</td>
<td>SBP</td>
<td>60 ± 21</td>
<td>63 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>DBP</td>
<td>42 ± 10</td>
<td>54 ± 19</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>51 ± 17</td>
<td>47 ± 23</td>
<td>NS</td>
</tr>
</tbody>
</table>

Notes: Values rounded to the nearest unit; ± standard deviation; NS = not significant. SBP = systolic blood pressure (mm Hg); DBP = diastolic blood pressure (mm Hg); HR = heart rate (bpm); CHS = clinically healthy subjects; AP = Alzheimer’s patients.

contrasts. From the tabulation, it can be inferred that AD patients are characterized by a significantly higher SBP oscillatory level. As a matter of fact, they show a significant increase in SBP mesor, as compared to the controls. Importantly, it can be seen that AD patients show a significant probability for the SBP, DBP, and HR CR, as shown by the p values of the first harmonic component. Biometrically, the BP and HR CR in AD patients shows both the oscillatory amplitude and phase timing to be comparable to those computed in CHS. By contrast, it can be realized that AD patients show a nonsignificant probability for the second and third harmonic component, suggesting that their BP and HR 24-h patterns have lost the multifrequency regulation that is detectable in CHS, being regulated only on the 24-h oscillation.

DISCUSSION

There is a plethora of research indicating that senile dementia of Alzheimer’s type is characterized by consistent disorders in those mental and somatic functions that fluctuate with a circadian periodicity. These disorders concern sleeping pattern, body core temperature, motor activity, some hormones, mainly cortisol, beta-endorphin, and melatonin (10–13). The reasons for this circadian susceptibility reside in the fact that AD affects the central nervous system, not only in the cognitive part, but also in the neuro-endocrine-vegetative sections, such as the hypothalamus and the suprachiasmatic nuclei (8,24–28), which notoriously regulate the circadian rhythmicity of many fundamental systems of human body (1–3). As far as the BP and HR circadian rhythm is concerned, the evidence existing in literature is in keeping with a possible loss of their circadian periodicity in most AD patients (15–17).

Interestingly, the results of the present study corroborate the view that the BP and HR CR is not abolished in AD patients because the diurnal increase and the nocturnal fall are not compromised. Therefore, the results of the present investigation can be considered conflicting with the reports found in the literature.

How to interpret such a discordance? It must be reemphasized that there is convincing evidence that the suprachiasmatic nuclei are the place of an endogenous pacemaker (internal clock) that drives the BP CR in mammalians (26-28). Therefore, one can surmise that the preservation of the BP and HR CR may be a sign that AD has not evolved enough to anatomically affect the suprachiasmatic pacemaker. In line with this thought, one can presume that the persistence of the BP and HR CR might be used as a clinical tool for staging AD in its early stage.

It is important to note that in any clinical condition in which there is a disturbance in sleep–wake cycle, there may be a "vicious circle" in that sleeping disorders can determine per se an "internal dyschronism," causing some circadian rhythms to disappear. There is convincing evidence that sleeping is severely compromised in Alzheimer’s patients, either severe or institutionalized (6–10). Therefore, one can argue that the described abolition of the BP and HR CR in AD might depend not only on the lesions of the BP neural pacemaker but also on the intercurring disturbances in sleeping pattern.

With respect to this, it must be stressed that the Alzheimer’s patients investigated in this study were all free of salient disorders in sleep–wake cycle. Accordingly, one can conclude that the persistence of the BP and HR CR may be taken as an indirect sign of the relative integrity of the sleep–wake cycle in AP at the onset of their disease.

Interestingly, the results of the present investigation document that Alzheimer’s patients exhibit a consistent increase in SBP during the entire day–night span. Such an elevation, however, is not due to abnormal values that exceed the WHO reference limits. As the finding is not a feature of arterial hypertension, one can argue that the SBP CR might be regulated at a higher level as a sign of an initial disturbance of the suprachiasmatic pacemaker, whose set-point is tonically overmodulated.

The results of this study reveal another interesting finding in AP, i.e., the lack of the two ultradian components that are ordinarily detectable in the BP 24-h pattern analyzed via a three-component harmonic model. The 12-h and 8-h ultradian components of a circadian oscillation reflect the synchronization to the diurnal repetitive cues, such as the social routines, psychophysical activity, and occupational schemes. As a matter of fact, less synchronized elderly adults, as compared to mature adults younger than 60 years, show an increase in the amplitude of 12-h and 8-h components of BP (29). Therefore, the disappearance of these two components in AP reinforces the idea that the BP CR is demultiplied in frequency because of a pathological disorder that is already effective at the early stage of AD. This disorder could reflect disability to internalization of synchronization cues, as it also appears from the greater dispersion, in terms of SD, of the acrophase timing for the first harmonic component in AP as compared to healthy controls.

It must be stressed that the time structure of bioperiodic functions (chronome) consists of multifrequency rhythms, trends,
and features of chaos (30). The alteration of the BP periodic structure in AD, thus, indicates an impairment of the chronome in the domain of the ultradian recursive regulations. It would be very important to know whether or not the infradian bioperiodicity as well is precociously altered in early stage AD. Unfortunately, the protocol of this study is not configured to give an experimental answer to this question.

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