Chronobiology International
Vol. 12, No. 1, pp. 37–45

Heart Rate Variation, Age, and Behavior in Subjects with Senile Dementia of Alzheimer Type

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Summary: Minute-by-minute heart rate (HR) recordings over a period of 24 h were obtained once for 30 elderly subjects diagnosed as having senile dementia of Alzheimer type (SDAT). Twenty-one of the subjects were studied in a hospital ward setting, and nine were studied in their own homes. Twelve were men and 18 were women. Eleven took some form of sedative medication; 10 took no medication. Thirty-minute mean values were unmasked to take account of the effects of activity and sleep on HR. Results indicate that the masked HR circadian rhythm of SDAT may be more often unimodal than that of normal subjects of similar age, and that phase shift of the endogenous, clock-mediated component of the rhythm (with higher HR at night) is to be expected in a proportion of individuals with SDAT. **Key Words:** Senile dementia of Alzheimer type—Alzheimer disease—Ambulatory heart rate—Circadian rhythm—Purified data.

Normal elderly women living in institutions for the aged in comparison with normal elderly women living in their own homes have a more sedentary life-style, lower waking heart rates (HRs), and flatter circadian rhythms (1,2). Cosinor analysis indicated that for the majority of these subjects a curve made up of a combination of two periodic components, with maxima around midday and 20:00 h, afforded a reasonable representation of the HR circadian variation. The bimodal curve for HR was to some extent a reflection of a bimodal activity pattern, with an initial activity span in the morning, a rest in the afternoon, a second active span in the evening, and a sleep at night. This raises the question of whether the measured HR variation is purely an exogenous or "masking" effect (i.e., the outcome of level of activity) or whether an endogenous component also exists that arises from the body clock. If the exogenous effect is dominant, then people with SDAT who very often are confused about the time of day and have no clear pattern of activity would be expected to show a less clear-cut bimodal rhythm of measured (masked) HR.

Submitted January 26, 1994; returned for revisions March 14, 1994; accepted for publication July 18, 1994.
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SUBJECTS AND METHODS

The study population (Table 1) was composed of 30 elderly people with SDAT (12 men and 18 women); 21 were institutionalized and studied in a hospital ward setting. The remaining nine subjects lived in the community and were studied in their own homes. All were ambulatory. Eleven of the institutionalized and two community subjects took some form of sedative medication before bedtime. None of the subjects had a history of cardiovascular disease.

Each participant wore a Sports Tester PE 3000 (Polar Electro OY, Kempele, Finland) HR monitor for 24 h. The Sports Tester included an electrode belt incorporating a digital signal transmitter and a receiver worn on the wrist that processed and recorded signals into 1-min HRs.

TABLE 1. *Heart rates in people with SDAT*

Subject	Sex	Age (yr)	HR24	HRD	HRN	HRD/HRN
Unsedated/institutionalized						
1	M	86	68.90	72.90	65.50	1.11
2	F	89	84.80	88.80	76.20	1.17
3	F	68	79.20	78.20	65.30	1.20
4	F	92	70.10	77.90	61.10	1.27
5	M	86	74.90	75.40	73.60	1.02
6	F	87	72.00	75.20	60.70	1.24
7	F	63	95.40	103.40	76.70	1.35
8	F	78	66.10	64.40	53.40	1.21
9	F	85	96.80	99.50	103.40	0.96
10	M	86	76.00	79.30	63.20	1.25
Mean		82	78.42	81.50	69.91	1.17
Sedated/institutionalized						
11	F	81	67.60	71.40	61.60	1.16
12	F	88	69.20	72.40	62.40	1.16
13	F	73	80.50	82.10	68.90	1.19
14	M	66	70.50	69.50	72.30	0.96
15	F	83	90.40	92.60	83.60	1.11
16	F	67	72.70	82.70	67.40	1.23
17	F	86	78.50	80.60	72.90	1.11
18	M	76	79.40	87.60	65.80	1.33
19	F	84	81.50	76.60	90.10	0.85
20	M	83	79.10	85.30	71.20	1.20
21	M	81	74.60	75.30	64.30	1.17
Mean			76.73	79.65	70.95	1.12
Community						
22	F	82	77.70	81.10	73.90	1.10
23	F	82	83.60	83.60	NA	NA
24	M	73	77.10	84.10	65.20	1.29
25	M	70	54.60	57.50	50.20	1.15
26	M	76	86.50	97.50	69.70	1.40
27	M	79	78.00	78.00	73.60	1.06
28	M	79	70.80	75.00	66.30	1.13
29	F	74	91.70	91.70	NA	NA
30	F	78	68.50	74.10	60.80	1.22
Mean		77	76.50	80.29	65.67	1.22

NA, not applicable.

A record was kept of each subject's activities. These were entered on a checklist at 15-min intervals by the experimenter or caregiver. In addition, the type and timing of medications were recorded for sedated patients.

Purification of masked HR data (3), to take into account the effects of sleep and activity and to assess more clearly the endogenous component of the circadian rhythm, was accomplished using a method already described for temperature and HR data (4,5). Briefly, the method assumes that the endogenous component of the HR rhythm, if not masked by sleep or activities, would be sinusoidal in shape and therefore amenable to cosinor analysis. The process of purification consists of estimating the mean sizes of the masking effects associated with sleep and the different types of activity. To achieve this, the mean measured HR for each half hour span was adjusted according to the main category of activity, taken from the activity record. These categories were "asleep," "awake, but lying down," "sitting," "light activity" (a mixture of sedentary and ambulatory behavior), "strenuous activity" (walking), and "eating a meal." Purification consisted of the following steps:

1. Increasing all HRs associated with "asleep" by 0–20 beats/min in increments of two (because sleep depresses the HR)
2. Leaving HRs associated with "awake, but lying down" unchanged [because this posture was taken as a baseline activity, defined as the zero masking effect (3)];
3. Lowering the HRs associated with each of the other categories by 0–20 beats/min in decrements of two (because activity increases the HR)

Each of the four categories of activity was treated independently. All combinations of masking factors ($11 \times 11 \times 11 \times 11 \times 11$) were used to produce 161,061 purified data sets, which were tested to find the "best" one. This was the combination that gave a "purified" or adjusted data set of 48 points that deviated least from the cosine curve fitted to this 24-h data set [by the conventional method (6)]. Deviation was assessed as the summed squared differences between the fitted cosine curve and the purified data set. The result enabled the cosinor parameters of the endogenous component to be calculated for that day (acrophase, mesor, and amplitude). Cosinor analysis is a regression analysis of the form:

$$HR = a + b \cos (x - \phi)$$

where a is the mesor, x is an angle ranging from 0–2 π in the 24 h starting at midnight, and ϕ, the acrophage, corresponds to the maximum HR. Here, ϕ is expressed in hours after midnight.

This analysis also gave the "masking profile"—the average changes in HR due to sleep and each of the four activities. Figure 1 illustrates the method for 1 day's data.

RESULTS

Table 1 shows the results using masked data for each subject in the SDAT sample, grouped into (a) unsedated/institutionalized, (b) sedated/institutionalized, and (c) community.

From Table 1 it can be seen that three subjects (9, 14, and 19) showed an inverted day–night HR ratio (i.e. HRD/HRN < 1.0), where HRD is defined as the mean daytime HR (between getting up and going to bed) and HRN is defined as the mean nighttime

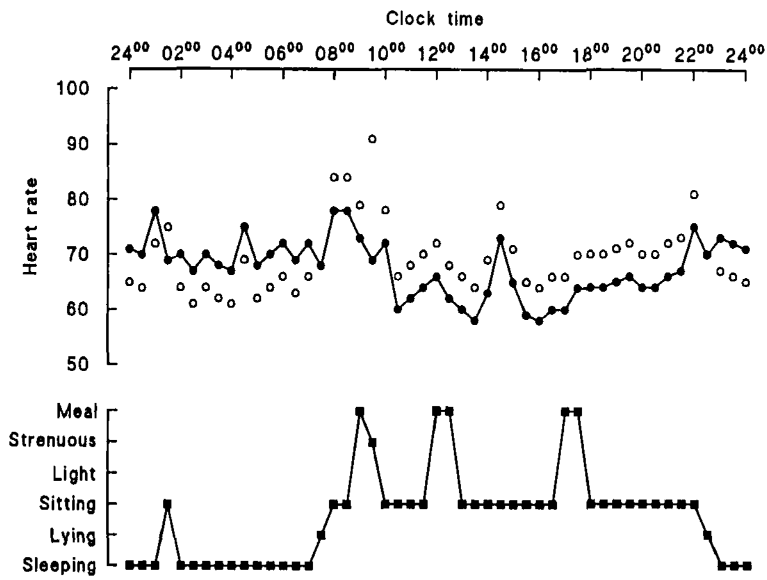

FIG. 1. Subject number 1: 30-min mean HR showing raw and purified data and activity profile. Closed circles, purified data; open circles, raw data; squares, activity profile.

HR (between going to bed and getting up). In many other cases the day–night difference was slight, supporting the view that the rhythm is flat and phase shifted on occasion.

Comparison Between SDAT Subgroups

There was very little difference in the types of activity shown by the three SDAT groups; in all cases it was less than healthy persons of the same age (2). The life-style of the people with SDAT could largely be described as sedentary, predominantly sitting awake interspersed with toileting, dressing, sleeping, or walking. There was little goal-orientated behavior, such as housework or meal preparation, other than dressing or eating.

However, considerable variation in sleep patterns was indicated. All unsedated subjects exhibited unbroken nocturnal sleep, whereas sleep of nine of the 11 sedated subjects was frequently interrupted by toileting, walking around the ward, or experiencing bouts of anxiety that influenced the shape and phase of the masked HR rhythm. Both unsedated and sedated subjects slept an average of 8 h per night, but on average sedated subjects went to bed at 22:30 h, 1 h later than unsedated subjects. On average, community subjects slept slightly longer (8.5 h) and went to bed at approximately the same time as sedated subjects.

Individual Variation in Night-Time HR

Subjective reports by nursing staff indicated that certain individuals responded to sedative drugs by becoming more agitated before and during sleep. Thus, high night-time HR might be accounted for by medication effects in some cases. However, the same phenomenon occurred in one unsedated patient.

Analysis of 24-Hour HR Rhythm

Figure 2 shows the mean 24-h HR curves (raw data) for each SDAT subgroup plotted at 30-min intervals. There are no significant differences in amplitude between the three groups. Community subjects show a lower night- time HR compared with the two institutionalized groups, and their predominantly continuous sleep pattern would have contributed to this. The interrupted sleep pattern of sedated subjects could account for their higher night-time HRs, but the higher night-time HRs of unsedated subjects is not explained.

Although the major peak in HR was in the afternoon for both institutional groups, it was in the morning for community subjects. Morning activities reported for community subjects were varied and included help with housework, travel by ambulance to a day center, and in one case golfing. In contrast, the predominant morning activity for institutionalized subjects was sitting.

During the afternoon and evening, the community group showed a steady decrease in HR, whereas the institutionalized groups both showed an evening increase. These patterns coincide with the activity records, which show that community subjects sat or even slept in the afternoon and evening. By contrast, the increase between 18.00 and 20.00 h in the institutionalized groups coincides with mealtimes, and these produce marked masking effects. This suggests that the evening meal in the institution is a "social

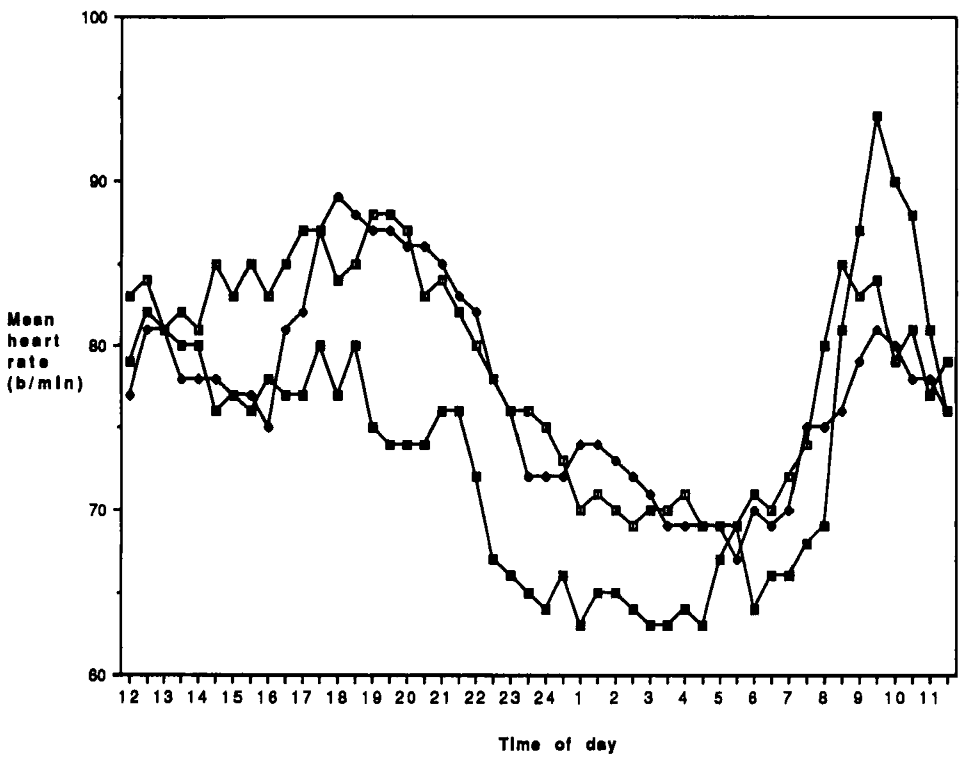

FIG. 2. 24-h HR for SDAT subgroups. Open squares, unsedated; diamonds, sedated; closed squares, community.

high point," with increases of alertness and social activity at that time. This was confirmed by general observations at that time.

The curve for sedated subjects shows a consistently lower evening trajectory compared with the unsedated subjects; the fact that sedated subjects exhibited more episodes of sitting asleep than did unsedated subjects, who were predominantly sitting awake, may explain this pattern.

A minimum night-time HR was reached by unsedated and sedated subjects at approximately the same time (06:00 h) despite sedated subjects going to bed on average 1 h later than unsedated subjects. For community subjects a shift to an earlier night-time minimum at 04:00 h is also difficult to explain because on average community subjects retired 1 h later than did unsedated subjects, at approximately the same time as sedated subjects. One might conclude therefore that the timing of the night-time HR minimum is not solely dependent on the time of going to bed.

In summary, the masked HR rhythms can be explained to a large extent from a knowledge of the activities of the various subgroups. The question remains whether differences are due to the endogenous, clock-driven component.

Cosinor Analysis

This question can be addressed by a cosinor analysis, fitting a single sine curve with period 24 h to both raw and purified data.

The results are shown in Table 2. The analysis of the raw data (columns 2–6) shows no statistically significant differences among the groups, and no obvious effect of age (66–88 years) or sex. The amplitude of the fitted curves was similar to that of elderly women living in institutions (2). The phase, in most cases, corresponded to an afternoon peak, as might be expected if the minimum occurred during the mid-sleep period ~12 h later.

Three patients showed no significant circadian rhythm, and a further three showed a significant effect with the peak between 02:00 and 04:00 h. A reversal of this type has previously been reported in one subject of 29 (2), but is certainly unusual even among elderly and healthy patients.

Purification of the Data

Purified data are shown in columns 7–11 of Table 2. The aim of purification is to separate the exogenous elements of the HR circadian rhythm associated with specific activities from the endogenous, clock-driven 24-h cycle. Because in most normal subjects activities vary during the 24-h period, purification tends to reduce the HR amplitude. Indeed, in patients with normal, significant, circadian rhythms, the effect generally amounted to a small reduction in amplitude with little effect on the phase, as expected. For one of the patients with reversed rhythm, the amplitude was markedly increased, and two of those with nonsignificant rhythms when raw data were analyzed showed significant but reversed rhythms after purification. An example of one of these patients is shown in Fig. 1. Note that the decrease produced by sleep in this patient, together with the marked increase at 08:00–10:00 h, led to the masked rhythm not being significant by cosine approximation (Table 2). After purification, a significant but inverted rhythm, with an amplitude of 5 beats/min, was present.

TABLE 2. *Cosine parameters: raw and purified data and masks*

Subject	Raw data					Purified data										
	Cosine parameters					Cosine parameters					Masks					
	φ	mes	Amp	ssd	%R	φ	mes	Amp	ssd	%R	1	2	3	4	5	6
Unsedated																
1	12.6	69.5	2.2	1,846	6	3.9	67.6	4.9	1,209	32	6	0	6	x	14	6
2	16.6	85.2	10.5	2,426	52	18.6	81.5	7.6	1.300	52	4	0	8	4	0	14
3	20.1	79.5	11.9	5,486	38	21.5	64.7	8.3	4,589	27	x	0	10	28	16	20
4	14	70.3	10.3	1,712	60	14	70.2	10.3	1,698	60	0	0	0	2	0	0
5	20.9	74.6	1.8	1,256	6	2.6	73	2.9	1,068	16	2	0	2	0	8	6
6	17.2	72.5	13.4	886	83	17.3	72.3	13.4	856	83	0	0	0	0	x	0
7	14.9	95.4	22.3	4,115	74	15.4	88.4	17.5	3,775	66	0	0	10	8	12	8
8	13.7	66.5	12.5	3,724	50	14	62.1	9.7	3,185	41	0	0	4	10	10	8
9	3.1	97.2	10.4	1,157	69	3	95.4	10.3	810	76	0	0	6	x	x	2
10	16	75.9	16.3	892	88	16.1	75.2	15.9	740	89	0	0	0	6	6	0
Sedated																
11	17.2	67.7	7.6	1,902	42	18.8	65.2	5.6	1,482	34	2	0	6	8	8	4
12	14.3	69.4	6.7	1,796	38	14.7	64.4	2.9	1,374	13	0	0	4	x	8	14
13	17.6	80.6	9.3	2,096	43	19.9	78.4	6.2	1,297	42	8	0	8	6	6	4
14	2.4	70.6	3.8	1,912	15	2.3	66.3	7.3	1,692	43	0	0	6	x	8	10
15	16.5	90.6	7.3	1,604	44	17.9	87.2	5.8	1,465	36	0	0	6	2	4	4
16	16.9	76.9	13.4	1,485	74	17.2	75.1	12.9	1,329	75	0	0	2	0	6	6
17	16.4	78.5	5.5	1,020	42	18.3	74.5	3.8	791	31	0	0	6	0	8	—
18	16.8	79.5	13.7	2,847	61	18.3	80.8	6.9	2,244	33	10	0	4	4	2	6
19	3.2	81.5	11.1	2,189	57	3.2	81.5	11.1	2,189	57	0	0	0	x	x	0
20	17.6	80.1	11.1	5,026	37	17.1	77.1	4.7	2,906	16	4	0	0	0	16	4
21	17.5	74.6	13.8	1,221	79	17.6	73.3	13.4	1,086	80	0	0	2	0	0	8
Communit																
23	14.3	76.8	2.6	2,055	7	1.1	73	1.8	1,629	4	2	0	4	4	8	12
24	10.6	54.7	10.7	3,316	45	7.4	49.6	7	1,881	38	4	0	6	0	20	6
25	14.9	86.5	18.3	2,318	77	15	85.5	17.5	2,244	77	0	0	2	4	2	0
28	16.6	77.8	4.3	1,237	26	17	76.6	3.4	1,214	19	0	0	2	0	x	2
29	13.2	71.8	9.6	3,716	37	11.1	74.7	6.9	3,116	27	10	0	0	0	12	0

φ, acrophase; mes, mesor; Amp, amplitude; ssd, summed, squared deviations; %R, percentage of the total variance accounted for by the cosine curve.

Thus, the purified data showed five of 26 patients with significant reversed rhythms peaking between 02:00 and 04:00 h, together with one showing no significant rhythm at all and one peaking at ~07:00 h. Although the number of patients examined is small, it seems clear that a proportion of them show 24-h purified HR rhythms that are abnormal compared with elderly non-SDAT institutionalized subjects. This cannot be attributed to the effects of sleep and activities.

The pattern of masks corresponding to different activities was as expected. The effect of sleep on HR differed only slightly from HR when lying awake, and this might reflect the altered sleep patterns found in some patients. Sitting, semiactive behavior and active behavior was associated with increasing effects on HR. Meals, certainly for patients in institutions, were associated with a large increase in HR [+5.77 ± 0.99 (n = 26) beats/min], comparable with that of the highest level of activity [+7.91 ± (n = 22) beats/min].

DISCUSSION

HR is a poor marker of the body clock. However, it has a number of unique advantages. In the case of ambulatory studies of Alzheimer patients, it is probably the best marker available for purposes of measurement and analysis. It gives valuable information about the effects of life-style, and purification does enable clues about the body clock.

Chronobiological studies have rarely been undertaken on Alzheimer disease or SDAT. One such study examined 26 patients' sleep–wake rhythms by wrist actigram and oral temperature for 4–7 consecutive days (7). Interestingly, some subjects exhibited reversed day–night rhythms and decreased amplitude of the sleep–waking rhythm as found in the present study. The investigators concluded that severe dementia might be closely related to disrupted sleep–wake and autonomic system rhythms. However, the cause of such disruption—exogenous or endogenous—was not ascertained.

The present work was undertaken to determine if the HR circadian rhythm of SDAT patients differed from that found in an earlier study of normal elderly people. In particular, the confusion about clock time common among SDAT patients provided a focus of interest: would such cognitive confusion be reflected in the circadian rhythm of HR?

Comparison with the normal subjects studied earlier has shown that to some extent the answer was positive. In five of 26 cases the purified data showed a reversal of the normal HR circadian rhythm, i.e., with a peak during the night. Other anomalies were also found.

As previously shown (2), the addition of a 12-h harmonic to the 24-h component made a significant contribution to rhythm analysis in many cases because it accounted for the secondary peak in the data at ~20:00 h. The same procedure was followed in the present study on the raw data. A measure of the contribution of the 12-h component was obtained by calculating the difference between the variance explained by fitting the 24-h component (V1) versus that explained by fitting the 12-h component (V2). Where the difference was large, this was due to the large contribution of the 12-h component, i.e., there was a marked secondary peak that this component explained. Where the difference was small, this indicated a relatively small contribution, i.e., the secondary peak was small or nonexistent. We have called the statistic V1–V2 the shape index (SI). The SI group mean for 29 non-SDAT subjects being 1,278.4 (2) was significantly higher than that for 30 people with SDAT, i.e., 725.5 ($t = -2.44$, $p = 0.018$). This indicates a stronger contribution by the 12-h component in non-SDAT individuals, i.e., a more strongly bimodal curve. A comparison of the mean 24-h profiles for the SDAT sample (Fig. 2) and non-SDAT subjects (2) suggests that more pronounced evening fluctuations for non-SDAT subjects may account for the stronger second component. This perhaps explains why the peak times of the 24-h cosine curves fitted to the raw data (Table 2) occurred earlier than did those of non- SDAT individuals (2). Summarizing the findings, non-SDAT subjects had sustained high values well into the evening, people with SDAT living at home lost this peak completely, and people with SDAT in institutions had a reduced evening peak.

We conclude that the presence of a reversed endogenous HR rhythm in five of 26 cases, together with the generally flatter more unimodal curves of the SDAT patients compared with non-SDAT subjects of like age, gives a positive answer to our initial question. In other words, the confused state of mind of most patients with SDAT (which was not tested directly in this study but was apparent from subjective interaction) is accompanied by irregularities in the HR circadian rhythm. The fact that the irregularities in the HR circadian rhythm became more rather than less evident as a result of purifying the data (i.e., removing the influence of type of activity on HR) would appear to indicate that there has been an endogenous alteration in the circadian activity of the heart. The altered rhythm might even be an aspect of the patient's confusion and irregularity. Further studies are needed to confirm this theory with more subjects, greater standardization of conditions than possible in the present study, and better control of medication effects. This result also raises the question of whether some improvement in the subjects might be achieved by attempting to impose a more marked dichotomy between daytime activities and nighttime sleep (8).

Acknowledgment: We thank Dr. K. Brockbank for making the patients with SDAT available to us and the Oxfordshire Regional Health Authority Ethics Committee for permission to undertake this study. We also thank the Oxfordshire Regional Health Authority for funding and the staff and patients at the Littlemore Hospital and the Rivendell Clinic, Radcliffe Infirmary, Oxford, for their help in making this study possible.

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