Long-Term Follow-up of the Circadian Rhythm of Heart Rate and Heart Rate Variability in Healthy Elderly Patients

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Background The long-term age-related changes in circadian rhythm of heart rate variability (HRV), that is, autonomic nervous activity, remain unknown in elderly people.

Methods and Results Holter monitoring was conducted twice at an interval of 15 years in 15 healthy elderly patients (age: 70.0±4.1 years, at first monitoring, female: 10) and assessed the age-related changes in 24-h mean and hourly mean normal sinus R-R interval (mean NN), HRV (high frequency (HF) component, low frequency (LF) component and LF/HF) and the circadian rhythms. As a result, 24-h mean mean NN (0.976±0.115 vs 0.903±0.117 (s), p=0.0019), LF/HF (1.681±0.731 vs 0.962±0.442, p=0.0022), and LF (278.88±176.43 vs 179.19±132.33 (ms²), p=0.0039) significantly decreased 15 years later, although 24-h mean HF (221.20±138.89 vs 310.78±296.73 (ms²), p=0.1102) increased slightly. The hourly mean NN closely correlated with hourly HF and LF/HF throughout circadian rhythms both at first and second monitoring. In the morning hours, amplitude rates of all HRV indices increased significantly 15 years later.

Conclusion In elderly people, age-related changes in the 24-h mean heart rate (HR) were conversely dissociated from those of the 24-h mean HRV. However, the close correlation between hourly HR and HRV was preserved, even in very elderly patients. Additionally, the amplitude rates in HRV in the morning increased with age. These age-related changes of HR and HRV might be characteristic of elderly people. (Circ J 2006; 70: 889–895)

Key Words: Age-related change; Autonomic nervous activity; Circadian rhythm; Healthy elderly patients; Heart rate variability

It has been reported that in healthy subjects younger than 70 years there are negative correlations between age and maximum exercise heart rate (HR), maximal and mean HR observed on Holter monitoring, or intrinsic HR after pharmacological autonomic block. Furthermore, HR variabilities (HRV) are thought to be closely associated with autonomic nervous activity (ANA) and both are also known to decrease with increasing age. However, recent reports have shown that the age-related changes in HR and HRV in elderly patients older than 70 are not necessarily the same as those in younger healthy adults.

Previous studies have shown that aging itself is a risk factor for cardiovascular events which occur with a circadian variation, increasing in the morning. Moreover, ANA is reported to be closely associated with the circadian rhythm of occurrence of cardiovascular events. However, the relationship between ANA and the development of cardiovascular events in elderly patients is still unclear because of a lack of studies especially concerning longitudinal age-related changes in circadian variation of HR and HRV.

Therefore, to elucidate the change in ANA and its circadian rhythm with aging in elderly people, we conducted Holter monitoring twice at an interval of 15 years in healthy elderly patients, and assessed the longitudinal age-related changes in HR, HRV, and their circadian rhythms.

Methods

Study Population and Holter Monitoring

We have described the methods in our previous study and briefly explain the methods used in the current study.

Among 164 healthy patients for whom we conducted the first Holter monitoring (age range of 14–87 (mean: 54.2±21.3 years) at that time and a sex distribution of 90 females and 74 males), there were 89 healthy individuals who were older than 60, with their ages ranging from 61 to 87 (mean: 72.0±4.9 years), and they consisted of 58 females and 31 males. The 89 healthy elderly individuals had been undergoing community-based annual health examinations as many times as possible, including physical examinations, electrocardiography, chest X-ray, complete blood counts, and bio-chemical examination by blood sampling. Among these individuals, we were able to confirm the medical history of 74 by telephone 15 years after the first monitoring. Forty-eight were still alive and 26 had died.

Furthermore, when conducting the second Holter monitoring 15 years later, the physicians or cardiologists checked the results of their health examinations and confirmed the
individuals did not have any heart diseases or take any drugs that could affect their HR and rhythm. We enrolled only the individuals who did not have any present illness or history of heart disease. We were able to conduct a second Holter monitoring for 19 individuals who gave informed consent. We then excluded the individuals whose Holter recording revealed a recording failure or pathological findings. As a result, there were only 15 patients whose second Holter recordings could be properly and precisely analyzed. We studied the first and second Holter monitorings of the 15 healthy elderly patients who had typical activities of daily living according to their ages. They had all lived in rural Japan and were capable of enjoying a short walk, a gateball game, Japanese ground golf or light farmwork such as gardening even 15 years later. Among them, only 1 patient had a smoking habit and 1 could not be asked about it.

Between the 89 healthy elderly patients undergoing the first Holter monitoring and the 15 healthy elderly patients undergoing the second monitoring, there were no significant differences in terms of age (72.0±4.9 vs 70.0±4.1; unpaired t-test; p=0.2191) and sex ratio (female:male = 58:31 vs 10:5; χ² test; p=0.1102), which suggests that they had similar statistical features and that there was no arbitrary procedure when enrolling the study patients.

The first and second mean Holter monitoring times were 22 h 52 min and 23 h 48 min, respectively. Furthermore, if the Holter monitorings were too noisy for frequency domain analysis, we excluded the terms of Holter monitorings by the hour. As a result, we obtained an average of 19.8/24 h (82.5%) of available Holter monitoring during the first monitoring period and 20.3/24 h (84.6%) for the second monitoring period. We filled in the blank hours because of deletion of noise with the mean values for the hours before and after the blanks.

**Data Analysis**

We assessed changes over 15 years in 24-h mean and hourly HR (ie, mean normal sinus R–R interval (mean NN; seconds)), as well as HRV estimated by frequency domain analysis by fast fourier transform (ie, high frequency (HF) component (HF: 0.148–0.398 Hz; ms²) as an index of parasympathetic activity, low frequency (LF) component (LF: 0.039–0.148 Hz; ms²) as a mixed vagal and sympathetic signal, and LF/HF ratio as an index of sympathetic activity or sympathovagal balance). We evaluated the age-related changes in HR, HRV, and their circadian rhythms in the healthy elderly patients. We also analyzed the correlations between every 2 indices among hourly HR and HRV over 24 h at the first monitoring and then 15 years later.

Furthermore, to assess the time course of those indices in the morning, we statistically compared the maximum hourly values (or the minimum hourly values in the case of LF/HF) of the mean NN or HRV in the morning hours between 04.00 and noon with the following hourly values during the time course in the morning hours, at the first and at the second monitoring period.

In addition, to elicit and characterize the dynamic individual changes of HR and HRV in the morning, we chose: (A) the maximum hourly value (or the minimum hourly value in the case of LF/HF) in the morning hours between 04.00 and noon; and (B) the following minimum hourly value (or maximum hourly value, respectively) in the morning hours individually, and then calculated the individual maximum change [B–A], which we defined as amplitude, and the individual maximum rate of the change [(B/A–1)×100], which we defined as amplitude rate, to compare the first monitoring with the second.

**Statistical Analysis**

Each comparison and evaluation of correlation between every 2 indices were made with the use of paired t-test and Pearson’s correlation coefficients, respectively. The p-values of <0.05 were considered to be significant.

**Results**

**Age-Related Changes in HR, HRV, and Their Circadian Rhythms**

**Mean NN** Twenty-four hours mean mean NN of the second monitoring period significantly decreased compared with that of the first (first monitoring vs second monitoring: 0.976±0.115 (s) vs 0.903±0.117 (s), p=0.0019; Fig 1). Every hourly mean NN except for the 05.00h had also clearly decreased and about three-fourths of them had significantly decreased 15 years later (Fig 2).

**HF** Twenty-four hours mean HF of the second monitoring period showed increasing tendency compared with that of the first (221.20±138.89 (ms²) vs 310.78±296.73 (ms²), p=0.0022*).
Fig 2. Age-related changes in circadian rhythm and time course in the morning of the hourly heart rate (HR) and heart rate variability (HRV) in healthy elderly patients. (Left) Horizontal and vertical axes show the time of day and the HRV values, respectively. The 2 vertical fine lines in each graph indicate 04.00 and 12.00. The hourly values at the first and second monitoring are shown by the open rhombus (˖) and the closed square (˗) with standard deviations, respectively. Significant changes in the second monitoring compared with the first are indicated by *. (Right) Time course of the hourly HR and HRV in the morning between 04.00 and 12.00. The maximum values (or minimum value in the case of low frequency/high frequency (LF/HF)) in the morning hours are shown with arrows (ˣ or ᵃ, respectively). Significant changes during the time course are shown with †, compared with the maximum (or minimum) values indicated with arrows. The scales of the vertical axes are magnified.
Most of the hourly HF in circadian rhythm also showed increasing tendency 15 years later, and the 2 hourly HF during the 06.00 h and the 19.00 h had significantly increased (Fig 2).

**LF/HF**

Twenty-four hours mean LF/HF of the second monitoring period had significantly decreased compared with that of the first (1.681±0.731 vs 0.962±0.442, p=0.0022; Fig 1). Every hourly LF/HF in circadian rhythm had also clearly decreased and around three-fourths of them had significantly decreased 15 years later (Fig 2).

**LF**

Twenty-four hours mean LF of the second monitoring period significantly decreased compared with that of the first (278.88±176.43 (ms²) vs 179.19±132.33 (ms²), p=0.0039; Fig 1). Every hourly LF in circadian rhythm also had clearly decreased 15 years later and about three-fourths significantly decreased (Fig 2).

### Correlation Between the 2 Indices Among Hourly HR and HRVs in Circadian Rhythm

Table 1 shows the correlations between every 2 indices among hourly NN and HRVs throughout the circadian rhythm at first and second monitoring, respectively; p<0.0001, *p<0.001, **p<0.05, †p>0.05. HR, heart rate; HRV, heart rate variabilities; HF, high frequency; LF, low frequency.

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<td>Mean NN (s)</td>
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*Pearson’s correlation coefficient (r) between every 2 indices among hourly HR and HRVs throughout the circadian rhythm at first and second monitoring, respectively; p<0.0001, *p<0.001, **p<0.05, †p>0.05.

**Mean NN**

The time course of hourly mean NN in the morning hours between 04.00 and noon in the first monitoring period showed decline after 04.00 h, when hourly mean NN was maximum in the morning hours. A significant decrease appeared from the early hours (ie, after 05.00). Afterward, the hourly mean NN rebounded (Fig 2). Fifteen years later, the time course of the hourly mean NN in the morning showed decline after 04.00, whereas this tendency occurred 1 h later than in the first monitoring period, that is, the significant decrease appeared 1 h later (ie, after 06.00). However, there was no obvious rebound phenomenon in the morning (Fig 2).

Furthermore, the amplitude of hourly mean NN in the morning and the amplitude rate showed increasing tendency 15 years later compared with the first monitoring period (mean NN; amplitude: −0.21±0.13 (s) vs −0.26±0.15 (s),

### Dynamics of HR and HRV in the Morning

We conducted the evaluation of the age-related changes in dynamics of HR and HRV in the morning hours between 04.00 and noon, when hemodynamics and ANA fluctuated drastically, and when cardiovascular events increased. In the morning hours, HR (ie, mean NN), and the indices of ANA (ie, HF and LF/HF), all inclined to increase sympathetic nervous activity at first monitoring and at 15 years later. The detailed results are as follows (Figs 2, 3).

**Mean NN**

The time course of hourly mean NN in the morning hours between 04.00 and noon in the first monitoring period showed decline after 04.00 h, when hourly mean NN was maximum in the morning hours. A significant decrease appeared from the early hours (ie, after 05.00). Afterward, the hourly mean NN rebounded (Fig 2). Fifteen years later, the time course of the hourly mean NN in the morning showed decline after 04.00, whereas this tendency occurred 1 h later than in the first monitoring period, that is, the significant decrease appeared 1 h later (ie, after 06.00). However, there was no obvious rebound phenomenon in the morning (Fig 2).

### Amplitude

**Amplitude Rate**

Fig 3. Age-related changes in the dynamics of heart rate (HR) and heart rate variability (HRV) in the morning in healthy elderly patients. Graphs show the age-related changes of the amplitude of all indices of HR and HRV and the amplitudes rates, respectively. *shows significant change between the first and second monitoring. LF, low frequency; HF, high frequency.
Circadian Rhythm of Elderly HRV

HF The time course of hourly HF in the morning between 04.00 and noon at the first monitoring period, such as hourly mean NN, showed decline after the 04.00 h, when hourly HF was maximum in the morning hours. A significant decrease appeared after 06.00. Afterward, the hourly HF rebounded (Fig. 2). However, the time course of hourly HF in the morning 15 years later showed a slight increase after 04.00 and maximum value at the 06.00 h, but remained almost unchanged until 08.00. Afterward, the hourly HF decreased sharply to the same level as in the first recording at the same hours, and thus the significant decrease appeared after 09.00. Accordingly, the hourly HF maintained almost the same level between 04.00 and 08.00 15 years later, regardless of the decrease in hourly mean NN during the same hours, which meant there was a dissociation between hourly HF and mean NN, namely HR (Fig. 2).

Moreover, the amplitude of HF in the morning showed an increasing tendency 15 years later compared with the first monitoring period, and the amplitude rate of the hourly HF increased significantly (HF; amplitude: –262.10±286.70 (ms²) vs –492.70±639.80 (ms²), p=0.0853; amplitude rate: –58.86±25.69 (%) vs –75.54±13.28 (%), p=0.0295; Fig. 3).

LF/HF The time course of hourly LF/HF in the morning between 04.00 and noon at the first monitoring period showed sharp increase after 04.00 h, when hourly LF/HF was minimum in the morning. A significant increase appeared in the relatively early hours (ie, during 07.00 h and 08.00 h). Afterward, the hourly LF/HF rebounded (Fig. 2). Also, 15 years later the time course of the hourly LF/HF in the morning showed gradual increase after 04.00 and the significant increase appeared after 10.00 (Fig. 2).

Moreover, the amplitude of LF/HF in the morning showed minimally decreasing tendency 15 years later compared with the first monitoring period, although the amplitude rate of LF/HF increased significantly (LF/HF; amplitude: 1.39±0.98 vs 1.14±0.86, p=0.2085; amplitude rate: 142.50±115.70 (%) vs 229.40±317.90 (%), p=0.0322; Fig. 3).

LF The time course of hourly LF in the morning between 04.00 and noon at the first monitoring period showed decrease after 04.00 h, when hourly LF was maximum in the morning. A significant decrease appeared in the relatively early hours (ie, during 07.00 h and 08.00 h). Afterward, the hourly LF rebounded. This tendency was similar to the pattern of the time course of hourly HF at the first recording (Fig 2). However, the time course of hourly LF in the morning after 15 years showed a slight increase after 04.00 and maximum value at 05.00 h. Afterward, the hourly LF gradually decreased without rebound and the significant decrease appeared after 10.00 (Fig 1). This tendency was also similar to the pattern of the time course of hourly HF at the second recording (Fig 2).

Moreover, the amplitude of LF in the morning showed increasing tendency 15 years later compared with the first monitoring period, and the amplitude rate of LF had increased significantly (LF; amplitude: –214.67±168.00 (ms²) vs –266.78±284.77 (ms²), p=0.1425; amplitude rate: –50.51±18.41 (%) vs –65.83±17.16 (%), p=0.0044; Fig 3).

Discussion

In general, cardiovascular events increase in the morning11–14,19 Furthermore, cardiovascular events occur more frequently in elderly people and aging itself is an independent risk factor. However, changes with aging in elderly patients and how ANA is involved in the occurrence of cardiovascular events are still unknown.

Previously, we reported changes in HR and HRV with aging over 15 years in healthy elderly patients during the night (00.00 to 05.00) and day (noon to 17.00) when HR and HRV are thought to be relatively stable in circadian rhythm.6–22 However, from a clinical point of view, it is in the morning that cardiovascular events most frequently occur. The hemodynamics fluctuate most dramatically in the morning, mainly because of postural change and mental activity, although ANA is thought to be associated with the hemodynamic change and thus, the occurrence of cardiovascular events.6–10 HRV obtained from Holter monitoring as indices of ANA is known to be reproducible and reliable measure.13,21–25 Longitudinal studies are expected to show the features of age-related change more precisely and in more detail than cross-sectional studies, especially in a small population. Thus, to characterize the age-related changes of ANA in elderly patients, we analyzed the longitudinal age-related changes in HR, HRV, and their circadian rhythms over 15 years in 15 healthy elderly patients at a mean age of 70 years, and assessed the age-related changes in the dynamics of ANA in the morning.

Age-Related Changes in HR and HRV

In the current study, there was a discrepancy between the age-related changes in 24-h mean HR and HRV as a parameters of ANA, consistent with the result of our previous report.6 The significant decrease in 24-h mean mean NN seen in the present study (ie, the significant increase in 24-h mean HR) might be derived from an increase in plasma norepinephrine or sympathetic nervous activities with age,6 a deterioration in cardiopulmonary function, a decrease in muscarinic receptors,27 an attenuation of the whole ANA with increasing age, etc.

However, the increasing tendency in 24-h mean HF as the index of parasympathetic activity over a whole day, which seems to be paradoxical in elderly patients in whom sympathetic activities are thought to increase,21 might imply a negative feedback phenomenon of parasympathetic nerves to such increased sympathetic activities with age,28 probably as a result of the decrease in metabolism of norepinephrine with age at the synapses of efferent sympathetic nerves in the sinus node10,29 or in the circulating blood.

Moreover, the significant decrease in 24-h mean LF/HF as the index of sympathetic activities or the sympathovagal balance might be derived from the negative feedback of sympathetic nerves to the increase in norepinephrine in the blood or the decreased physical activity with age. However, in the current study HR obviously increased with age.

Several recent studies have reported that the dissociation between HR and HRV appears just before the onset of arrhythmias,30,31 and the development of vasospastic angina.32,33 Accordingly, there is a possibility that the paradoxical changes in HR and HRV with age observed in our study are associated with a susceptibility to various cardiovascular events in the very elderly.

Correlation Between the 2 Indices Among Hourly HR and HRV in Circadian Rhythm

As we mentioned earlier, the changes over 15 years in 24-h mean HR and ANA calculated from HRV were dissociated from each other. However, as far as circadian
Dynamics of HR and HRV in the Morning

We evaluated the age-related changes in HR and HRV in healthy elderly patients in the morning between 04.00 and noon, when sympathetic nervous activity is expected to increase and, thus, the fluctuation of those indices was expected to be most dynamic and to be associated with the occurrence of cardiovascular events.11,12

Among those indices, mean NN, HF, and LF/HF shifted to the side of increase in sympathetic nervous activity most remarkably in the circadian rhythms of the healthy elderly patients. The average fluctuation pattern of every index in the morning hours showed a pattern peculiar to each index as shown in Fig 2.

At the first monitoring period at the mean age of 70, the morning time courses of HR and HRV showed that the fluctuations began relatively early in the morning and that the following significant changes appeared also at a relatively early hour (Fig 2). Those fluctuations in the morning were most drastic in the circadian rhythms and inclined to increase sympathetic nervous activity, that is, HR increased, LF/HF increased and HF decreased in the morning. Afterward, the rebound phenomenon appeared, which seemed to prevent further excessive change.

Fifteen years later, the fluctuations in the morning were also most drastic in the circadian rhythm. However, the fluctuation was delayed and the significant change also appeared later. Furthermore, the following rebound disappeared, which might reflect age-related attenuation in the whole ANA.

Moreover, the amplitude rate of the mean NN showed an increasing tendency 15 years later compared with the first monitoring period in the healthy elderly patients. Regarding HRV, the amplitude rates of HF, LF, and LF/HF increased significantly 15 years later. The increases in the amplitude rates of HRV in the healthy elderly patients might be attributed to the disappearance of the rebound phenomenon of HRV in the morning, probably because of the attenuation of ANA with age.

In general, it is thought that atherosclerosis progresses and total blood volume decreases in elderly people, whereas ANA attenuate. Therefore, it is possible that the disappearance of the rebound in HR and HRV and the increase in the amplitude rates of HRV in the morning might be attributed to arteriosclerosis and a decrease in the total blood volume at the mean age of 85 years. Arntz et al also reported that more cardiovascular events in the morning occurred in subjects over 65 years old.11,12

Accordingly, these age-related changes in the time course, or the fluctuation, of the ANA in the morning might be a characteristic of elderly people and the background to their susceptibility to cardiovascular events in the morning.

Conclusion

In healthy elderly individuals, we showed a paradoxical dissociation between 24-h mean and hourly HR (or mean NN) and ANA (or HRV) with aging. Moreover, as far as the circadian rhythms of HR and ANA in healthy elderly patients are concerned, the close correlations between hourly HR and ANA were preserved, not only at first monitoring but also 15 years later, irrespective of the common concept of attenuated tendency in the whole ANA with age. Furthermore, the amplitude rate of HRV increased in the morning with age, when the balance of ANA inclined to sympathetic nervous activity in the circadian rhythm.

These features of age-related changes in HR and ANA might be characteristic of elderly people and associated with their susceptibility to cardiovascular events in the morning.

References


