Association Between Regional Difference in Heart Rate Variability and Inter-prefecture Ranking of Healthy Life Expectancy: ALLSTAR Big Data Project in Japan

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Abstract. As a physiological big-data project named ALLSTAR, we have developed a 24-hr ambulatory electrocardiogram database of 81,615 males and 103,038 females (≥20 yr) from all over Japan. With this database, we examined if regional differences in heart rate (HR) and HR variability (HRV) are associated with the inter-prefecture rankings of healthy life expectancy (HALE) and of average life expectancy (ALE) in Japan. According to reports by the Japanese Ministry of Health, Labour and Welfare (2013), subjects in each sex were grouped into short, middle, and long HALE and ALE tertiles by their living prefectures. Standard deviation of 24-h normal-to-normal R-R intervals (SDNN) increased progressively with increasing HALE tertiles in both sexes (Ps < 0.001), while it showed no consistent associations with ALE. Conversely, HR decreased progressively with increasing ALE tertiles in females (P < 0.001), while it showed no consistent association with HALE. These suggest HRV may reflect a biological property relating to long HALE.

Keywords: Allostatic State Mapping by Ambulatory ECG Repository (ALLSTAR) · Physiological big data · Healthy life expectancy · Heart rate variability

1 Introduction

Healthy life expectancy (HALE) is defined as the period in the life when people might live without restriction of their daily activities due to health problems. According to reports by the Japanese Ministry of Health, Labour and Welfare (2013) [1], HALE of Japanese men and women are 71.19 and 74.21 yr, respectively. Because their average life expectancy (ALE) are reported to be 80.21 and 86.61 yr, respectively, there are gaps of 9.02 yr for men and 12.40 yr for women, which detract individual quality of life, reduce the activities of society, and cause a substantial social burden. Shortening of this gap is currently one of the most urgent challenges to mankind. In order to address to this problem effectively, however, it seems important to clarify the biological properties that determine HALE separately from ALE.

J.J. Jung and P. Kim (Eds.): BDTA 2016, LNICST 194, pp. 23–28, 2017.
DOI: 10.1007/978-3-319-58967-1_3

As a physiological big-data building project named Allostatic State Mapping by Ambulatory ECG Repository (ALLSTAR) [2], we have developed a database of 24-h ambulatory electrocardiograms (ECGs) collected from all over Japan since 2007 and currently, the size has reached about 240 thousand cases. All data are associated with date and geographic location (postal code) of recording, which allow us to analyze the regional differences in ECG-derived indices such as 24-h heart rate (HR) and heart rate variability (HRV) [3]. The above mentioned reports by the Japanese Ministry of Health, Labour and Welfare (2013) [1] have also shown the presence of regional differences in HALE and ALE and provided their inter-prefecture rankings for each sex. In the present study, we combined our ECG big data and these databases and examined if regional differences in HR and HRV are associated with the inter-prefecture ranking of HALE and ALE.

2 Methods

2.1 ECG Data

We used 24-h Holter ECG big data of ALLSTAR project [2]. The data were collected between November 2007 and July 2014 at three ECG analysis centers (Sapporo, Tokyo, and Nagoya) in Japan. We used data only from subjects aged ≥20 yr who have agreed with the usage of their data for this study. The study protocol has been approved by the Research Ethics Committee of Nagoya City University Graduate School of Medical Sciences (No. 709).

The inclusion criteria of data for this study were those of subjects aged ≥20 yr, record length ≥21.6 h (90% of 24 h), and ECG showing sinus rhythm (normal heart rhythm) ≥19.2 h (80% of 24 h). Exclusion criteria were ECG data from patients with cardiac pace maker and those showing persistent or paroxysmal atrial fibrillation.

2.2 Analysis of HRV

Holter ECG recordings were processed according to the standard method [3]. Briefly, ECG recordings were analyzed with an ambulatory ECG scanner (Cardy Analyzer 05, Suzuken Co., Ltd., Nagoya, Japan) by which QRS complexes were detected and labeled automatically. QRS complexes were considered as sinus rhythm only when (1) they had a narrow supraventricular morphology, (2) R-R intervals were between 300 and 2000 ms and differed ≤20% from the average of 5 preceding sinus rhythm R-R intervals, and (3) consecutive R-R interval differences were ≤200 ms. Results of the automatic analysis were reviewed and any errors in R-wave detection and in QRS waveform labeling were edited manually.

Time series of 24-h R-R intervals data were analyzed for HRV measures according to the recommendations by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [3]. Mean HR was calculated from the 24-h average of normal-to-normal R-R intervals consisting of two consecutive QRS complexes in sinus rhythm and standard deviation of normal-to-normal R-R interval over 24-hr (SDNN) [4] was calculated.

2.3 Statistical Analysis

The subjects in ALLSTAR database were classified into 47 prefectures according to the postal code of their recording locations. Then, the prefectures were sorted by the inter-prefecture rankings of HALE and ALE in each sex and were further categorized into tertiles of short, middle, and long HALE and ALE, so that the number of subjects becomes as equivalent as possible among the tertiles.

We used SAS 9.4 software (SAS Institute, Cary, NC) for the statistical analysis. Differences in HR and SDNN among tertiles of HALE and ALE were evaluated by ANCOVA with General Linear Model procedure adjusted for the effects of age in each sex. Bonferroni correction was used for post-hoc multiple comparisons between tertiles. We used $\alpha < 0.001$ to guard against type 1 statistical error.

3 Results

According to the inclusion and exclusion criteria, 24-hr ambulatory ECG data in 79,354 men (median age [IQR], 65 [56–76] yr) and 99,961 women (67 [59–78] yr) were extracted for this study. They were categorized into HALE and ALE tertiles by their inter-prefecture rankings of their living prefectures in each sex. Table 1 shows the number of subjects and the range of HALE and ALE in each tertile.

Table 1. Subjects grouped into tertiles according to inter-prefecture rankings of healthy life expectancy (HALE) and average life expectancy (ALE) of their living prefectures by sex

Tertile	HALE		ALE	
	N	Range (yr)	N	Range (yr)
Male				
Short	24,872	68.9–69.9	25,687	77.3–79.6
Middle	28,969	70.0–70.8	15,229	79.7–79.8
Long	25,513	70.9–71.7	38,438	79.9–81.0
Female				
Short	34,650	72.3–73.0	32,922	85.4–86.2
Middle	31,391	73.1–73.7	27,796	86.3–86.5
Long	33,920	73.8–75.3	39,243	86.6–87.2

ANCOVA revealed that 24-h SDNN (SDNN) increased progressively with increasing HALE tertiles for both sexes ($P < 0.001$ for both), while no consistent associations was observed between 24-hr mean HR and HALE tertiles in either sexes (Fig. 1). Conversely, mean HR decreased progressively with increasing ALE tertiles only in women ($P < 0.001$), while mean HR in men and SDNN in both sexes showed no consistent association with ALE tertiles. The same results were obtained even when the analyses were performed separately in subjects with age <70 yr (45,271 males and 50,763 females) and in those ≥70 yr (34,083 males and 49,198 females).

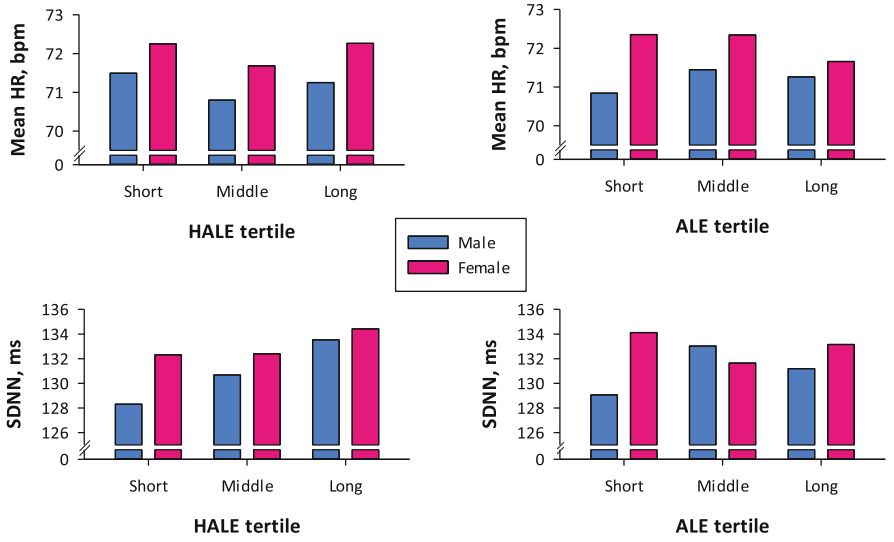

Fig. 1. Mean heart rate (HR) and standard deviation of normal-to-normal R-R intervals (SDNN) over 24 h in the tertiles of inter-prefecture rankings of healthy life expectancy (HALE) and average life expectancy (ALE) in each sex.

4 Discussion

To our knowledge, this is the first study to report the association between HRV and HALE. We found that reginal difference in HRV measured as SDNN is associated with inter-prefecture ranking of HALE but not with the ranking of ALE. We observed that SDNN increased progressively in the order of short, middle, and long HALE tertiles, while it showed no consistent association with ALE tertiles. Conversely, mean HR decreased with increasing ALE tertiles in women, while it showed no consistent association with HALE tertiles. These findings suggest that HR and HRV may involve differently in HALE and ALE and that HRV may reflect a biological property relating to long HALE.

As aging of population is progressing in the global scale, the paradigm of medicine is shifting from the extension of ALE to the shortening the gap between ALE and HALE. Unlike the causes of death that shorten ALE, the major factor that shortens HALE is thought to be the decay and loss of mental and physical activities, which creep unconsciously under daily life. To cope with this issue, not only conventional medical approaches such as preventions, rescues, and therapies of diseases but also the early detections of activity decay and the self-management of biological or behavioral properties that are associated with early/rapid development of mental and physical inactivation seem essential. In this aspect, the findings of this study seem to provide an important insight into this issue, suggesting the association of HRV with HALE.

Although the mechanisms of the association between HRV and HALE cannot be determined by the present study because of its observational nature, some speculations may be possible. First, because the significant association between SDNN and HALE

was observed even when the analysis was performed only in subjects with age <70 yr, the association may not be attributable to the results of a greater proportion of people who had already lost their healthy life in the short and middle tertiles of HALE. If this is true, lower SDNN might be a predictor of early/rapid development of inactivity that could lead to short HALE. Second, in a previous study of ALLSTAR big-data project, we have reported that regional difference in physical activity is associated with inter-prefecture ranking of HALE [5]. In this previous study, we have assessed physical activity by 3-axis accelerometer installed in Holter ECG recorders in 18,875 men and 23,541 women. We observed that physical activity level is increasing progressively with increasing tertiles of HALE. This suggests that the maintenance of physical activity may be a factor promoting longer HALE. By contrast, because SDNN is known to reflect mainly parasympathetic activity [3] and 24-h SDNN is mostly determined by SDNN during nighttime [6]. Thus, the findings of the present study combined with those of our previous study lead to the speculation that the maintenance or enhancement of rest-activity rhythm in daily life may be an important factor for long HALE.

The present study has several limitations. First, the big data were collected from patients who underwent Holter ECG for certain clinical reason(s). Thus, we need to consider the presence of sampling bias, although it would cause common effects on data in all prefectures. Second, although the number of subjects was about 200 thousand, it may still not be sufficient to represent the regional characteristics. This seems critical to the indirect analyses of the relationships between sampled observations (HR and HRV) and population characteristics (HALE and ALE). Expansion of the size of database and inclusion of healthy people's data seem important to confirm the findings in the future studies.

5 Conclusions

As ALLSTAR big-data project, we have developed a database of 24-hr ambulatory ECG from all over Japan. With this database, we analyzed the associations between regional differences in HR and HRV and the inter-prefecture rankings of HALE and ALE. We found that HRV measured as SDNN increases progressively in short, middle, and long HALE prefectures, while it showed no consistent associations with ALE. Our findings suggest that HRV may reflect a biological property relating to long HALE.

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