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REVIEW ARTICLE

HOLTER ECG BIG DATA PROJECT: ALLOSTATIC STATE MAPPING BY AMBULATORY ECG REPOSITORY (ALLSTAR)

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ABSTRACT

Holter electrocardiography (ECG) is the most successful bio-signal monitoring during daily activities. There is no other example in the history of human beings that such long-term, well-standardized physiological data were globally corrected. To utilize this precious information resource, the Allostatic State Mapping by Ambulatory ECG Repository (ALLSTAR) project has started since 2007 in Japan. The purpose of the project is to build a cumulative database of 24-h ambulatory ECG recorded all over Japan, which were anonymized and stored with age, sex, and recording date, time, and location (postal code). Tri-axial acceleration data have also been added since December 2010.At present, a total of 301,848 data has been collected from 140,144 males and 161,704 females, along with 46,114 body acceleration data. The data distributed over all ages from 0 to >100 years (median age [5-95 percentile range], 69 [26-87] yr), all prefectures in Japan, and all months of years. The basic rhythm of ECG was sinus rhythm in 253,673 (84.0%) and persistent a trial fibrillation in 17,159 (5.7%). The analyses of the database not only provided the age and sex reference values of dynamic ECG, particularly the indices of heart rate variability, but also revealed the factors associated with their variances, including physical activities of the day and the natural and social environments of the place of monitoring.

INTRODUCTION

Holter electrocardiography (ECG) is a clinical examination that records continuous ECG signal in freely moving subjects under their daily activities (Dynamic electrocardiography, 2004; Romero, 2013). In usual 24-hexamination in adult, about one hundred thousand beats of ECG waveforms and interbeat interval time series are obtained per recording. Information included in each recording is huge, but only a small part of it has been used clinically and even in researches (Dynamic electrocardiography, 2004; Camm *et al.*, 1996; Kiyono *et al.*, 2016).Given that Holter ECG examinations are performed worldwide with well-standardized quality, the entire amount of information left unused had been unduly extravagant. Along with the rapid progress in computer sciences and computation power, the practical utility of such big-data information hasbeen improving progressively (Dinov, 2016; Toga *et al.*, 2015). This situation may be a fortunate opportunity rarely seen from the viewpoint of human history, which has motivated us to start a Holter ECG big data project named the Allostatic State Mapping by Ambulatory ECG Repository (ALLSTAR).The purpose of this project is to build a cumulative database of 24-h ambulatory ECG. The database would beuseful not only for determining reference values of the dynamic properties of ambulatory ECG, such as heart rate variability (HRV), but also for examining the temporal and topographical influences of natural and social environmental factors on the properties, through relating the database with other demographic, geographic, meteorological, and socioeconomic databases. In this article we report the characteristics of the ALLSTAR database and the recent studies from the project.

ALLSTAR project

The ALLSTAR project is performed according to the protocol that has been approved by the Ethics Review Committee of Nagoya City University Graduate School of Medical Sciences (No. 709). According to the Ethical Guidelines for Medical and Health Research Involving Human Subjects (by the Ministry of Education, Culture, Sports, Science and

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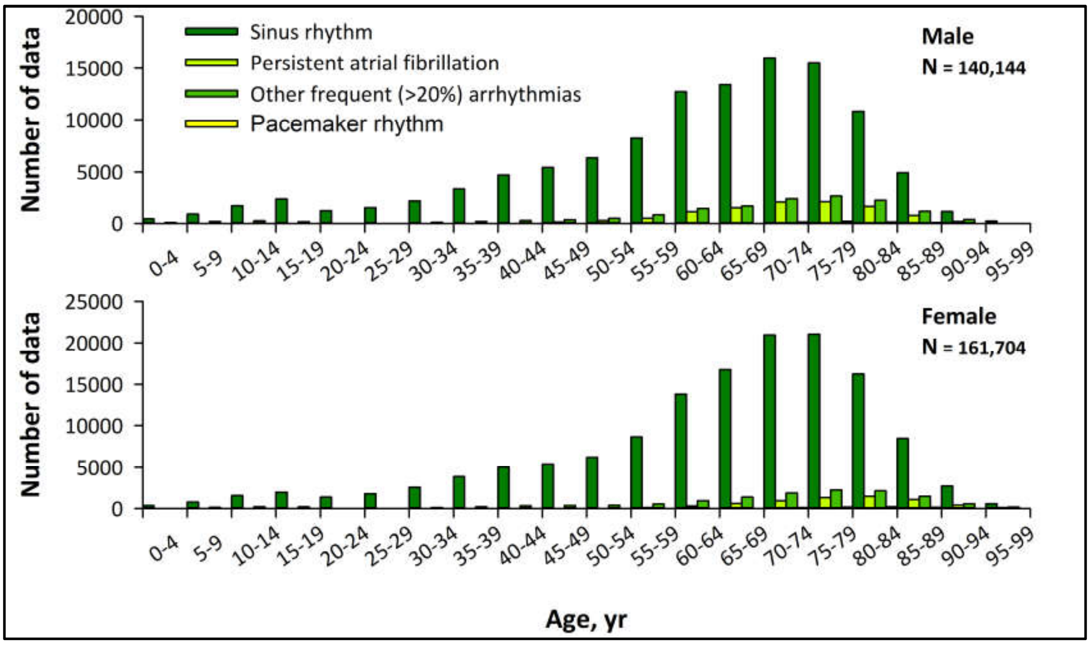


Fig. 1. Age distributions of male and female subjects by basic cardiac rhythms

Technology and the Ministry of Health, Labour and Welfare, Japan, December 22, 2014), the purpose and information utilized in this research project have been public through the homepages of the ECG analysis centers (http://www.suzuken.co.jp/product/holter/detail/) and of the ALLSTAR project (http://www.med.nagoya-cu.ac.jp/mededu.dir/allstar/), in which opportunities to refuse the uses of information are ensured for the research subjects.

Holter ECG data

The database has been consisting of 24-hambulatory ECGs that were recorded for some clinical purpose by medical facilities and were referred for analysis to three ECG analysis centers (Suzuken Co., Ltd.) located in Tokyo, Nagoya, and Sapporo in Japan. The data were anonymized by the center and stored with accompanying information, including age, sex, and recoding date, time, and location (postal code); the information of clinical diagnosis and medications reported by the attending physicians was also included, when it was available (30-40%).
The data were recorded with the Cardy series of Holter recorders (Cardy 2, Cardy 2P, Cardy 203, Cardy 301,Cardy 302 Mini and Max, Cardy 303 pico and Cardy 303 pico+, Suzuken Co., Ltd., Nagoya, Japan), by which 24-h multi-channel ECG data were digitized at 125 Hz and stored in memory. The digitized ECG data were sent to one of the three ECG analysis centers, where the data were analyzed with Holter ECG analyzers (Cardy Analyzer05, Suzuken Co., Ltd., Nagoya, Japan) by skilled medical technologists; the temporal positions of all R-waves were detected, the rhythm annotations were given to all QRS complexes, and all errors in automated analysis were corrected manually by the technologists. The suspicious outcomes of the analysis (approximately 40% of data) have been reviewed by contracted cardiologists.

Acceleration data

After December 2010, along with the introduction of new Holter recorders with tri-axial accelerometers (Cady 303 pico and pico+), 24-h body acceleration data have also been recorded with ECG data. For these data, the mediolateral, anteroposterior, and longitudinal acceleration signals were digitized at 31.25 Hz and stored.

Database

From the results of analysis, beat-to-beat time series of the following information for the entire recording length (usually for 24 h) have been stored in the database: (1) times of all R waves after the start of recoding in ms, (2) R-R intervals in ms, (3) rhythm annotation labels of all QRS complexes, and (4) ST levels following the QRS complexes for channels 1 and 2.Together with these beat-to-beat time series data, entire 24-h tri-axial acceleration data and accompanying information have been stored into the database.

Characteristics of ALLSTAR database

Since November 2007, a total of 301,848 analyzable ECG data together with accompanying information have been collected and stored in the database. The data distributed over all ages from 0 to >100 years (median age [IQR, 5-95 percentile range], 69 [57-78, 26-87] yr) for both sexes. The gender distributions were 140,144 men (age, 68 [56-77, 23-86] yr) and 161,704 women (70 [58-79, 28-88] yr). Among these ECG data, 46,114 (20,694 men and 25,420 women) were accompanied by body acceleration data. “Sinus rhythm” indicates data with sinus rhythm >80% of the total recorded beats; “Other frequent (>20%) arrhythmias” indicates data with frequent (>20% of the total recorded beats) arrhythmias (paroxysmal atrial fibrillation, atrial flutter, and ventricular and supraventricular ectopic beats). Fig. 1 shows data distributions by 5-yr bin of age in male and female subjects separated by basic cardiac rhythms. For both genders, the data distributed to all ages, while they were concentrated between 60 to 85 yr old. Basic cardiac rhythm was sinus rhythm (defined as >80% of all recorded beats are in sinus rhythm) in 253,673 (84.0%) subjects (113,341 [80.9%] men and 140,332 [86.8%] women). Persistent atrial fibrillation was detected in 17,159 (5.7%) of the total subjects; 10,631 (7.6%) men and 6,528 (4.0%) women. Other frequent (>20% of total recorded beats) arrhythmias, which included paroxysmal atrial fibrillation, atrial flutter, and ventricular and supraventricular ectopic beats, were detected in 29,078 (9.6%) of the total subjects; 15,264 (10.9%) men and 13,814 (8.5%) women. The number of data from 47 prefectures in Japan (left panel) and those in each month (right panel). The green bars in the right panel indicate the number of 24-h ECG data and overlapping dark-green bars the number of body acceleration data. Fig. 2 shows the geographic and temporal distributions of data. Collected data distributed over all prefectures of Japanand all months of year. After December 2010, acceleration data have also been collected with ECG data.The data collections will continue in the future, and >50 thousand 24-h ECG data are added annually. To our knowledge, there is no well-standardized database of continuous physiological signals of this size.

Studies from ALLSTAR project

Reference values for HRV indices: The analysis of HRV from24-h Holter ECG is widely used for delineating the diurnal variations of autonomic neural functions under daily activities(Hayano, 2016)and for predicting the risk of adverse cardiovascular events(Watanabe *et al.*, 2016)in patients after acute myocardial infarction(Bauer *et al.*, 2006; Bigger *et al.*, 1992; Hayano *et al.*, 2017a; Huikuri *et al.*, 2000; Kleiger *et al.*, 1987; Schmidt *et al.*, 1999), those with chronic heart failure(Hayano *et al.*, 2017a; Kiyono *et al.*, 2008), and hemodialysis patients with end-stage renal failure(Fukuta *et al.*, 2003; Hayano *et al.*, 2017a; Suzuki *et al.*, 2012). These parameters are not estimated reliablyby other methods(Dynamic electrocardiography, 2004; Camm *et al.*, 1996).HRV indices from Holter ECG, however, are known to show both large inter-individual differences(Stuckey *et al.*, 2014)and substantial intra-individual changes due presumably to day-to-day differences in physical activities and environmental factors(Buteau *et al.*, 2016; Huang *et al.*, 2015; Ren *et al.*, 2011). As the result, reliable reference values for the HRV indices are still lacking (Bauer *et al.*, 2017; Sammito *et al.*, 2016). The ALLSTAR database may be useful for resolving this situation(Hayano *et al.*, 2018a; Hayano *et al.*, 2017b; Yuda *et al.*, 2018). Fig. 3 is the results of a study(Hayano *et al.*, 2018a) reporting age-dependent changes in HRV indices in male and female subjects in the ALLSTAR database. Data were extracted uniformly for all ages from 0 to 100 yr old (100 subjects per 5-yr strata for each sex) from those with Holter ECG showing normal sinus rhythm for >80% of 24 h without ECG findings suggesting abnormal conduction or myocardial ischemia. The results indicated that the patterns of age dependency are not uniform but differ among HRV indices and that they are not linear, suggesting the necessity of nonlinear models for adjusting the effect of age in statistical analyses. The observed value of an HRV index during daily life, however, is the result that true reference value was modified by responses to stimuli that are determined by daily activities and responsiveness of HRV; all of which could be affected by age. To examine this hypothesis, the ALLSTAR database was analyzed for the relationship between individual basal heart rate (HR), minimum HR of the day, and 24-h average HR, assuming basal HR as individual reference HR(Hayano *et al.*, 2017b). As shown in Fig. 4, basal HR decreased until 20 yr and it increases slightly thereafter with advancing age in both sexes. The difference between 24-h mean and basal HR decreased linearly with advancing age. The averages of clock times to reach basal HR were observe between 02 and 05 h, although the distribution was wide for 0-4 yr and for over 80 yr old (Fig. 5). If basal HR can be assumed as individual reference HR, these observations indicate that age-dependent decline in 24-h mean HR after 20 yr is attributable to age-dependent decrease in HR responses to daily stimuli. Additionally a recent study(Yuda *et al.*, 2018) from the ALLSTAR project reported the time when basal HR occurs among subjects grouped by sleep time in the day. The study showed that the time of basal HR is affected by the time of sleep only slightly; basal HR occurred at 01:30, 02:35, and 03:18 for daytime, evening, and nighttime sleepers, respectively. Along with the widespread use of wearable sensors, the HR becomes available in real time and is often used as an index of physical and mental responses and stresses(Ho *et al.*, 2014; Khan *et al.*, 2015). Give the inter- and intra-individual differences in HR, individual reference value is required to interpret HR data appropriately. These studies from the ALLSATR project suggest that basal HR seems the most promising candidate for this purpose. Similar analyses seem desirable for each index of HRV.

Influences of physical activity (PA) on HRV: Increase in PA is an important life style modification for preventing cardiovascular diseases (Fletcher *et al.*, 1996; Thompson *et al.*, 2003), but PA itself is known to decrease HRV(Hayano *et al.*, 1994; Yamamoto *et al.*, 1991). Because high HRV is related to low mortality risk among cardiovascular patients (Kleiger *et al.*, 1987; Watanabe *et al.*, 2016), it is a paradox why both increased PA in daily life and increased 24-h HRV can be associated with low mortality risk. The simultaneous records of ECG and acceleration in the ALLSTAR database were perfect for answering this question. In 21,682 male and 29,446 female subjects with ECG and acceleration data, the relationships between the standard deviation of normal-to-normal R-R intervals during 24 h (SDNN) and PA levels during four time zones (daytime, evening, nighttime, and early morning) of the day were examined(Hayano *et al.*, 2018b). As shown in Table 1, SDNN was associated most strongly with daytime PA in both sexes after adjusting for the effect of age. This result suggests that the higher the level of daytime PA contributes to increase SDNN by increasing the contrast of R-R intervals between daytime and nighttime. Another paradox of HRV is the association between decreased low-frequency-to-high-frequency ratio (LF/HF) of HRV and increased mortality risk among cardiac patients. Because LF/HF has widely been used as an index of sympathetic predominance (Camm *et al.*, 1996; Malliani, 1999; Pagani *et al.*, 1986), its increase is expected to be associated with adverse prognosis in cardiovascular disease. But the fact is the opposite; decrease rather than increase in LF/HF is associated with increased risk of mortality in patients after acute myocardial infarction (Huikuri *et al.*, 2000; La Rovere *et al.*, 1998; Tsuji *et al.*, 1994)and those with end-stage renal disease(Suzuki *et al.*, 2012). This paradox was also resolved by a study of the ALLSTAR database, which revealed that the LF/HF of 24-h HRV is correlated negatively with the ratio of lying positions during the day(Yoshida *et al.*, 2016). This is because LF/HF increases with standing (Hayano, 2016; Hayano *et al.*, 2001; Pagani *et al.*, 1986) and thus, it tends to be low in patients who need to spent more time in lying positions.

Natural and socioeconomic environments: 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. As the elderly population rapidly advances, the reduction of the gap between HALE and the

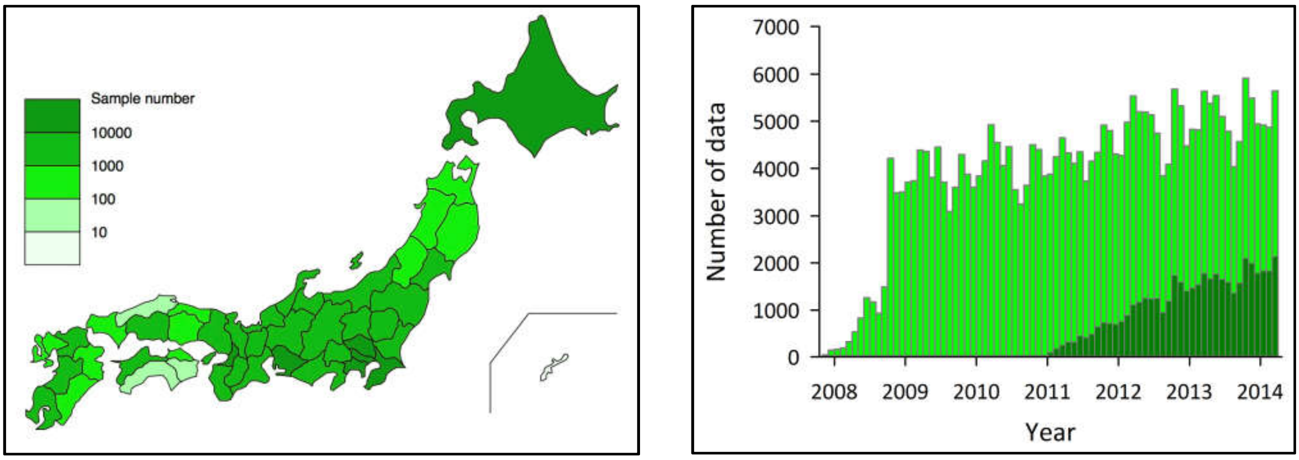
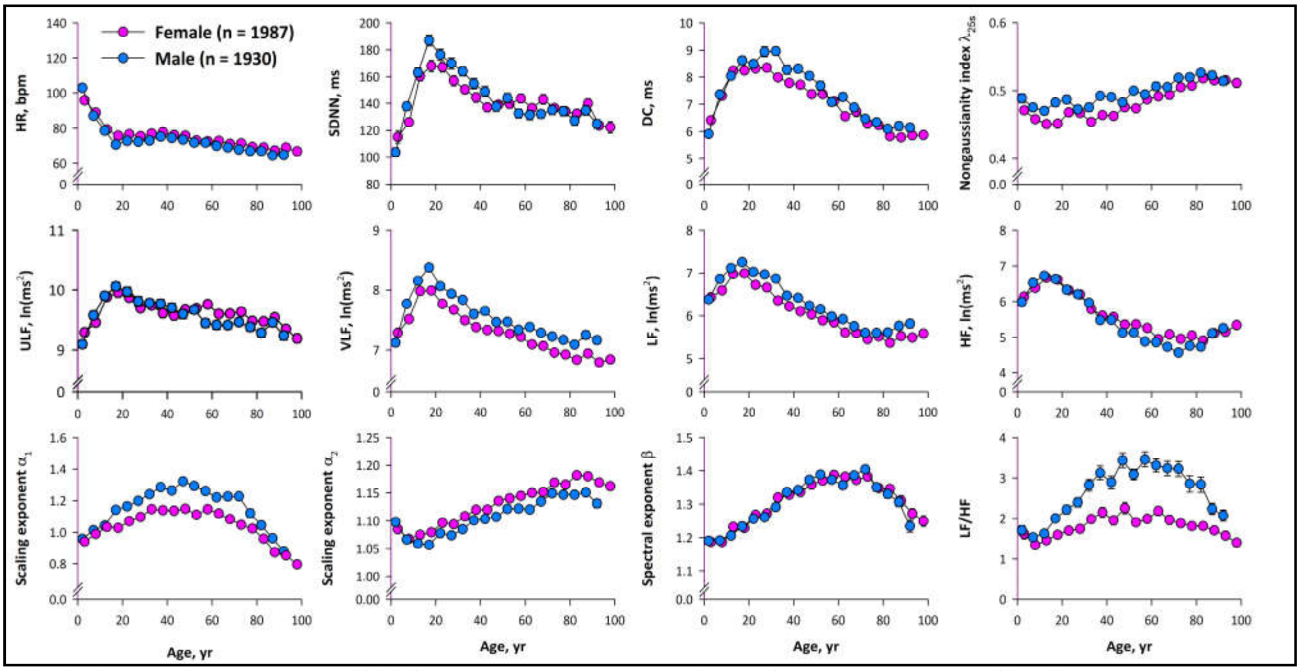


Fig. 2. Geographic and temporal distribution of ALLSTAR data



DC = deceleration capacity, HF = power of high frequency component, HR = 24 h mean heart rate, LF = power of low frequency component, SDNN = standard deviation of 24-h normal-to-normal (NN) R-R interval, ULF = power of ultra-low frequency component, VLF = power of very low frequency component.

Fig. 3. Age-dependent changes in HRV indices in samples extracted from the ALLSTAR database (From reference(Hayano *et al.*, 2018a))

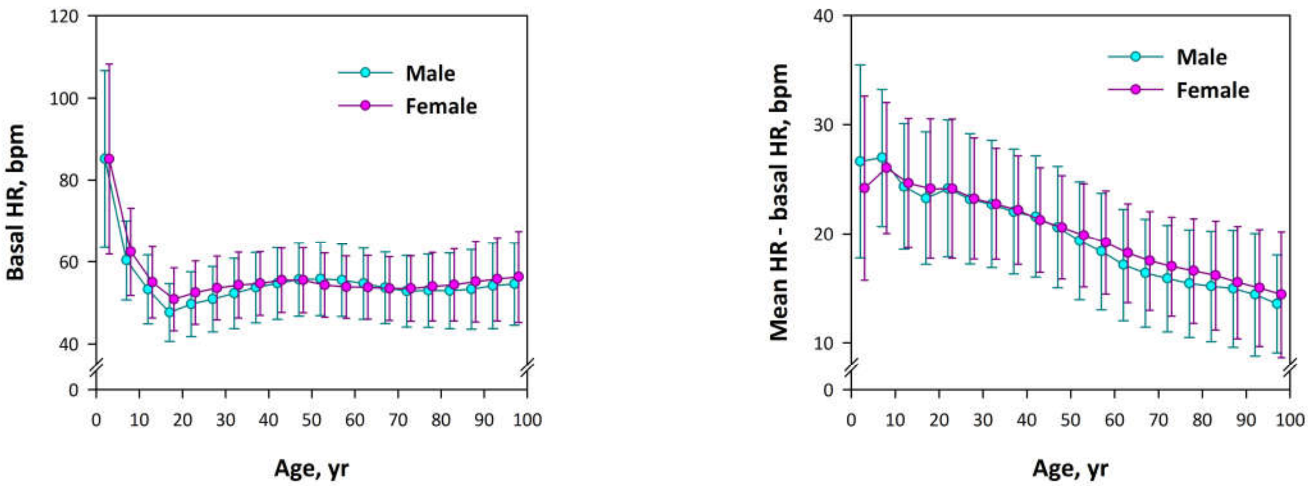


Fig. 4. Basal HR(left panel) and the difference of 24-h mean HR from the basal HR(right panel) in subjects with sinus rhythm (113,341 men and 140,332 women) from the ALLSTAR database (from reference(Hayano *et al.,* 2017b))

Table 1. Regression models of SDNN by age and physical activity (PA) in different time zones of the day

	Explained variance, %	Regression coefficient (SE)	F (5,1)	P
Male				
Age	0.57	−0.23 (0.02)	125.8	<.0001
PADT	7.63	1.49 (0.05)	861.7	<.0001
PAEV	0	0.05 (0.07)	0.5	0.4
PANT	0.24	−0.82 (0.11)	57.8	<.0001
PAEM	0.37	0.43 (0.04)	108.9	<.0001
Female				
Age	0.51	−0.22 (0.02)	191.7	<.0001
PADT	7.43	1.64 (0.05)	1057.9	<.0001
PAEV	0.05	−0.26 (0.07)	14.7	0.0001
PANT	0.51	−1.95 (0.14)	196.2	<.0001
PAEM	0.41	0.48 (0.04)	139.3	<.0001

PA_{DT}, PA_{EV}, PA_{NT}, and PA_{EM} indicate PA in daytime (09:00-17:00), evening (17:00-24:00), nighttime (00:00-06:00), and early morning (06:00-09:00), respectively (from reference(Hayano *et al*., 2018b)).

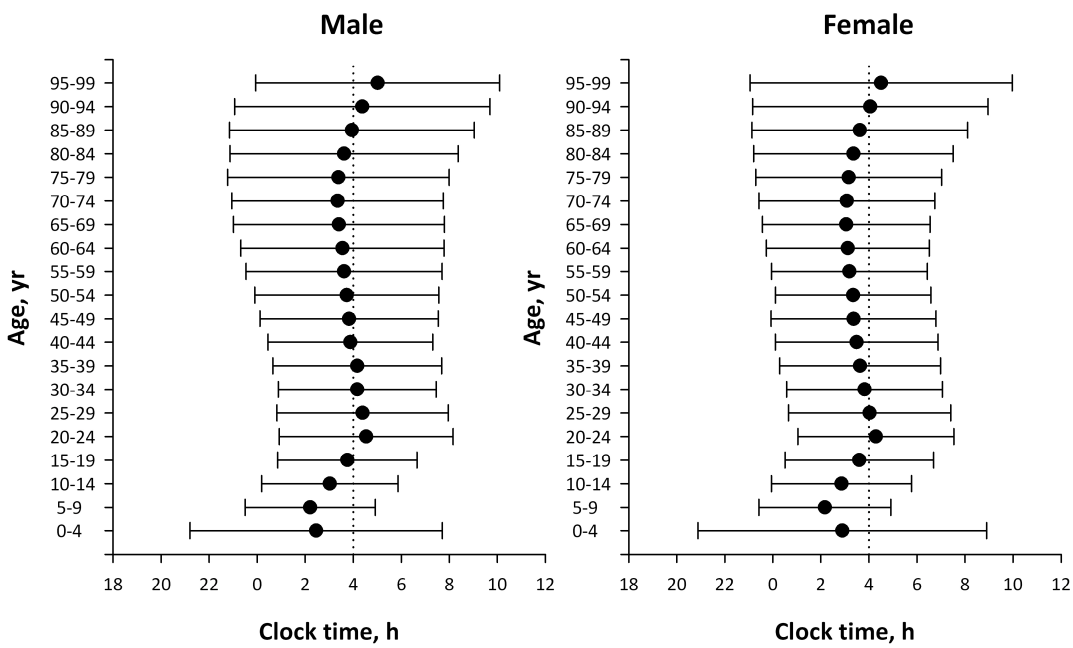


Fig.5. Distributions (mean and SD) of clock time to reach basal HR in subjects with sinus rhythm from the ALLSTAR database (from reference(Hayano *et al.*, 2017b))

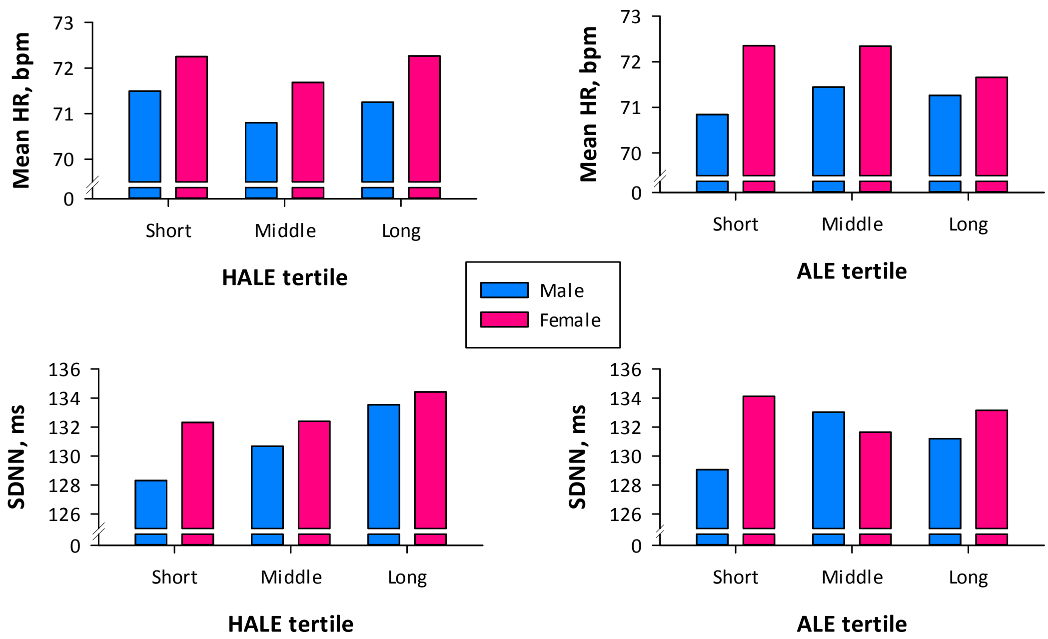


Fig. 6. Mean HR and SDNN in the tertiles of inter-prefecture rankings of healthy life expectancy (HALE) and average life expectancy (ALE) in each sex (from reference(Yuda *et al.*, 2017a))

average life expectancy (ALE) is an important change 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. The ALLSTAR database has been used for addressing this issue(Yuda *et al.*, 2017a; Yuda *et al.*, 2017c).While HALE of Japanese men and women are 71.19 and 74.21 yr, respectively (the Japanese Ministry of Health, Labour and Welfare, 2013), it differs among prefectures (differences between longest and shortest prefecture are 2.79 and 2.95 yr for men and women, respectively). This regional difference may provide a clue to explore the factors associated with the shortening of HALE. To examine this possibility, the reginal difference in HALE was compared with the regional difference in HRV indices using the data of subjects aged >20 yr with sinus rhythm in the ALLSATR database(Yuda *et al.*, 2017a). As shown in Fig. 6, SDNN increased progressively from short to long HALE areas for both sexes, while no consistent associations was observed between mean HR and HALE tertiles in either sex. Conversely, mean HR decreased progressively from short to long ALE areas in women, while mean HR in men and SDNN in both sexes showed no consistent association with ALE 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. Finally, the ALLSTAR database was also combined with meteorological database in a study examining the effect of sunshine hours during the day on the circadian rhythm of HR(Yuda *et al.*, 2017c). Skylight is abundant of blue wavelength light which stimulates arousal functions through non-image-forming function of the eyes(Berson *et al.*, 2002; Yuda *et al.*, 2017b).The study revealed that longer sunshine hour increased daytime HR and day-night HR difference even after adjusting for the effects of average temperature, atmospheric pressure, and humidity, which supports the hypothesis that longer sunshine hours enhance circadian rhythm of HR.

Conclusion

Holter ECG is bio-signal monitoring during daily activities performed worldwide with well-standardized quality. To build a cumulative database of 24-h ECG and acceleration data, ALLSTAR project has started in Japan since 2007. The analyses of ALLSTAR database not only provide the reference values for dynamic ECG, particularly for HRV indices, but also revealed the underlying determinants of the variances in observed values. The database would provide information for the associations between the physiological measures under daily activities and anthropological and environmental parameters by being linked with other demographic, geographic, meteorological, and socioeconomic databases, which will increase the value of Holter ECG monitoring for health care and studies in a plenty of fields.

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Appendix

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Author Contributions: Conceived and designed the project: K. Kiyono, I. Kodama, Y. Yamamoto, and J. Hayano.Data security and ethical issues: K. Kiyono, I. Kodama, Y. Yamamoto, E. Yuda, and J. Hayano. Concepts on statistical processing: K. Kiyono, Y. Yamamoto, and J. Hayano. Management of the database: E. Yuda and J. Hayano.Analysis of the data: K. Kiyono, Y. Yamamoto, and J. Hayano. Wrote the paper: K. Kiyono and J. Hayano.

REFERENCES

Bauer, A., Camm, A.J., Cerutti, S., Guzik, P., Huikuri, H., Lombardi, F., Malik, M., Peng, C.K., Porta, A., Sassi, R., Schmidt, G., Schwartz, P.J., Stein, P.K., andYamamoto, Y. Reference values of heart rate variability. *Heart rhythm : the official journal of the Heart Rhythm Society*, 2017; 14: 302-303.

Bauer, A., Kantelhardt, J.W., Barthel, P., Schneider, R., Makikallio, T., Ulm, K., Hnatkova, K., Schomig, A., Huikuri, H., Bunde, A., Malik, M., andSchmidt, G. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. *Lancet*, 2006; 367: 1674-1681.

Berson, D.M., Dunn, F.A., andTakao, M. Phototransduction by retinal ganglion cells that set the circadian clock. *Science*, 2002; 295: 1070-1073.

Bigger, J.T., Jr., Fleiss, J.L., Steinman, R.C., Rolnitzky, L.M., Kleiger, R.E., andRottman, J.N. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation*, 1992; 85: 164-171.

Buteau, S., andGoldberg, M.S. A structured review of panel studies used to investigate associations between ambient air pollution and heart rate variability. *Environ. Res.*, 2016; 148: 207-247.

Camm, A.J., Malik, M., Bigger, J.T., Jr., Breithardt, G., Cerutti, S., Cohen, R.J., Coumel, P., Fallen, E.L., Kleiger, R.E., Lombardi, F., Malliani, A., Moss, A.J., Rottman, J.N., Schmidt, G., Schwartz, P.J., andSinger, D.H. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation*, 1996; 93: 1043-1065.

Dinov, I.D. Volume and Value of Big Healthcare Data. *Journal of medical statistics and informatics*, 2016; 4.

Dynamic electrocardiography. Wiley-Blackwell, New York, 2004.

Fletcher, G.F., Balady, G., Blair, S.N., Blumenthal, J., Caspersen, C., Chaitman, B., Epstein, S., Sivarajan Froelicher, E.S., Froelicher, V.F., Pina, I.L., andPollock, M.L. Statement on exercise: benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation*, 1996; 94: 857-862.

Fukuta, H., Hayano, J., Ishihara, S., Sakata, S., Ohte, N., Takahashi, H., Yokoya, M., Toriyama, T., Kawahara, H., Yajima, K., Kobayashi, K., andKimura, G. Prognostic value of nonlinear heart rate dynamics in hemodialysis patients with coronary artery disease. *Kidney Int.*, 2003; 64: 641-648.

Hayano, J. Introduction to heart rate variability. In: Iwase, S., Hayano, J., Orimo, S., (Eds.), Clinical assessment of the autonomic nervous system. Springer, Japan. 2016. pp. 109-127.

Hayano, J., Mukai, S., Fukuta, H., Sakata, S., Ohte, N., andKimura, G. Postural response of low-frequency component of heart rate variability is an increased risk for mortality in patients with coronary artery disease. *Chest*, 2001; 120: 1942-1952.

Hayano, J., Ohashi, K., Yoshida, Y., Yuda, E., Nakamura, T., Kiyono, K., andYamamoto, Y. Increase in random component of heart rate variability coinciding with developmental and degenerative stages of life. *Physiol. Meas.*, 2018a; 39: 054004.

Hayano, J., Taylor, J.A., Mukai, S., Okada, A., Watanabe, Y., Takata, K., andFujinami, T. Assessment of frequency shifts in R-R interval variability and respiration with complex demodulation. *J. Appl. Physiol.*, 1994; 77: 2879-2888.

Hayano, J., Yasuma, F., Watanabe, E., Carney, R.M., Stein, P.K., Blumenthal, J.A., Arsenos, P., Gatzoulis, K.A., Takahashi, H., Ishii, H., Kiyono, K., Yamamoto, Y., Yoshida, Y., Yuda, E., andKodama, I. Blunted cyclic variation of heart rate predicts mortality risk in post-myocardial infarction, end-stage renal disease, and chronic heart failure patients. *Europace*, 2017a; 19: 1392-1400.

Hayano, J., Yoshida, Y., andYuda, E. 2017b. Characteristics of basal heart rate during daily life: Relationships with age, gender, and mean heart rate, The 11th EAI International Conference on Pervasive Computing Technologies for Healthcare (PervasiveHealth 2017), Barcelona, Spain.

Hayano, J., Yuda, E., Furukawa, Y., andYoshida, Y. Association of 24-hour heart rate variability and daytime physical activity: ALLSTAR big data analysis. *International Journal of Bioscience, Biochemistry and Bioinformatics*, 2018b; 8: 61-67.

Ho, J.E., Larson, M.G., Ghorbani, A., Cheng, S., Coglianese, E.E., Vasan, R.S., andWang, T.J. Long-term cardiovascular risks associated with an elevated heart rate: the Framingham Heart Study. *Journal of the American Heart Association*, 2014; 3: e000668.

Huang, W.L., Hwang, B.T., Lai, C.T., Li, J.Y., Kuo, T.B., andYang, C.C. Is Heart Rate Variability Related to Season of Birth? *Clin. Cardiol.*, 2015; 38: 407-412.

Huikuri, H.V., Mäkikallio, T.H., Peng, C.K., Goldberger, A.L., Hintze, U., Moller, M., andGrp, D.S. Fractal correlation properties of R-R interval dynamics and mortality in patients with depressed left ventricular function after an acute myocardial infarction. *Circulation*, 2000; 101: 47-53.

Khan, H., Kunutsor, S., Kalogeropoulos, A.P., Georgiopoulou, V.V., Newman, A.B., Harris, T.B., Bibbins-Domingo, K., Kauhanen, J., Gheorghiade, M., Fonarow, G.C., Kritchevsky, S.B., Laukkanen, J.A., andButler, J. Resting heart rate and risk of incident heart failure: three prospective cohort studies and a systematic meta-analysis. *Journal of the American Heart Association*, 2015; 4: e001364.

Kiyono, K., Hayano, J., Watanabe, E., Struzik, Z.R., andYamamoto, Y. Non-Gaussian heart rate as an independent predictor of mortality in patients with chronic heart failure. *Heart Rhythm.*, 2008; 5: 261-268.

Kiyono, K., Hayano, J., Watanabe, E., andYamamoto, Y. Heart rate variability (HRV) and sympathetic nerve activity. In: Iwase, S., Hayano, J., Orimo, S., (Eds.), Clinical assessment of the autonomic nervous system. Springer, Japan. 2016. pp. 147-161.

Kleiger, R.E., Miller, J.P., Bigger, J.T., Jr., Moss, A.J., andthe Multicenter Post-Infarction Research, G. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am. J. Cardiol.*, 1987; 59: 256-262.

La Rovere, M.T., Bigger, J.T., Jr., Marcus, F.I., Mortara, A., Schwartz, P.J., andInvestigators, A. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. *Lancet*, 1998; 351: 478-484.

Malliani, A. The Pattern of Sympathovagal Balance Explored in the Frequency Domain. *News in physiological sciences : an international journal of physiology produced jointly by the International Union of Physiological Sciences and the American Physiological Society*, 1999; 14: 111-117.

Pagani, M., Lombardi, F., Guzzetti, S., Rimoldi, O., Furlan, R., Pizzinelli, P., Sandrone, G., Malfatto, G., Dell'Orto, S., Piccaluga, E., Turiel, M., Baselli, G., Cerutti, S., andMalliani, A. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circul. Res.*, 1986; 59: 178-193.

Ren, C., O'Neill, M.S., Park, S.K., Sparrow, D., Vokonas, P., andSchwartz, J. Ambient temperature, air pollution, and heart rate variability in an aging population. *Am. J. Epidemiol.*, 2011; 173: 1013-1021.

Romero, I. Ambulatory electrocardiology. *Cardiol. Rev.*, 2013; 21: 239-248.

Sammito, S., andBockelmann, I. Reference values for time- and frequency-domain heart rate variability measures. *Heart rhythm : the official journal of the Heart Rhythm Society*, 2016; 13: 1309-1316.

Schmidt, G., Malik, M., Barthel, P., Schneider, R., Ulm, K., Rolnitzky, L., Camm, A.J., Bigger, J.T., Jr., andSchomig, A. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. *Lancet*, 1999; 353: 1390-1396.

Stuckey, M.I., Tulppo, M.P., Kiviniemi, A.M., andPetrella, R.J. Heart rate variability and the metabolic syndrome: a systematic review of the literature. *Diabetes. Metab. Res. Rev.*, 2014; 30: 784-793.

Suzuki, M., Hiroshi, T., Aoyama, T., Tanaka, M., Ishii, H., Kisohara, M., Iizuka, N., Murohara, T., andHayano, J. Nonlinear Measures of Heart Rate Variability and Mortality Risk in Hemodialysis Patients. *Clin J Am Soc Nephrol*, 2012; 7: 1454-1460.

Thompson, P.D., Buchner, D., Pina, I.L., Balady, G.J., Williams, M.A., Marcus, B.H., *et al.*Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on

Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). *Circulation*, 2003; 107: 3109-3116.

Toga, A.W., Foster, I., Kesselman, C., Madduri, R., Chard, K., Deutsch, E.W., Price, N.D., Glusman, G., Heavner, B.D., Dinov, I.D., Ames, J., Van Horn, J., Kramer, R., andHood, L. Big biomedical data as the key resource for discovery science. *J. Am. Med. Inform. Assoc.*, 2015; 22: 1126-1131.

Tsuji, H., Venditti, F.J., Jr., Manders, E.S., Evans, J.C., Larson, M.G., Feldman, C.L., andLevy, D. Reduced heart rate variability and mortality risk in an elderly cohort: The Framingham Heart Study. *Circulation*, 1994; 90: 878-883.

Watanabe, E., Kiyono, K., Yamamoto, Y., andHayano, J. Heart rate variability and cardiac diseases. In: Iwase, S., Hayano, J., Orimo, S., (Eds.), Clinical assessment of the autonomic nervous system. Springer, Japan. 2016. pp. 163-178.

Yamamoto, Y., Hughson, R.L., andPeterson, J.C. Autonomic control of heart rate during exercise studied by heart rate variability spectral analysis. *J. Appl. Physiol.*, 1991; 71: 1136-1142.

Yoshida, Y., Furukawa, Y., Ogasawara, H., Yuda, E., andHayano, J. 2016. Longer lying position causes lower LF/HF of heart rate variability during ambulatory monitoring, 2016 IEEE 5th Global Conference on Consumer Electronics (GCCE), Kyoto, Japan.

Yuda, E., Furukawa, Y., Yoshida, Y., Hayano, J., andinvestigators, A.p. Association between regional difference in heart rate variability and inter-prefecture ranking of healthy life expectancy: ALLSTAR Big Data Project in Japan. In: Jung, J.J., Kim, P., (Eds.), Big Data Technologies and Applications: Proceedings of the 7th EAI International Conference, BDTA 2016. Springer Nature, Seoul, Korea. 2017a. pp. 23-28.

Yuda, E., Ogasawara, H., Yoshida, Y., andHayano, J. Enhancement of autonomic and psychomotor arousal by exposures to blue wavelength light: importance of both absolute and relative contents of melanopic component. *Journal of physiological anthropology*, 2017b; 36: 13.

Yuda, E., Yoshida, Y., andHayano, J. 2017c. Longer sunshine hours enhances heart rate circadian rhythm: Analysis of ambulatory ECG and weather big data, 19th International Conference on Chemistry, Biomedical and Environment Engineering (ICCBEE 2017), Osaka, Japan.

Yuda, E., Yoshida, Y., andHayano, J. Impacts of sleeping time during the day on the timing and level of basal heart rate: Analysis of ALLSTAR big data. *Wireless Network*, 2018: 1-5.

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