Eur J Appl Physiol (2005) 94: 602–610
DOI 10.1007/s00421-005-1364-x

ORIGINAL ARTICLE

Masari Amano · Eiichi Oida · Toshio Moritani

Age-associated alteration of sympatho-vagal balance in a female population assessed through the tone–entropy analysis

Accepted: 14 March 2005 / Published online: 8 June 2005

Abstract Through our recent studies on heart rate variability (Oida et al. J Appl Physiol 82:1794–1801, 1997; J Gerontol 54A:M219–M224, 1999a; Acta Physiol Scand 165:129–134, 1999b; Acta Physiol Scand 165:421–422, 1999c), we discover that autonomic functions could be assessed quantitatively in time domain by the *tone–entropy* (T–E) methodology, where the *tone* represents sympatho-vagal balance, and the *entropy*, autonomic regulatory activity. The purpose of this study was then to elucidate an age-associated alteration of sympatho-vagal balance in a female population through this T–E method. ECG R–R time intervals at rest were acquired on 10 min for 73 female subjects. Ageing influence was examined by comparisons between two groups: middle-aged group (40–50), (51.5 ± 0.7 year, $n = 28$) and old-aged (60–70), (69.5 ± 0.8 year, $n = 45$)]. Evaluated *tone*: [-0.058 ± 0.011 (40–50), and 0.027 ± 0.003 (60–70) ($P < 0.01$)], and *entropy*: [3.46 ± 0.11 (40–50), and 3.06 ± 0.08 bit (60–70) ($P < 0.01$)]. The result showed that the *tone* was high and the *entropy* was low in the old-aged compared with the middle-aged group. When the result was plotted in two-dimensional T–E space, it revealed a curvi–linear relation between the *tone* and the *entropy*, consistent with our previous studies on pharmacological blockades, on heart recovery after dynamic exercise and on a male ageing. In conclusion, the result suggested that the sympatho-vagal balance altered or the vagal predominance was impaired with age significantly in this female population. Interestingly, comparing with corresponding male, the female had better autonomic functions.

Keywords Autonomic nervous system · Heart rate variability · Spectral analysis

M. Amano · T. Moritani (✉)
Laboratory of Applied Physiology, Graduate School of Human and Environmental Studies, Kyoto University,
Sakyo-ku, Kyoto 6068501, Japan
E-mail: moritani@virgo.jinkan.kyoto-u.ac.jp
Tel.: +81-75-7536888
Fax: +81-75-7536888

E. Oida
Department of Preventive Medicine,
Clinical Research Institute,
National Hospital Organization Kyoto Medical Center,
Kyoto 6128555, Japan

Introduction

Ageing alters cardio–vascular systems significantly. Alterations not only concern the histological structures, but also the neural regulatory systems (Folkow and Svanborg 1993). Interestingly, recent advances in measuring technology made it possible to detect the neural regulation mechanisms non-invasively. Spectral analysis applied on heart rate variability (HRV) showed a possibility to trace each autonomic pathway's activity separately, and defined the autonomic sympatho-vagal balance by a ratio between powers in frequency domain (Task Force 1996). Then, a number of attempts have been or are being carried out to assess age-associated alterations of autonomic balance through the spectral analysis. However, notwithstanding almost decades of investigation, no agreement was achieved on the alteration of the autonomic balance to date. Some showed that the balance declined with age (Schwartz et al. 1991; Ryan et al. 1994; Piccirillo et al. 1998; Kuo et al. 1999), but others insisted that the balance did not correlate with age (Jensen-Urstad et al. 1997; Ramaekers et al. 1998). In addition to this inconsistency, recently a controversy arose on the validity of the spectral index itself (Eckberg 1997; Goldberger 1999; Malpas 2002). As a matter of fact, the defined spectral index showed a reasonable transition for a body posture change (Montano et al. 1994; Task Force 1996), but failed to trace for other physiological situations such as pharmacological blockade (Højgaard et al. 1998; Houle and Billman 1999), dynamic exercise (Casadei et al. 1995) or animal experiments (Hedman et al. 1995).

We started our investigation on HRV from another point of view. We focused our attention on the beat-to-beat successive variations of heart period (instantaneous R–R intervals) in time domain, and evaluated the variations in a new algorithm, where HRV characteristics were defined through two indices, the *tone* and the *entropy*. The *entropy* was introduced to improve the conventional standard variation used in time domain analyses, because standard variation was used sometimes without rigidly defined statistical basis (Task Force 1996). The information *entropy* was introduced and defined by Shannon (1948), whereby, we defined the heart period variations neither depending on baseline heart rates nor on measurement time period (see Methods). However, in the course of this construction process, it was noticed that the first-order moment of heart period variations, insignificant in usual time domain analyses, has the significance: it reflects also autonomic conditions. The moment became high for sympathetic stimulated conditions, and low for parasympathetic enhanced conditions (Oida et al. 1997, 1999a, 1999b, 1999c). Then, we named it the *tone*.

The purpose of this study was to elucidate an age-associated alteration of sympatho-vagal balance in a female population through this *tone–entropy* (T–E) analysis. Seventy-three female subjects were studied from forties to seventies. Influence of age was examined by classifying the population into two age groups, middle- and old-aged one. Physiological implications of acquired *tone* and *entropy* were examined by comparing with our previous studies on typical physiological situations, pharmacological blockades and recovery after dynamic exercise (Oida et al. 1997, 1999a). A gender difference was also examined by a comparison with our previous study on a male population (Oida et al. 1999a). Conventional frequency domain analysis was also done for a reference.

Methods

Subjects

Seventy-three female volunteers participated in this study. Subjects under treatment of oral hypotensive agents or hormone replacements were ineligible. Subjects who had frequent ectopic beats were also ineligible. The participants were requested to abstain from foods and beverages in the night and morning before the experiment. They underwent a medical examination comprising physical status and blood chemistry preceding inclusion. All the subjects gave the written informed consent before the experiment. The study protocol was approved by the Ethics Committee of Kyoto University Graduate School of Human and Environmental Studies, and of Foundation Kyoto Preventive Medical Center where the data acquisition was carried out.

Experimental design

All data acquisitions were performed in the morning. The subject sat on a comfortable chair, and was given enough time relax. No instruction was given regarding respiration. An ECG signal was recorded for every 10 min by bipolar electrodes positioned at CM5. The signal was digitized by an analog-to-digital converter at a sampling rate of 1 kHz, and was simultaneously transformed into heart period time series on-line through the computer software developed in our laboratory. Detection of ECG R-wave peak was performed in a precision of 1 ms under an inspection on a computer display.

Tone-entropy method

The methodology was described in detail in the previous reports (Oida et al. 1997, 1999a, 1999b, 1999c). In brief, acquired heart periods (ECG R-R intervals) are transformed into percentage index (PI) time series:

$$\mathrm{PI}(n) = [H(n) - H(n+1)] \bullet 100/H(n) \quad \text{(non-dimensional)} \tag{1}$$

where $H(n)$ is a heart period time series, and n a serial number of beats. The *tone* is defined as a first-order moment (or arithmetic average) of this PI time series as

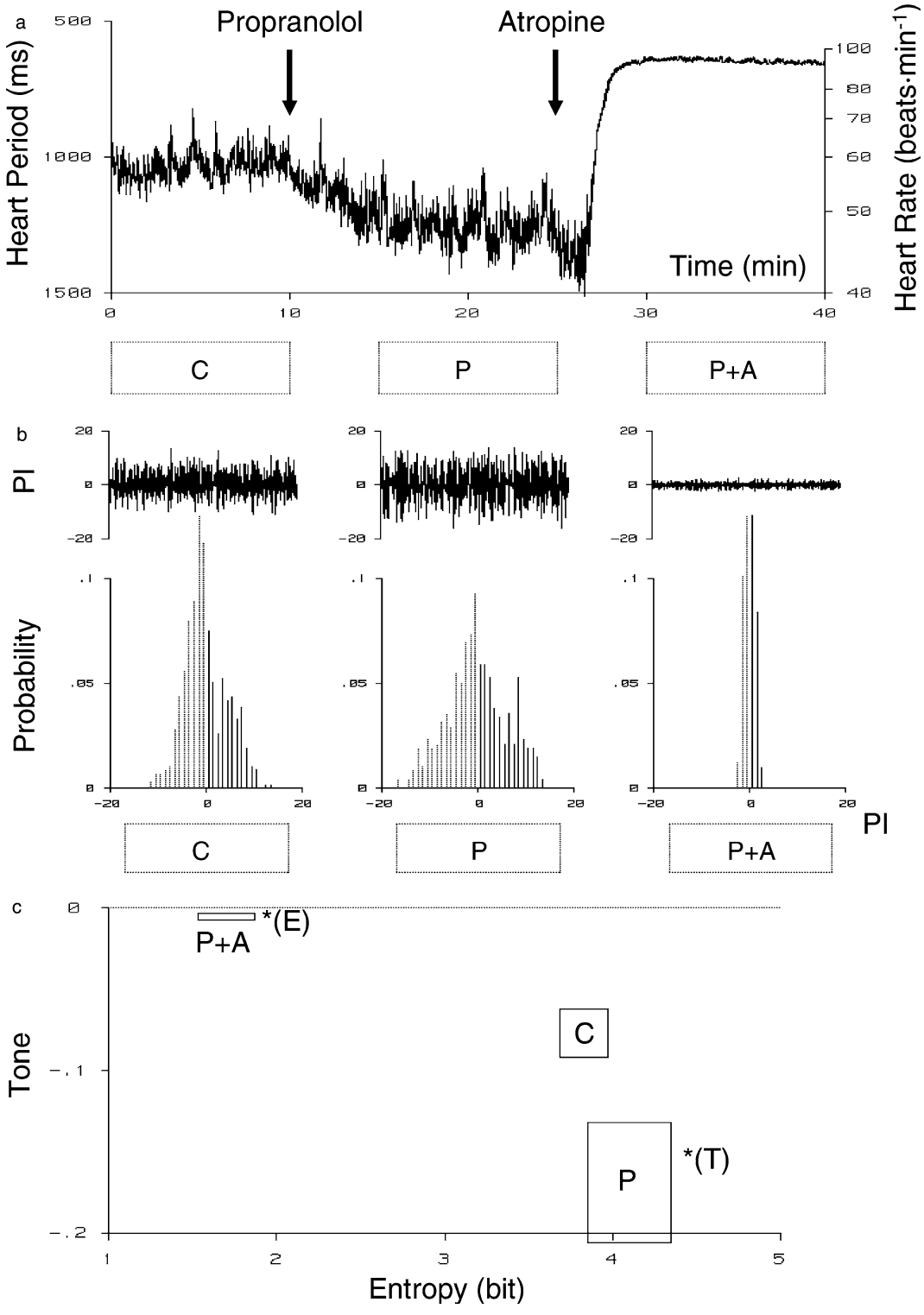
$$\sum_n \mathrm{PI}(n)/N \quad \text{(non-dimensional)} \tag{2}$$

where N is a total number of PI terms. The *tone* represents the balance between accelerations (decrease of heart period) and inhibitions (increase of heart period) of the heart, because positive PI reflects instantaneous accelerations and negative PI instantaneous inhibition of the heart, respectively. At first sight, one might consider that the *tone* is to be zero for stable heart rate process. However, the actual *tone* is not zero, rather reflects the sympto-vagal balance faithfully as seen in the following.

The *entropy* was defined on PI distribution by using Shannon's formula (Shannon 1948):

$$-\sum_i P(i) \log_2 P(i) \quad \text{(bit)} \tag{3}$$

where $[P(i)]$ is a probability that $\mathrm{PI}(n)$ has a value in the range $i \leq \mathrm{PI}(n) < i+1$, i an integer. It has been verified that the *entropy* gave almost the same results as conventional variance parameters e.g., standard deviation (unpublished). Then as a logical consequence (from mathematic deduction), the *entropy* is equivalent to the total power in frequency domain. The superiority of the *entropy* compare to conventional indices would be: (1) differences of baseline heart rate have no influence on the evaluation because of PI normalisation, (2) measurement time ranges have no influence because of probability distribution, and (3) deduction process has



no ambiguities such as limiting process used in other entropy assessment (Elbert et al. 1994).

To clarify the fundamental nature of the *tone* and the *entropy*, here we show a typical case of pharmacological blockade experiment [n = 8; all were male aged 31 ± 4 (SE) year], (Oida et al. 1999a). Figure 1a illustrates a time course of heart periods of a subject in the experiment. Autonomic blockade agents were intravenously injected with (at the time positions indicated in the figure:) propranolol (0.2 mg kg^{-1}) and atropine (0.04 mg kg^{-1}). The following considerations were given for three typical autonomic conditions (10 min) of control (C), after propranolol (P), and after additional blockade by atropine (P + A). Figure 1b illustrates PI

◀

Fig. 1 Pharmacological blockade experiment. In **a**, typical time course of heart period and its successive difference was shown. Autonomic block agents were intravenously injected at the time positions indicated as propranolol (0.2 mg kg^{-1}), and atropine (0.04 mg kg^{-1}). Analyses were done for time periods (10 min of duration) designated as C, control, as P, after propranolol, and as P + A, after additional blockade by atropine. In **b**, PI time series and their probability distributions for three-time periods were shown. In **c**, the derived *tone* and *entropy* was shown in T–E space. *Open rectangles* show mean ± SE. Statistical significance was shown only for a comparison to *C* *T for the *tone*; *E for the *entropy*, $P < 0.05$

time series (*top*) and their distributions in histogram (*bottom trace*) for C, P, and P + A. Figure 1c represents the ensemble averaged *tone* and *entropy* in two-dimensional T–E space. At the C, the *tone* was -0.077 ± 0.015, and the *entropy*, 3.83 ± 0.14 bit. The beta-adrenergic blockade by P decreased the *tone* significantly to -0.169 ± 0.037, and increased the *entropy* slightly to 4.10 ± 0.25 bit. The additional cholinergic blockade by atropine (P + A) made the *tone* almost zero to -0.005 ± 0.002 and the *entropy* reduced almost to the minimum value 1.70 ± 0.17 bit.

The results first suggested a possibility that the *tone* reflects the sympatho-vagal balance quantitatively. There is no doubt that the negativity of the *tone* was due to autonomic nervous activities in both pathways, because its negativity annihilated for the double blockade condition (Fig. 1, P + A). It is of interest that the negativity was intensified for a sympathetic blockade (Fig. 1, P), a reduction in sympathetic activity or a relative enhancement of para-sympathetic activity made the *tone* decreased significantly, and an additional parasympathetic blockade by atropine made the *tone* increased. These findings suggested that the negativity might be an expression of a vagal predominance in autonomic systems. Second, the result showed that the *entropy* represents the autonomic regulatory activity. It became almost minimum value for the double blockade condition, i.e., the *entropy* became almost a minimum for complete autonomic blockades. It is to be remarked that the obtained *entropy* value in control resting (C) was about 4 bit (Fig. 1c). One should pay attention whether this *entropy* value is adequate or not in what follows.

Spectral analysis

The used methodology was described in detail in our previous report (Oida et al. 1997). In brief, ECG R–R interval time series was sampled off-line at 1 Hz for folded heart periods (Rompelman et al. 1977) on the same data used in the above T–E method. Fast Fourier transformation (1,024 points, ~8.5 min) was performed after a linear trend elimination and Hamming window processing. Spectral powers were evaluated according to the *consent document* (Task Force 1996), low frequency power (LF) on the range of 0.04–0.15 Hz, high frequency power (HF) on the range of 0.15–0.4 Hz, and total power (TP) as sum of LF and HF. A representative index of autonomic balance, a ratio of LF to HF (LF/HF) was also calculated from these LF and HF. The LE and HE power were calculated in normalised units as well, LF NU by LF/TP×100, HF NU by HF/TP×100, respectively.

Statistics

Data were expressed as means ± SE. Unpaired *t* test was carried out for comparison between two groups.

Results

Influence of age was examined in classifying the studied population into two age groups: middle-aged of 40–59 years (40–50) ($n = 28$), and old-aged of 60–79 years (60–70) ($n = 45$). As for clinical conditions, no significant differences were found between the two age groups (Table 1).

Figure 2 illustrates typical heart period time series selected in each age group, 40–50 in (a) and 60–70 in (b). No significant difference is found in the ensemble averaged heart period between two groups: [922 ± 21 (66 ± 1) (40–50), and 931 ± 18 ms (66 ± 1 beats min^{-1}) (60–70) ($P > 0.05$)].

Figure 3 illustrates PI time series (*top*) and their histograms (*bottom traces*) derived from the data shown in Fig. 2. Differences in HRV characteristics came out explicitly in PI ranges and in distribution forms. PI range was larger in 40–50 (a) than in 60–70 (b). The distribution form was wider for 40–50 than for 60–70.

Figure 4 shows derived *tone* and *entropy* values in two-dimensional co-ordinate system of T–E space,

Table 1 Clinical characteristics

	40–50 ($n = 28$)	60–70 ($n = 45$)
Age (year)	51.5 ± 0.7	69.5 ± 0.8**
Height (m)	1.54 ± 0.01	1.52 ± 0.01*
Body mass (kg)	55.9 ± 2.1	54.0 ± 1.3
Body mass index (kg m^{-2})	23.2 ± 0.8	23.1 ± 0.5
SBP (mmHg)	122 ± 4	127 ± 2
DBP (mmHg)	71 ± 2	69 ± 1
Fasting blood sugar (mg dl^{-1})	135 ± 9	127 ± 5
HbA1c (%)	6.4 ± 0.4	6.4 ± 0.2
Total cholesterol (mg dl^{-1})	215 ± 6	208 ± 4
HDL cholesterol (mg dl^{-1})	68 ± 3	67 ± 2
Triglycerides (mg dl^{-1})	111 ± 18	112 ± 7

(1) 40–50 group; eight females were pre-menopause, four females were peri-menopause, who had had their last menstrual period between 3 months and 6 months prior to the study, 16 females were post-menopause, who had had no menstruation for 12 months. (2) 60–70 group; all individuals in old-aged group were post-menopause

Values are as means ± SE

SBP systolic blood pressure; *DBP* diastolic blood pressure; *HDL* high density lipoprotein

*$P < 0.05$, **$P < 0.01$

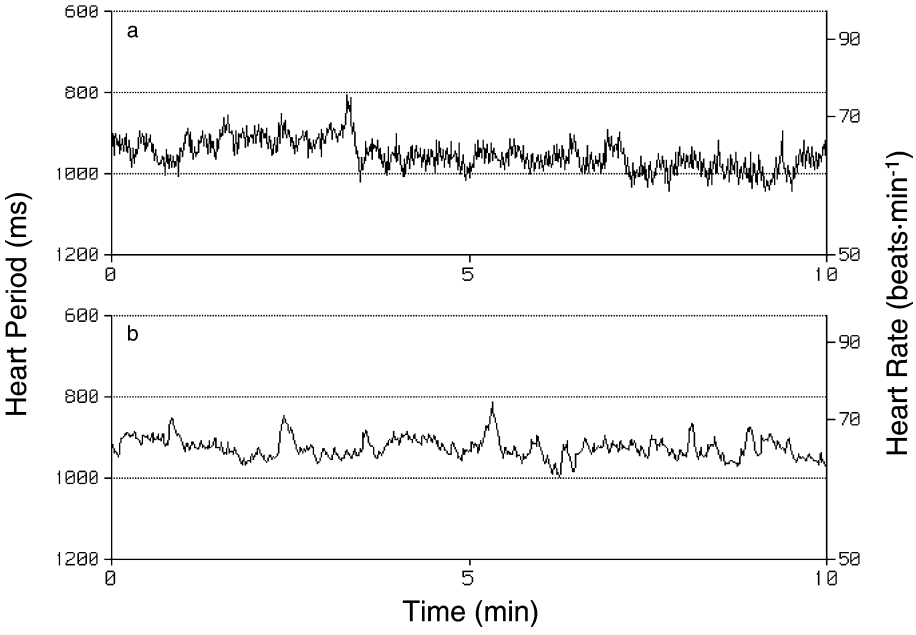


Fig. 2 Typical heart period time series selected in two age groups, 40–50 in **a**, and 60–70 in **b**

ensemble averaged with open rectangles (averages ± SE), and individual values with dot-plots. The *tone* was significantly lower in the middle-aged than in the old-aged group: [-0.058 ± 0.011 (40–50), and -0.027 ± 0.003 (60–70) ($P < 0.01$)]. The *entropy* was significantly higher in the middle-aged than in the old-aged group: [3.46 ± 0.11 (40–50), and 3.06 ± 0.08 bit (60–70) ($P < 0.01$)]. As a result, two age groups were located in T-E space at definitely separate positions: old-aged on *left-top*, and middle-aged on *right-bottom*. Interestingly, individual values were scattered forming a curvi–linear relation in T–E space, a physiological meaning of which would be appreciated in the next figures.

Figure 5 shows the present result together with the pharmacological blockade experiment shown in Methods. Two age groups were found at intermediates on the curvi–linear route from C to P + A: middle-aged group (40–50) at *left* to C, and old aged-group (60–70) at *right* to P + A.

Figure 6 shows the present result superimposed on our previous result in a heart recovery experiment (Oida et al. 1997). In this experiment, an exercise (Ex) was performed for 30 min on a bicycle ergometer at ventilatory threshold level by 12 female athletes (21 ± 0.8 year). Its recovery was observed for 70 min, in which the *tone* and the *entropy* were evaluated at three time points, at 10 min (R1), at 35 min (R2), and at

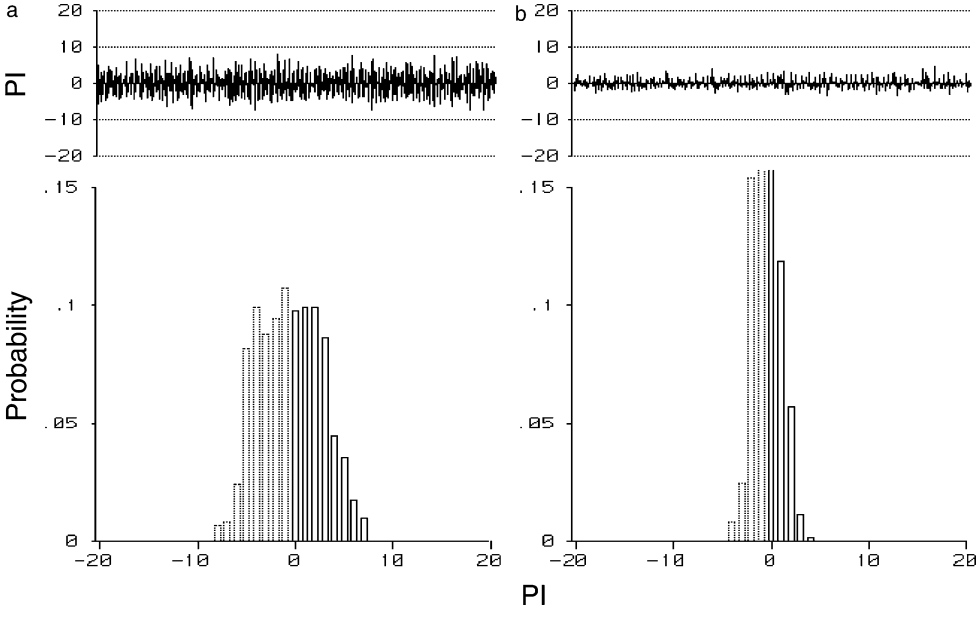


Fig. 3 PI time series (*top traces*) and their histograms (*bottom traces*) derived from the data shown in Fig. 2. *Dotted lines* represent PI < 0 in histograms

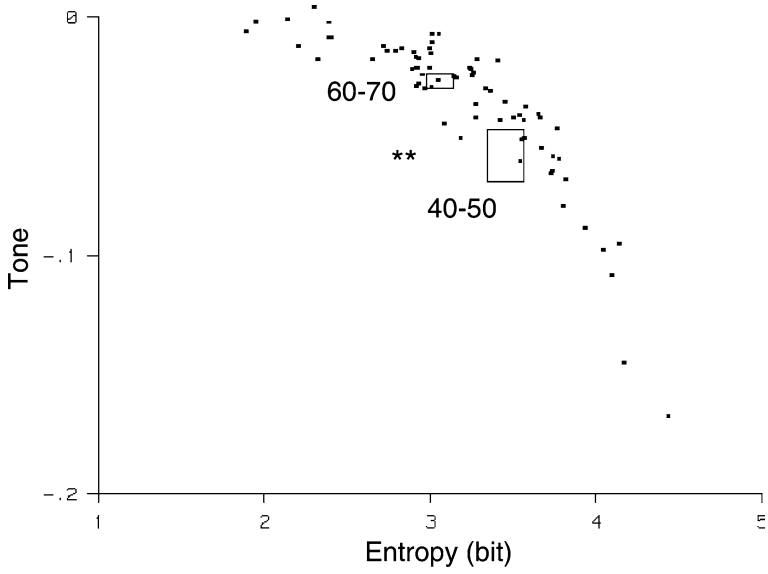


Fig. 4 Derived *tone* and *entropy* of the female population. *Open solid* rectangles show the ensemble averaged mean ± SE, and *dot plots*, the individual values. Statistical significance was shown between two groups: $^{**}P < 0.01$ for both the *tone* and the *entropy*

60 min (R3). It is of interest that the *tone* decreased and the *entropy* increased by degrees in the course of recovery in tracing the same curvi–linear route as the present ageing process from *left-top* to *right-bottom*, though the directions were mutually opposite. The ageing groups were found to be located on this recovery route, 40–50 in an intermediate between R1 and R2, and 60–70, between Ex and R1, respectively.

Figure 7 shows the present result together with a male ageing previously published (Oida et al. 1999a), where 142 male subjects were examined by a classification into four age groups, 30–39 (30, $n = 19$), 40–49 (40, $n = 47$), 50–59 (50, $n = 36$) and 60–69 years (60, $n = 40$) (designated in the figure by dotted open rectangles). This superimposition revealed that the female ageing process traced almost the same route as the preceding male route. It showed that female 40–50 corresponded to male 40, and female 60–70, to male 60. As a matter of fact, no significant difference was found between male and female corresponded groups both for the *tone* and for the *entropy* ($P > 0.05$). However, significant differences were found between corresponded groups not only in their age: [51.5 ± 0.7 (female 40–50) vs 45.1 ± 0.4 year (male 40) ($P < 0.01$); and 69.5 ± 0.8 (female 60–70) vs 63.5 ± 0.4 year (male 60) ($P < 0.01$)], but also their diabetic conditions, for example, HbA1c: [6.4 ± 0.4 (female 40–50) vs 5.7 ± 0.1 (male 50) ($P < 0.01$)]; and [6.4 ± 0.2 (female 60–70) vs 5.9 ± 0.1 (male 60) ($P < 0.01$)]. All showed that the female groups corresponded to younger and less diabetic male groups.

Table 2 shows spectral parameters derived on the same heart period data. In absolute unit, all parameters

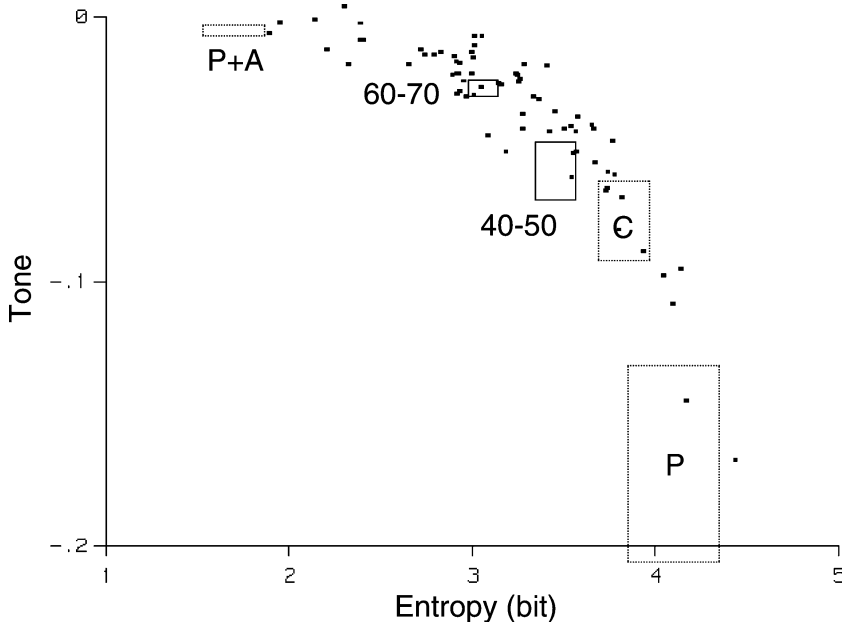


Fig. 5 Female ageing superimposed on the pharmacological blockade conditions. Abbreviations are the same as Fig. 2

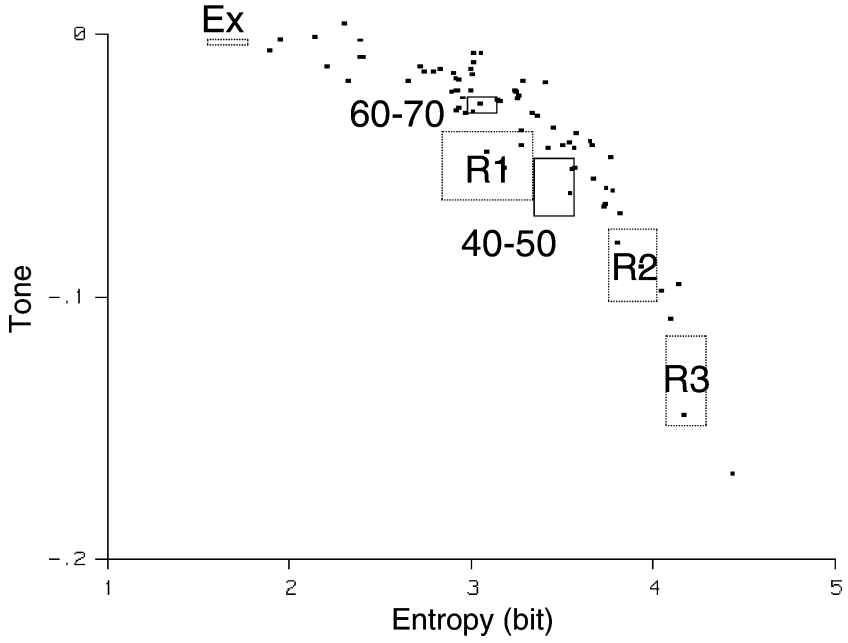


Fig. 6 Female ageing superimposed on a heart recovery process. Exercise (*Ex*) was performed for 30 min on a bicycle ergometer at the ventilatory threshold level by 12 female athletes (21 ± 0.8 year). Recovery after the exercise was observed for 70 min, in which the *tone* and the *entropy* were evaluated at three time points, at 10 min (R1), at 35 min (R2), and at 60 min (R3) (T–E values were derived in this case from 8.5 min of ECG data)

of LF, HF and TP, were significantly higher for middle-aged compared with old-aged groups. However, the observed significant differences were disappeared when used normalised unit. The most remarkable index of the sympatho-vagal balance, LF/HF, did not show any significant difference between the two age groups.

Discussion

Through a newly developed HRV analysis method, *tone–entropy* analysis, cardiac autonomic functions in a female population were evaluated. It was found that the *tone* was high, and the *entropy* was low for the old-aged compared with the middle-aged group. The result, plotted in T–E space, revealed a curvi–linear relation between two indices consistent with various physiological situations such as pharmacological blockades, heart recovery after dynamic exercise and male ageing. On the basis of these findings, influence of age on autonomic sympatho-vagal balance in the female population was examined in this discussion. Results in frequency domain analysis were also examined for a reference.

Sympatho-vagal balance with age

A major finding of the present study was an existence of a curvi–linear relation between the *tone* and the *entropy* with advancing age in a female population. It is of

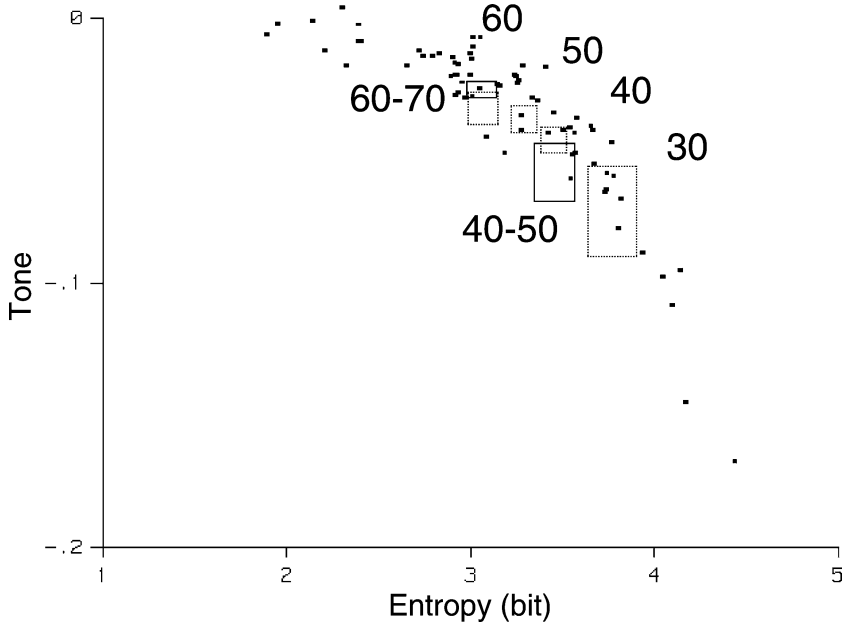


Fig. 7 Female ageing superimposed on a previously published male ageing. This male study was performed for 142 males (30–69 years), who came to the Foundation Kyoto Preventive Medical Center, by classifying into four age groups. Ensemble averaged values were shown by *dotted open rectangles* (means ± SE), thirties (30, $n = 19$), forties (40, $n = 47$), fifties (50, $n = 36$) and sixties (60, $n = 40$)

Table 2 Spectral parameters

	40–50 ($n = 28$)	60–70 ($n = 45$)
LF (10^4 ms^2)	3.00 ± 0.46	1.67 ± 0.31**
HF (10^4 ms^2)	3.57 ± 0.71	1.64 ± 0.27**
TP (10^4 ms^2)	6.58 ± 1.04	3.31 ± 0.54**
LF NU (%)	49.5 ± 3.88	48.7 ± 2.51
HF NU (%)	50.4 ± 3.89	51.3 ± 2.51
LF/HF	1.42 ± 0.24	1.23 ± 0.14

Values are as means ± SE
TP total power; *LF* low frequency; *HF* high frequency; *NU* normalised unit
**P < 0.01

interest that the found relation was the same as that of our previous studies (Figs. 5–7). Then a first matter to be discussed should be physiological implications of this curvi–linear relation. A comparison with a pharmacological blockade experiment (Fig. 5) showed that the present ensemble averaged values were located between the C and the double blockade (P + A) conditions, the middle-aged near to the C and the old-aged near to the denervated condition (P + A). From these finding, it would be natural to consider that the autonomic regulatory activities were reduced in old-aged compared with middle-aged group, because the old-aged group was located near to double blockades condition. Further interest was in a fact that the *tone* increased with this reduction of autonomic regulatory activity. It is to be remarked that the direction of this *tone* transition was opposite to that of sympathetic blockade, for which the *tone* became significantly low (Fig. 5). Thus, the result suggested that the sympatho-vagal balance altered significantly with age, and the *tone* reflected this alteration.

The suggestions were strengthened by the second comparison with a heart recovery after dynamic exercise (Fig. 6). This comparison revealed that the ageing traces the same route as that of a heart recovery after dynamic exercise except its direction. The recovery process traced from *left-top* to *right-bottom* on the route; in contrast, the ageing traced the same route in an opposite direction. As well appreciated, in the recovery after exercise, the autonomic regulatory activity gradually regained, and in the course of which the parasympathetic predominance was being recovered (Arai et al. 1989; Oida et al. 1997; Kannankeril and Goldberger 2002). Thus, the second comparison strengthened the above suggestion from another point of view. In conclusion, the present result would permit to surmise that the autonomic regulatory activity reduced, and the sympatho-vagal balance altered significantly with age in the female population.

A similarity and a difference between female and male ageing

A similarity was shown by the same curvi–linear relation in T–E space. Both in female and in male cases, representative points traced from *right-bottom* to *left-top* with advancing age on the same curvi–linear route (Fig. 7). The sameness showed that the autonomic alteration process with age would be almost identical between female and male. However, when one looks at their mutual positions, one could appreciate a delicate gender differences. As shown in Results, it was female middle-aged group (40–50) that corresponded to male (40), and female old-aged group (60–70) that corresponded to male (60). Furthermore, female diabetic condition was worse than that of male (Results). As shown in our previous studies (Oida et al. 1999a; 1999b), ageing and diabetes were found to be two important factors to alter the autonomic regulatory systems, that made the *tone* increase and, the *entropy* decrease significantly. It was remarkable that the *tone* and the *entropy* were almost equivalent between female and male, notwithstanding advancing age and aggravated diabetic conditions in female. An origin of this gender difference is an interesting problem to be examined in future studies, but it would not be meaningless to attempt a brief explanation here. In fact, there were reports that described beneficial effects of estrogen on cardiovascular functions (Hazzard 1986; Maxwell 1998). It suggested that autonomic functions were robust in pre-menopausal female compared with equivalent male (Ryan et al. 1994; Ramaekers et al. 1998; Kuo et al. 1999). The present observation would be an example of this sort of beneficial effects of female hormonal environment.

Frequency domain analysis

It was shown that LF, HF and TP were significantly reduced with age in absolute unit (Table 2). The observation was consistent with the above *entropy* result, because the total variance in time domain is mathematically equivalent to the total power in frequency domain (Task Force 1996). Moreover, it was also consistent with a number of the previous studies (Vita et al. 1986; Schwartz et al. 1991; Ryan et al. 1994; Craft and Schwartz 1995; Jensen-Urstad et al. 1997; Piccirillo et al. 1998; Ramaekers et al. 1998; Kuo et al. 1999) that described that the powers in frequency domain reduced significantly with age. However, this clear tendency disappeared when the results were described in normalised unit. All the indices did not show any alteration with age (Table 2). A representative index of autonomic balance, LF/HF, was almost constant despite of advancing age. It is to be noted that, as to the autonomic balance, the frequency domain studies have not succeeded in showing any consistent view. Some shows a stagnancy of the balance (Jensen-Urstad et al. 1997; Ramaekers et al. 1998), but the others insisted that the balance had a definite tendency with age (Schwartz et al. 1991; Ryan et al. 1994; Piccirillo et al. 1998; Kuo et al. 1999). Our frequency domain study was consistent with the former, but contradict with the latter. It should be further examined in future studies.

Advantages of T–E method

A hard problem in assessment autonomic regulatory mechanism with age is that it concerns so many factors, and often these factors interact mutually. Then tremendous number of reports rather causes confusion than give a solution (Lakatta 1993). An origin of this labyrinth would be a lack of scale applicable to any cases freely. In spectral study, no attempts were made to have standard values in frequency domain. In time domain study, it was pointed out in the *consent document* (Task Force 1996) that the standard deviation has some statistical flaws for being a comparable index. A real advantage of T–E methodology would be on this point. Acquired values of the *tone* and the *entropy* could be compared without any preliminaries in the same coordinate system of T–E space, where the comparisons were performed consistently between various physiological situations (Figs. 5–7). The present results showed that the *tone* and the *entropy* could be used as a universal scale of autonomic functions without any troubles.

Conclusion

Autonomic function in a female population was evaluated through the *tone–entropy* analysis, and an age-associated alteration of sympatho-vagal balance was examined by classifying the population into two age groups. The result suggested that the para-sympathetic predominance was significantly impaired corresponding with a reduction in autonomic regulation activities with age in the female population. Interestingly, there found a delicate gender differences that female was robust against autonomic ageing compared with male, although the verification of the findings should be accomplished in further studies.

Acknowledgements We thank Dr. Toshiko Kannagi, Dr. Noboru Saitoh and Ms. Tokie Nakagawa for their assistance in collecting data at the Foundation Kyoto Preventive Medical Center, Kyoto.

References

Arai Y, Saul JP, Albrecht P, Hartley LH, Lilly LS, Cohen RJ, Colucci WS (1989) Modulation of cardiac autonomic activity during and immediately after exercise. Am J Physiol 256:H132–H141

Casadei B, Cochrane S, Johnston J, Conway J, Sleight P (1995) Pitfalls in the interpretation of spectral analysis of the heart rate variability during exercise in humans. Acta Physiol Scand 153:125–131

Craft N, Schwartz JB (1995) Effects of age on intrinsic heart rate, heart rate variability, and AV conduction in healthy humans. Am J Physiol 268:H1441–H1452

Eckberg DL (1997) Sympathovagal balance: a critical appraisal. Circulation 96:3224–3232

Elbert T, Ray WJ, Kowalik ZJ, Skinner JE, Graf KE, Birbaumer N (1994) Chaos and physiology: deterministic chaos in excitable cell assemblies. Physiol Rev 74:1–47

Folkow B, Svanborg A (1993) Physiology of cardiovascular aging. Physiol Rev 73:725–764

Goldberger JJ (1999) Sympathovagal balance: how should we measure it?. Am J Physiol 276:H1273–H1280

Højgaard MV, Holstein-Rathlou NH, Agner E, Kanters JK (1998) Dynamics of spectral components of heart rate variability during changes in autonomic balance. Am J Physiol 275:H213–H219

Hazzard WR (1986) Biological basis of the sex differential in longevity. J Am Geriatr Soc 34:455–471

Hedman AE, Tahvanainen KU, Hartikainen JE, Hakumaki MO (1995) Effect of sympathetic modulation and sympatho-vagal interaction on heart rate variability in anaesthetized dogs. Acta Physiol Scand 155:205–214

Houle MS, Billman GE (1999) Low-frequency component of the heart rate variability spectrum: a poor marker of sympathetic activity. Am J Physiol 276:H215–H223

Jensen-Urstad K, Storck N, Bouvier F, Ericson M, Lindblad LE, Jensen-Urstad M (1997) Heart rate variability in healthy subjects is related to age and gender. Acta Physiol Scand 160:235–241

Kannankeril PJ, Goldberger JJ (2002) Parasympathetic effects on cardiac electrophysiology during exercise and recovery. Am J Physiol 282:H2091–H2098

Kuo TBJ, Lin T, Yang CCH, Li CL, Chen CF, Chou P (1999) Effect of aging on gender differences in neural control of heart rate. Am J Physiol 277:H2233–H2239

Lakatta EG (1993) Cardiovascular regulatory mechanisms in advanced age. Physiol Rev 73:413–467

Malpas SC (2002) Neural influences on cardiovascular variability: possibilities and pitfalls. Am J Physiol 282:H6–H20

Maxwell SR (1998) Women and heart disease. Basic Res Cardiol 93:79–84

Montano N, Ruscone TG, Porta A, Lombardi F, Pagani M, Malliani A (1994) Power spectrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. Circulation 90:1826–1831

Oida E, Moritani T, Yamori Y (1997) Tone-entropy analysis on cardiac recovery after dynamic exercise. J Appl Physiol 82:1794–1801

Oida E, Kannagi T, Moritani T, Yamori Y (1999a) Aging alteration of cardiac vagosympathetic balance assessed through the tone-entropy analysis. J Gerontol 54A:M219–M224

Oida E, Kannagi T, Moritani T, Yamori Y (1999b) Diabetic alteration of cardiac vago-sympathetic modulation assessed with tone-entropy analysis. Acta Physiol Scand 165:129–134

Oida E, Kannagi T, Moritani T, Yamori Y (1999c) Physiological significance of absolute heart rate variability in postural change. Acta Physiol Scand 165:421–422

Piccirillo G, Bucca C, Bauco C, Cinti AM, Michele D, Fimognari FL, Cacciafesta M, Marigliano V (1998) Power spectral analysis of heart rate in subjects over a hundred years old. Int J Cardiol 63:53–61

Ramaekers D, Ector H, Aubert E, Rubens A, Van de Werf F (1998) Heart rate variability and heart rate in healthy volunteers. Is the female autonomic nervous system cardioprotective? Eur Heart J 19:1334–1341

Rompelman O, Coenen AJRM, Kitney RI (1977) Mesurement of heart-rate variability: part 1-comparative study of heart-rate variability analysis methods. Med Biol Eng Comput 15:233–239

Ryan SM, Goldberger AL, Pincus SM, Mietus J, Lipsitz LA (1994) Gender- and age-related differences in heart rate dynamics: are women more complex than men? J Am Coll Cardiol 24:1700–1707

Schwartz JB, Gibb WJ, Tran T (1991) Aging effects on heart rate variation. J Gerontol 46:M99–M106

Shannon CE (1948) A mathematical theory of communication. Bell Sys Tech J 27:379–423

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Circulation 93:1043–1065

Vita G, Princi P, Calabro R, Toscano A, Manna L, Messina C (1986) Cardiovascular reflex tests. Assessment of age-ajusted normal range. J Neurol Sci 75:263–274