

# A comparative scale of autonomic function with age through the tone-entropy analysis on heart period variation

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**Abstract** Tremendous numbers of heart rate variability studies have aimed to elucidate age-associated alterations of autonomic function in the past decades. However, the studies, far from clarifying ageing mechanisms, fell into confusion by a lack of common scales. The purpose of this study is to show a possibility to establish a comparative scale of autonomic function through a method, tone-entropy (T-E) analysis on heart period variation, whose validity has been already examined on typical physiological cases (Oida et al. in *J Appl Physiol* 82:1794–1801, 1997; Oida et al. in *J Gerontol* 54A:M219–M224, 1999a; Oida et al. in *Acta Physiol Scand* 165:129–134, 1999b; Oida et al. in *Acta Physiol Scand* 165:421–422, 1999c; Amano et al. in *Eur J Appl Physiol* 94:602–610, 2005). In this study, 276 subjects from teens to seventies were examined at rest by T-E analysis together with conventional time and frequency domain analyses. The tone (negativity represents vagal predominance) became significantly high [ $-0.174 \pm 0.026$  (teens) to  $-0.024 \pm 0.004$  (seventies),  $P < 0.05$  for one-way ANOVA], and the entropy (total autonomic activity), significantly low [ $4.40 \pm 0.12$  (teens) to  $2.90 \pm 0.09$  bit (seventies),  $P < 0.05$ ] with advancing age. The result, plotted in 2-D T-E space, showed that the ageing traced a curvi-linear relation

from right-bottom to left-top, and was consistent with previously studied typical physiological cases. The conventional analyses showed almost the same autonomic reduction as T-E did, but failed in detecting delicate alteration of autonomic balance. The results, showing that autonomic activity reduced in both pathways impairing vagal predominance significantly with ageing, suggested a possibility to assess autonomic function in 2-D T-E space in a comparative way.

**Keywords** Autonomic nervous system · Heart rate variability · Spectral analysis · Sympatho-vagal balance

## Introduction

Tremendous numbers of heart rate variability (HRV) studies have aimed to elucidate age-associated alterations of autonomic function in the past decades: for example, Jensen-Urstad et al. (1997) on Swedish with the ages ranging 20–69 years, Ramaekers et al. (1998) on Belgians with 18–71 years, Schwartz et al. (1991) on Americans with 20–81 years, Ryan et al. (1994) on Americans with 20–90 years, Piccirillo et al. (1998) on Italians with 20–107 years, and Kuo et al. (1999) on Taiwanese with 40–79 years. Numerous studies elucidated many interesting aspects of autonomic function with age on numerous populations, but a crucial problem remained to be solved is a lack of comparative scales. The studies have been performed using various so-called time and frequency domain parameters; however, the parameters were not defined on well statistical basis (Task Force 1996), and prevented us from examining the results in comparison among others. Thus, notwithstanding

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considerable results, the studies have not succeeded in defining the autonomic function with age clearly, rather caused the controversy that continues now without any issues (Schwartz et al. 1991; Ryan et al. 1994; Jensen-Urstad et al. 1997; Piccirillo et al. 1998; Ramaekers et al. 1998; Kuo et al. 1999).

The purpose of this study is to show a possibility to establish a comparative scale through a method, tone-entropy (T-E) analysis on heart period variation. In the method, autonomic function was evaluated by two parameters: sympatho-vagal balance by the tone and total autonomic activity by the entropy. The validity of the method has been examined in a series of studies on typical physiological cases: on pharmacological autonomic blockades (Oida et al. 1999a), on recovery after dynamic exercise (Oida et al. 1997), on body posture change (Oida et al. 1999c), on diabetic aggravation (Oida et al. 1999b), on the ageing of middle-aged males (Oida et al. 1999a), and on gender differences in ageing (Amano et al. 2005). In this study, autonomic function at rest was assessed through T-E method together with conventional time and frequency domain methods on 276 subjects from teens to seventies. The results, elucidating ageing mechanisms of autonomic systems in a new paradigm of T-E space, would suggest a possibility to establish a comparative scale to be used in common for assessing autonomic function.

## Methods

### Subjects

Two hundred and seventy six subjects with ages from eighteen to seventies were examined. Medical examinations comprising physical status and blood chemistry were carried out preceding inclusion. Subjects under treatment of oral hypoglycemic, hypotensive agents, or hormone replacements, and subjects who had frequent ectopic heartbeats were excluded. Written informed consent was obtained before the experiment. The study protocol was approved by the Ethics Committee of Kyoto University Graduate School of Human and Environmental Studies.

### Experimental protocol and data processing

An ECG signal (bipolar electrodes positioned at CM5) was recorded on 10 min at rest in a comfortable chair. No instruction was given regarding respiration [forced respiration altered autonomic activity significantly (Brown et al. 1993; Penttilä et al. 2001)]. The signal was

digitised by an analog-to-digital converter at a sampling rate of 1 kHz, and was simultaneously transformed into heart period (ECG R-R interval) time series on-line through the computer software developed in our laboratory. Detection of ECG R-wave peaks was performed in a precision of 1 ms under a visual inspection on a computer display.

### Tone-entropy method

The methodology was described in detail in the previous reports (Oida et al. 1997, 1999a, b, c; Amano et al. 2005). In brief, acquired heart periods are transformed into percentage index (PI) time series:

$$PI(n) = [H(n) - H(n + 1)] \times 100/H(n) \quad (1)$$

(non-dimensional)

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

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

where  $N$  is a total number of PI terms. The tone, balance between accelerations ( $PI > 0$ ) and inhibitions ( $PI < 0$ ) of the heart, represents the sympatho-vagal balance faithfully as appreciated in all the previous studies (Oida et al. 1997, 1999a, b, c; Amano et al. 2005). The entropy is defined on PI probability distribution by using Shannon's formula (Shannon 1948):

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

where  $[p(i)]$  is a probability that  $PI(n)$  has a value in the range,  $I \leq PI(n) < i + 1$ ,  $i$  an integer. The entropy evaluates total acceleration-inhibition activities, or total heart period variations, in a familiar unit of bit.

It is to be remarked that the tone has no corresponding parameters in conventional methods. The tone has an origin in the investigations in the last century of Rosenbluth and Simeone (1934), where autonomic control of heart rate was studied as an antagonistic interactive operation between accelerations and inhibitions. On the contrary, the entropy evaluates HRV almost the same way as conventional second-order moments, for example, as standard deviation. An interesting thing is that there are cases for which the entropy differs substantially from the conventionals. The present study would show this case in the following.

## Time domain method

Parameters were evaluated according to the consent document (Task Force 1996). Standard deviation of all normal-to-normal (NN) intervals (SDNN), square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), and percentage of number of pairs of adjacent NN intervals differed by more than 50 ms in the entire recording (pNN50).

## Frequency domain method

The method used was described in detail in the previous reports (Oida et al. 1997; Amano et al. 2005). 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 ECG data used in T-E analysis. Fast Fourier transformation (1,024 points, ~8.5 min) was performed after a linear trend elimination and Hamming window processing. Spectral parameters were evaluated according to the consent document (Task Force 1996). Low frequency power (LF) was evaluated 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 the sum of LF and HF. The powers were also evaluated in normalised units, low (LF NU) by  $LF \times 100/TP$  and high (HF NU) by  $HF \times 100/TP$ , respectively. The ratio of LF to HF (LF/HF) was evaluated as well.

## Statistics

Data were expressed as means  $\pm$  SE. One-way analysis of variance and Scheffé's post hoc examination were carried out for comparisons among age groups. Significant level was fixed as  $P < 0.05$  for all the examinations.

## Results

Examination was carried out by classifying the subjects into seven age groups: teens (10) ( $n = 15$ ), twenties (20) ( $n = 20$ ), thirties (30) ( $n = 22$ ), forties (40) ( $n = 66$ ), fifties (50) ( $n = 54$ ), sixties (60) ( $n = 69$ ), and seventies (70) ( $n = 30$ ). Clinical conditions of the groups are shown in Table 1. No significant differences were found except a tendency to hyperglycemia (high fasting blood sugar) in 50, 60, and 70.

Figure 1 shows typical individual data selected in each age group, heart period time series (Fig. 1a), PI time series deduced from left (Fig. 1b), and its

probability distribution in histogram (Fig. 1c). Heart period variations were the highest in ten, and monotonously decreased with age. PI time series and histograms made clear the decrease of instantaneous accelerations and inhibitions of the heart with age (nota bene distributions are sometimes differ from Gaussian). Incidentally, it was found that the ageing process was not accompanied with any clear tendency in baseline heart period:  $[838 \pm 30 (73 \pm 3) (10), 842 \pm 28 (73 \pm 2) (20), 908 \pm 23 (67 \pm 2) (30), 932 \pm 14 (65 \pm 1) (40), 972 \pm 18 (63 \pm 1) (50), 965 \pm 17 (63 \pm 1) (60), \text{ and } 928 \pm 20 \text{ ms } (66 \pm 1 \text{ beats min}^{-1}) (70)$  ( $P < 0.05$ , the significance was detected only for 50 and 60 when compared with 10)].

Figure 2 shows evaluated tone and entropy in 2-D T-E space, ensemble averages with open rectangles (averages  $\pm$  SE), and individuals with scattered dots. Ensemble averages traced a curvi-linear relation from right-bottom to left-top with age, on which the tone became high:  $[-0.174 \pm 0.023 (10), -0.124 \pm 0.020 (20), -0.084 \pm 0.018 (30), -0.055 \pm 0.006 (40), -0.038 \pm 0.004 (50), -0.032 \pm 0.004 (60), \text{ and } -0.024 \pm 0.004 (70)$  ( $P < 0.05$ ); and the entropy became low with advancing age:  $[4.40 \pm 0.12 (10), 4.11 \pm 0.11 (20), 3.84 \pm 0.12 (30), 3.52 \pm 0.07 (40), 3.29 \pm 0.06 (50), 3.09 \pm 0.06 (60), \text{ and } 2.90 \pm 0.09 \text{ bit } (70)$  ( $P < 0.05$ )]. Interestingly, individuals scattered closely fitted to the curvi-linear relation.

Figure 3 shows the present result with previous studies in T-E space. In (Fig. 3a), the present result is with a pharmacological blockade study ( $n = 8$ , males aged  $31 \pm 4$  years) (Oida et al. 1999a), where three typical autonomic conditions were realised by intravenous injection of pharmacological agents, control (C), sympathetic blockade by propranolol ( $0.2 \text{ mg kg}^{-1}$ ) (P), and double blockades by propranolol plus atropine ( $0.04 \text{ mg kg}^{-1}$ ) (P + A). The present 30 was precisely on C (in fact, the subjects of the pharmacological experiment were in thirties). The present, 10 and 20, were found around P, sympathetic blockade condition of the thirties. The older groups over 30 were located corresponding to their age between C and P + A, that is, between the control and the pharmacologically denervated condition of thirties. In (Fig. 3b), the present result is with a heart recovery after dynamic exercise (Oida et al. 1997), in which an exercise (Ex) was performed for 30 min on a bicycle ergometer at ventilatory threshold level by 12 female athletes ( $21 \pm 1$  years), and its recovery was observed at 10 min (R1), at 35 min (R2), and at 60 min (R3) after the exercise. It indicated that the curvi-linear relation was the same between the recovery and the ageing. Only difference was found in the tracing

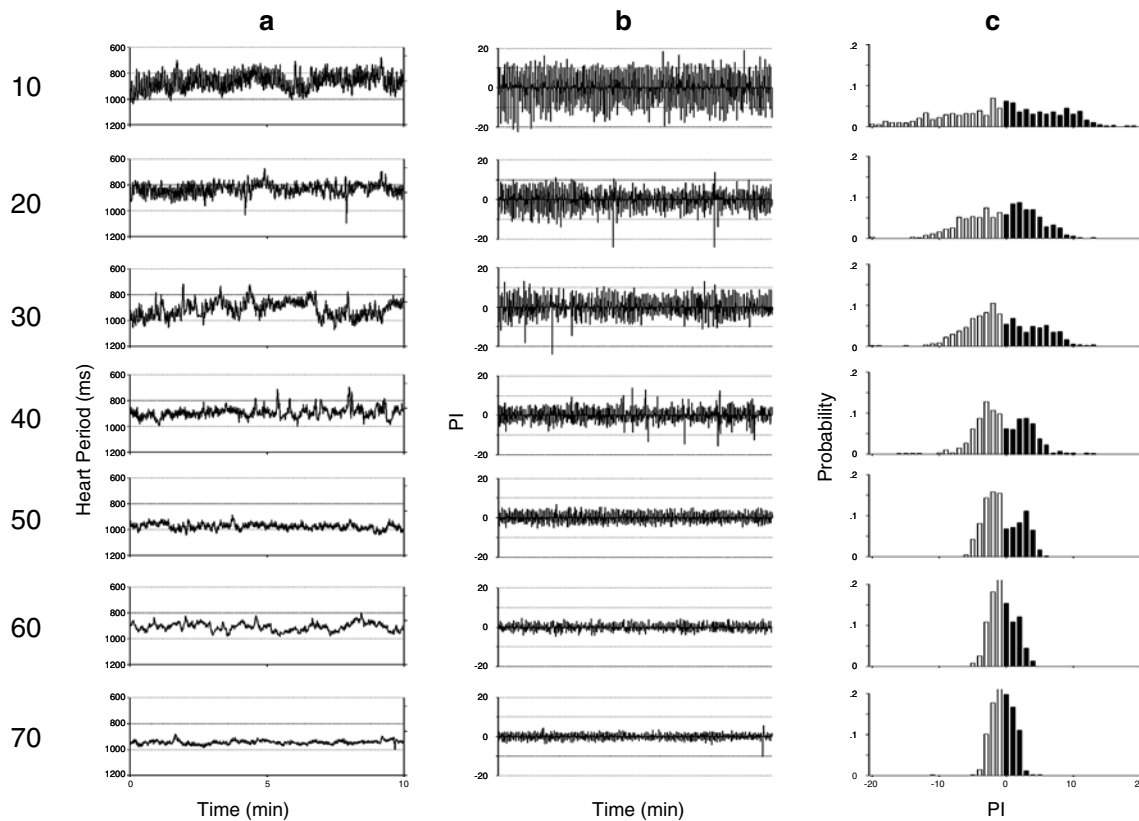
**Table 1** Clinical characteristics of age groups

	10 ( <i>n</i> = 15)	20 ( <i>n</i> = 20)	30 ( <i>n</i> = 23)	40 ( <i>n</i> = 66)	50 ( <i>n</i> = 54)	60 ( <i>n</i> = 69)	70 ( <i>n</i> = 30)
Age (years)	18.9 ± 0.1	22.3 ± 0.5*	35.5 ± 0.7*	45.7 ± 0.3*	54.7 ± 0.4*	63.9 ± 0.3*	73.5 ± 0.5*
Height (m)	1.62 ± 0.02	1.66 ± 0.02	1.68 ± 0.01	1.66 ± 0.01	1.64 ± 0.01	1.60 ± 0.01	1.52 ± 0.01*
Body mass (kg)	56.2 ± 2.2	61.2 ± 2.6	66.1 ± 2.6	64.0 ± 1.1	62.6 ± 1.3	61.3 ± 1.0	52.1 ± 1.8
SBP (mmHg)	112 ± 2	115 ± 3	115 ± 3	117 ± 2	122 ± 2	125 ± 2	129 ± 3
DBP (mmHg)	72 ± 2	70 ± 3	71 ± 3	73 ± 1	75 ± 1	74 ± 1	68 ± 2
Fasting blood sugar (mg dl <sup>-1</sup> )	87 ± 2	92 ± 2	102 ± 5	109 ± 3	127 ± 5*	121 ± 4*	121 ± 6*
Total cholesterol (mg dl <sup>-1</sup> )	183 ± 7	193 ± 10	205 ± 7	206 ± 4	214 ± 5	207 ± 4	209 ± 4
HDL cholesterol (mg dl <sup>-1</sup> )	72 ± 4	69 ± 4	51 ± 2*	58 ± 2	58 ± 2	57 ± 2	67 ± 3
Triglycerides (mg dl <sup>-1</sup> )	67 ± 9	85 ± 11	144 ± 26	136 ± 14	126 ± 12	126 ± 8	102 ± 8

Values are as mean ± SE

SBP Systolic blood pressure, DBP diastolic blood pressure, HDL high-density lipoprotein

Statistical significant was shown only for a comparison to ten: \**P* < 0.05



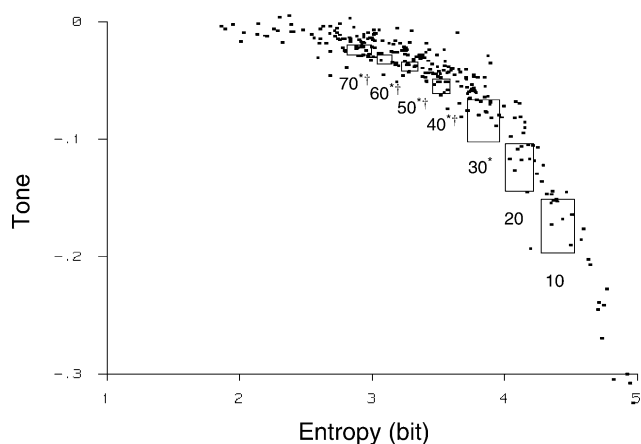
**Fig. 1** Typical heart period time series (a), PI time series deduced from left (b), and its probability distributions in histogram (c) selected in each age group. In histograms, filled

bars represent accelerations (PI > 0), and open bars, inhibitions of the heart (PI < 0), respectively. Abbreviations are defined in the text

direction: the recovery traced the relation from left-top to right-bottom. In (Fig. 3c), the present is with a previously studied ageing (Oida et al. 1999a), where a 142 males were examined in four age groups, 30–39 (m30, *n* = 19), 40–49 (m40, *n* = 47), 50–59 (m50, *n* = 36) and 60–69 years (m60, *n* = 40) (averages ± SE was shown by open rectangles of spaced dots). The

present middle-aged groups, 30–60, occupied almost the same positions as the previous m30–m60. To be remarked is that the young, 10 and 20, were found at right-bottom, and the old, 70, at left-top on the curvilinear relation.

Figure 4 shows conventional parameters, time domain (Fig. 4a), frequency domain in absolute unit



**Fig. 2** Evaluated tone and entropy in T-E space, ensemble averages by *open rectangles* (averages  $\pm$  SE), and individuals, by *dots*. Statistical significance was shown only with comparisons to ten: *asterisk* is for the tone and *dagger* for the entropy,  $P < 0.05$ . Abbreviations are defined as in the text

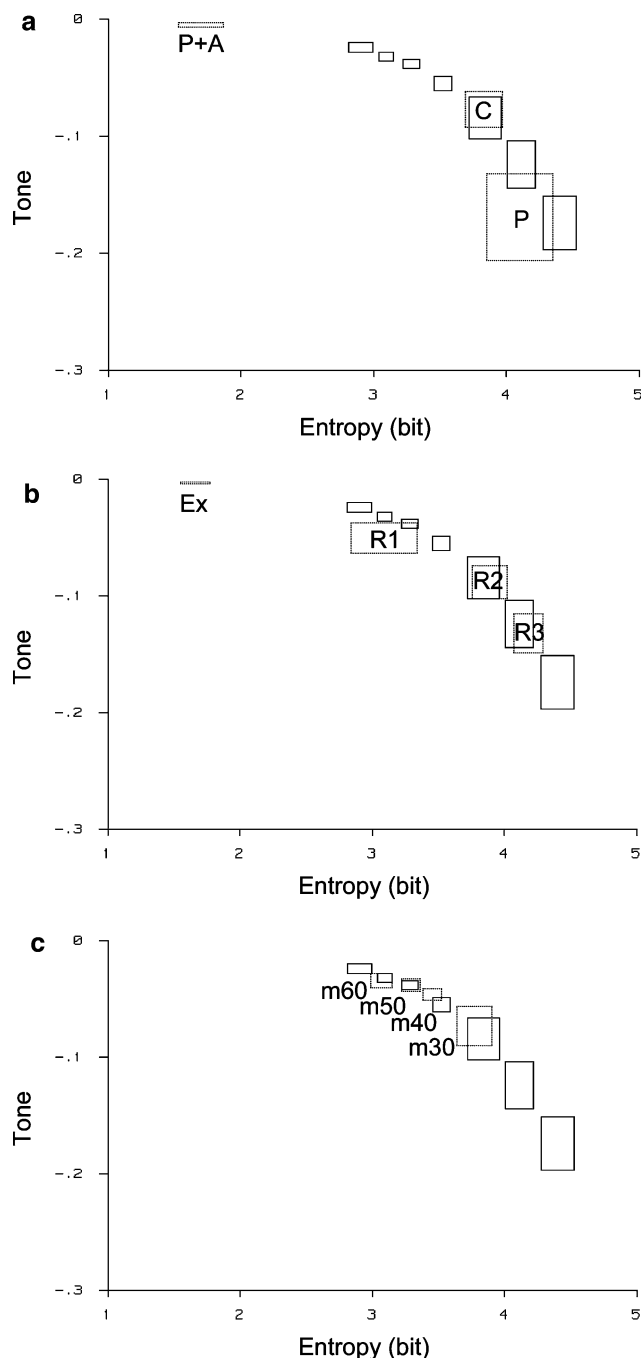
(Fig. 4b), and frequency domain in normalised unit (Fig. 4c). Time domain parameters decreased significantly with age, except one case in SDNN (from 10 to 20). Frequency domain parameters in absolute unit also decreased significantly except in two cases, in LF and TP (from 10 to 20). In contrast, frequency domain parameters in normalised unit showed a reciprocal interplay: LF NU attained to the maximum, and HF NU, to the minimum for 20. As a consequence, a most remarkable parameter of the sympatho-vagal balance, LF/HF, became the highest for 20.

## Discussion

Age-associated alteration of autonomic function was studied on 276 subjects from teens to seventies through T-E and conventional HRV analyses. T-E analysis showed that the ageing traced a curvi-linear relation from right-bottom to left-top in 2-D T-E space. Time domain parameters and frequency domain parameters in absolute unit reduced significantly with age except in a few exceptions. Frequency domain parameters in normalised unit showed a reciprocal interplay. In this discussion, examining these diversified results in detail, we will show a possibility to establish a comparative scale of autonomic function to be used in common.

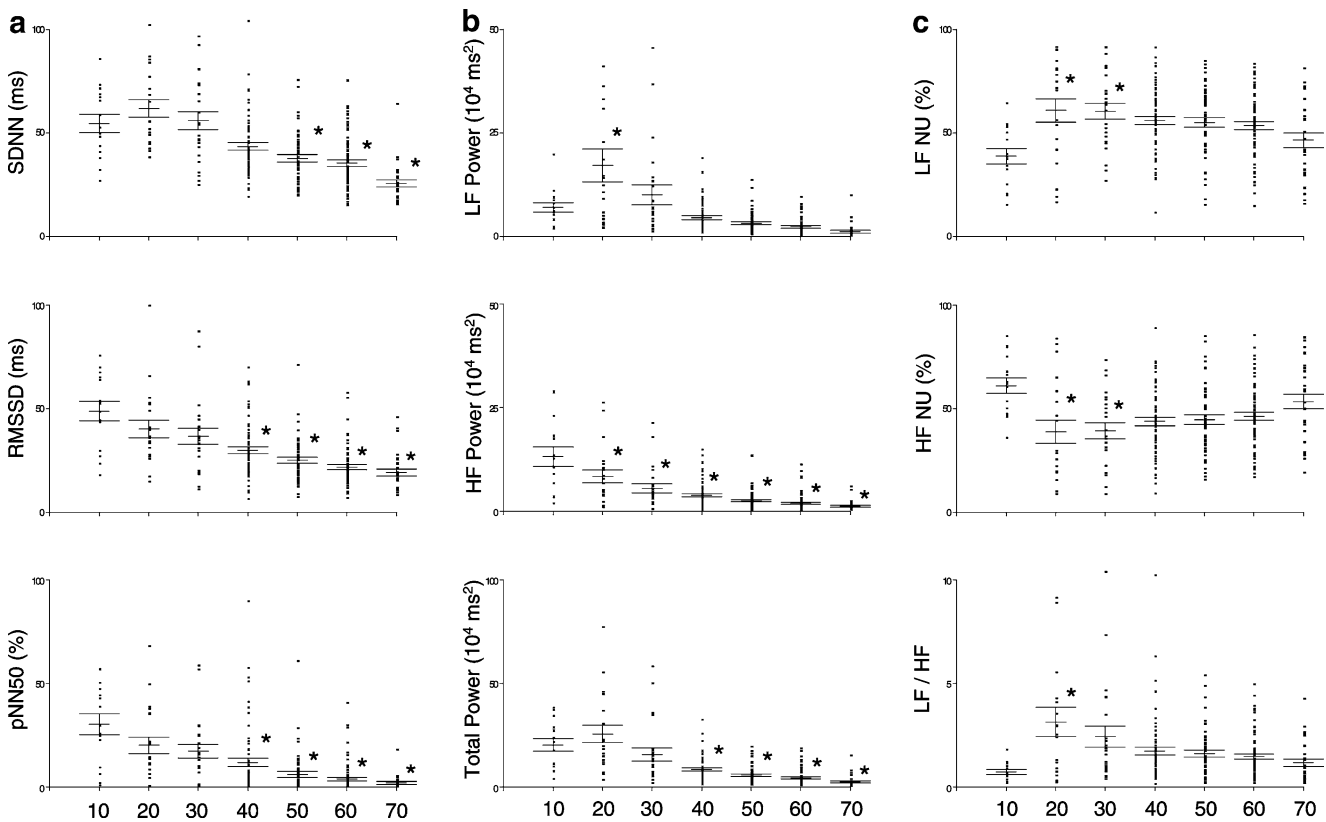
### T-E analysis

Physiological implications of a trace on a curvi-linear relation with age could be derived from the comparisons realised in Results (Fig. 3). First a pharmacolog-



**Fig. 3** Three superimpositions of the present T-E result, on a pharmacological blockade experiment (a), on a heart recovery after dynamic exercise (b), and on a male ageing (c). Ensemble averages were shown by *open rectangles* (averages  $\pm$  SE) of *spaced dots*. Abbreviations are defined in the text

ical blockade experiment revealed a specific relevance of the trace to autonomic mechanisms. A fact that the present 40, 50, 60, and 70 were found between C and P + A (between control and pharmacologically denervated condition of thirties, Fig. 3a) would suggest that the autonomic condition became near to that of



**Fig. 4** Conventional parameters: time domain (a), frequency domain in absolute unit (b), and frequency domain in normalised unit (c). Statistical significance was shown only for comparisons

with ten: \* $P < 0.05$ . Individuals were shown in *dots*. Abbreviations are defined in the text

denervated heart with advancing age. The other fact that 10 and 20 were found around P (sympathetic blockade condition of thirties, Fig. 3a) would suggest that the sympathetic activity was reduced, or the parasympathetic activity was relatively enhanced in young populations. Second a recovery after dynamic exercise strengthened these suggestions, where the recovery traced the same curvi-linear relation in an opposite direction (Fig. 3b). Here it would be sufficient to recall that autonomic pathways regain their activity enhancing parasympathetic predominance in such recovery process (Arai et al. 1989; Oida et al. 1997; Terziotti et al. 2001). Third with a male ageing showed that the positions on the curvi-linear relation were not determined by chance. Not only middle-aged groups occupied the same positions as the previous, but also the young (10 and 20) and old (70) were found at expected positions (Fig. 3c). In this way, T-E method, expressing the ageing by a trace on a curvi-linear relation in T-E space, suggested that the cardiac autonomic activity was being reduced with advancing age in impairing vagal predominance significantly.

#### Time and frequency domain analyses

Time domain parameters decreased monotonously with age except one case in SDNN from 10 to 20 (Fig. 4a). The result would be consistent with previous studies that reported significant decreases with age of various time domain parameters (Kleiger et al. 1992; Jensen-Urstad et al. 1997; Ramaekers et al. 1998). Frequency domain parameters in absolute unit decreased with age also monotonously except in two cases in LF and TP from 10 to 20 (Fig. 4b). The result would also be consistent with a number of studies that described significant decrease of powers with age in all frequency ranges (Schwartz et al. 1991; Ryan et al. 1994; Jensen-Urstad et al. 1997; Piccirillo et al. 1998; Ramaekers et al. 1998; Kuo et al. 1999). In contrast, frequency domain parameters in normalised unit showed a reciprocal interplay: LF NU became the highest, whereas HF NU, the lowest for 20. As a result, LF/HF attained to the maximum for 20 (Fig. 4c). However, for this, we could not find any studies that stand for it.

Two points are to be considered. Firstly, the exception in time domain (SDNN was low in 10, Fig. 4a) might be a result of imperfection of SDNN. However, SDNN contradicted not only to visual inspection of HRV intensities (HRV was high in 10, Fig. 1) but also to the other time domain parameters (Fig. 4a). R-R interval distribution sometimes significantly differs from Gaussian (cf. Fig. 1c), and it is natural that the conventional variance parameter fails in the evaluation for such skewed distribution. Then it would be plausible that SDNN failed for these non-Gaussian distributions that are common in young (unpublished). Secondly, the exceptions in the frequency domain in absolute unit correspond to this exception in time domain. As well known, the power in frequency domain is mathematically equivalent to the variance in time domain (Parseval's equation). It is not by chance that TP in frequency domain showed the same tendency as SDNN did in time domain (Fig. 4). Then, as a logical consequence (from the mathematical relation stated above), TP in frequency domain also failed in evaluation of these non-Gaussian HRV time series as SDNN did in time domain (it permits to surmise that LF also failed for the same reason). In this way, the consideration suggests that the exceptions would not be the reflection of any physiologically definite alterations of autonomic systems, but be the flaw of conventional methods. As a consequence, the interplay observed in normalised unit might be doubtful because the interplay was caused by these exceptions in TP and in LF.

If the exceptions are excluded, the results in conventional methods would be restated as: all the time domain parameters reduced monotonously with age, all the frequency powers reduced monotonously with age, and the frequency powers in normalised unit were almost stagnant with age. On the basis of general comprehension of spectral parameters (LF reflects autonomic activities in both pathways, but HF, those in parasympathetic pathway) (Task force 1996), the restated result suggests that the autonomic activities reduced in both pathways significantly, maintaining the autonomic balance almost constant with age.

#### Comparative scale of autonomic function

T-E and conventional methods achieved almost the same conclusion on the total autonomic activity, but not on the autonomic balance. It is to be noted that, as for the autonomic balance with age, the frequency domain methods still have not succeeded in defining it clearly: some insisted a sympathetic enhancement in old population (Schwartz et al. 1991; Ryan et al. 1994; Piccirillo

et al. 1998; Kuo et al. 1999), but others denied it (Jensen-Urstad et al. 1997; Ramaekers et al. 1998). It is impossible to show an issue of this problem here, but the present consideration made supposed that the problem would be due to the lack of comparative scales. As well known, frequency powers depend on data acquisition time length, on choices of frequency ranges, and on deduction algorithms different from authors to authors (Task Force 1996). Then it is impossible to compare spectral results among experiments performed by different authors. As a result, we could not find whether the results really reflected the underlying physiological significance or the used modalities (Eckberg 1997; Goldberger 1999; Malpas 2002).

An advantage of T-E method is in the point of comparativeness. The tone and the entropy have been evaluated free from acquisition time length (due to probability distribution), from baseline heart rate (due to PI), and from complex deduction algorithms (see Methods). Then the tone and the entropy enabled any comparisons without preliminary preparations between experiments (Fig. 3). To be noted is that it was these comparisons (Fig. 3) that suggested the significant alteration of autonomic systems with age in a clear way.

#### Conclusion

Age-associated alteration of autonomic function was assessed on 276 subjects from teens to seventies through T-E and conventional methods. The two methods achieved almost the same conclusion on the autonomic reduction with age, but showed a delicate difference on sympatho-vagal balance with age. The consideration permitted to surmise that the difference has an origin in flaws of conventional parameters. The results, showing that the autonomic activity reduced in both pathways impairing vagal predominance significantly with advancing age, suggested a possibility to assess autonomic function in T-E method in a comparative way.

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