Tone-entropy analysis on cardiac recovery after dynamic exercise

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Oida, Eiichi, Toshio Moritani, and Yukio Yamori. Tone-entropy analysis on cardiac recovery after dynamic exercise. J. Appl. Physiol. 82(6): 1794–1801, 1997.—Autonomic controls on heart rate variability have been investigated; however, sympathovagal interactive modulations remain unexplored. The purpose of this study is to present a new method, tone-entropy analysis (T-E analysis) of heart period fluctuations, and to make clear an intensive cooperation of autonomic networks in heart recovery. On the basis of evidence obtained in animal experiments, we hypothesized that heart periods are lengthened or shortened beat to beat by assumed physiological mediators: accelerator and inhibitor. Their operations were evaluated through a normalized successive variation of the period, that is, the percentage index (PI). The process was described through PI distributions by using two indexes, tone and entropy, standard values of which were obtained through pharmacological autonomic blockade experiment. T-E analysis was applied to heart recovery (70 min) after dynamic exercise by 12 female athletes. Interactive autonomic modulations were expressed by a curved path in tone-entropy space. Results suggested that heart rate decay proceeds not by withdrawal of one pathway but by increasing activity of both pathways as vagosympathetic balance inclines slightly but significantly to the vagus division in the course of recovery. The process was examined through Fourier spectral analysis as well.

Heart rate variability has been analyzed through various methods (9, 32) for investigating cardiac autonomic functions; however, sympathovagal interactive modulations still remain to be elucidated.

None of the reports has succeeded in describing the interaction satisfactorily. Statistical indexes of heart rate variability have been verified to be useful for assessments, but on the whole almost all were concerned only with characteristics (32): information on the interaction could not be found in such indexes. Spectral analysis (SA) of heart rate fluctuations was introduced as a method that could measure each autonomic activity separately (2, 19, 22). Sympathovagal balance was represented in SA by a ratio of power, i.e., low frequency-to-high frequency ratio (LF/HF) (22). Although LF/HF has been reported to adequately provide an evaluation of balance for a case of body tilting (20), all studies on dynamic exercise faced a difficulty: power in the frequency domain was extremely reduced during exercise (3, 6, 21, 23, 25, 34). As a result, the ratio presented no useful information on the interaction during exercise, except for one report (34). Further investigations would be needed to explain the interactive modulations consistently in SA. New conceptions related to “nonlinear dynamics” or “chaos theory,” such as phase plane plot, return map, Poincaré section, and fractal dimension (5, 8, 9), were proposed as advanced techniques in the latest investigations. Although new features were disclosed in fascinating descriptions, unfortunately it was sometimes difficult to interpret the results in familiar physiological terms.

There is, apart from above investigations, a well-known series of experiments. Through electric stimuli on cardiac autonomic nerves in animal experiments, it was appreciated that heart rates were accelerated by sympathetic nerves and inhibited by vagus ones (4, 18, 27, 28). Activity of cardiac autonomic efferent nerves was observed, by direct recording in animals, to be synchronous with respiratory cycles: the sympathetic system was active in the phase of inspiration (1, 7, 11), the vagus system in expiration (12, 14). Rhythmic fluctuation of heart rate was thus considered to be generated by these reciprocal operations of both autonomic pathways (15, 16).

Reflecting on these experimental results, we advanced the thinking. If these mechanisms are working precisely beat by beat, what could be said about instantaneous heart period variations? When the sympathetic pathway is active, heart rates would be increased and the heart period would be shortened compared with the previous one; on the contrary, when the vagus pathway is active, the heart period would be lengthened. Is it possible, then, to evaluate cardiac autonomic operations through these successive variations of the heart period?

We started from an undoubted fact that heart rates are controlled through the two operations of acceleration and inhibition. Heart periods (inverse of heart rate) were thus considered to be made shorter or longer on a beat-by-beat basis by assumed physiological mediators: accelerator and inhibitor. Works of the mediators were expressed, accordingly, by successive differences of the period, for example, by plus differences for acceleration and by minus ones for inhibition. We normalized the successive difference in percentage and analyzed their distributions. Two indexes were contrived for the distributions: tone, for balance between two operations, and entropy, for total activity of both mediators. The physiological significance of the indexes was clarified in a pharmacological autonomic blockade experiment, in which the distributions had specific forms corresponding to vagosympathetic balance in a definite way.

The purpose of the study was to apply tone-entropy (T-E) analysis to the heart recovery process and to make clear an interactive aspect of cardiac autonomic regulations in a new paradigm. Heart recovery was chosen because interactive operations were expected to
be in higher degrees for a course of heart rate decay. Observed was heart recovery for 70 min after exercise by 12 female athletes. Interactive cooperation between two mediators, accelerator and inhibitor, was expressed as a nonlinear path in T-E space. Results suggested an unexpected but natural control mecha-

nism, that is, heart rate decay in recovery is carried out by a withdrawal of one autonomic pathway but by the intensive cooperation of both pathways. Results were examined through SA as well.

**METHODS**

**Percentage Index (PI) of Heart Period Variation**

Heart periods are obtained as the time series [H(n)], where (n) is a serial number of beats. Successive differences of the heart period are calculated as \( H(n) - H(n+1) \) for \( 1 \leq n \leq N - 1 \), where N is a total number of beats in a time range. When heart rate is increased, the heart period becomes shorter than the previous one. Acceleration of the heart is, therefore, expressed as a plus difference, inhibition as a minus one.

However, a problem must be first be examined, namely, whether it is appropriate to use absolute values of the difference. The heart period is varied over a wide range; it comprises 1,000 ms for 60 beats/min and 500 ms for 120 beats/min. In animal experiments, it was verified that electrical stimuli of cardiac autonomic nerves induced the same percent changes in heart rates whether heart rates were high or not (27); difference in animal species disappeared when heart period variations were expressed as the percentage of the basal cardiac interval (13). It would thus be preferred to express the successive differences in a normalized form, the PI of heart period variation

\[
PI(n) = \left( \frac{H(n) - H(n+1)}{100/H(n)} \right)
\]

for

\[
1 \leq n \leq N - 1
\]

**Tone and Entropy**

From the time series PI(n), we can easily constitute a PI distribution through classification of PI(n) as an integer. Distribution is generally characterized by two indexes: average and standard deviation (SD). The average of PI distribution was calculated as "tone" but, for a second index, instead of SD, we employed entropy for the reason noted below.

Tone. Tone is defined as a simple average

\[
1/N \sum_n PI(n)
\]

where N is a total number of terms in PI(n) in a time range. We named it tone because it represents a balance between acceleration and inhibition of the heart. If acceleration were superior, tone would be a plus in the "accelerator field"; if inhibition were superior, tone would be a minus in the "inhibitor field." The relationship of tone to autonomic balances could be well appreciated when it is calculated for standard conditions provided with pharmacological blockades (cf. Standard Distributions).

Entropy. We judged that SD was not appropriate for the second index because the distribution was not a simple Gaussian one. PI distributions were sometimes obtained clearly separated into two components, as seen below (see Figs. 2 and 6). Then, entropy, a new conception, was introduced from the information theory that we owed to the fundamental work of Shannon (31). To introduce entropy, we had to define a probability distribution of PI(n) in the following manner. Frequencies (\( f_i \)) are figured as a number of times that PI(n) has a value in a range in which i is an integer. [The calculation PI(n) = 0 is omitted because it is neither acceleration nor inhibition.] Probabilities (\( p(i) \)) for events in which PI(n) has a value in a range \( i \leq PI(n) < i + 1 \) are naturally calculated

\[
p(i) = \frac{f_i}{f}
\]

where

\[
f = \sum_i f_i
\]

Entropy is defined on a probability distribution as a quantity of information contained in the distribution (31). Information is evaluated by the negative logarithm of a probability to the base 2 in a unit of "bit." For example, if a probability of an event is one-half, the information of this event is calculated to be 1 bit because the negative logarithm of one-half to the base 2 is 1. Thus an event in which PI(n) has a value in a range \( i \leq PI(n) < i + 1 \) has information \( -\log_2 p(i) \). Entropy of the distribution is defined as an average of all the events as follows

\[
-\frac{1}{f} \sum_i p(i) \log_2 p(i) \quad \text{(bit)}
\]

or

\[
-\sum_i p(i) \log_2 p(i) \quad \text{(bit)}
\]

The meaning of entropy could be also appreciated through evaluations for distributions obtained under pharmacological autonomic blockades (cf. Standard Distributions).

**Spectral Analysis**

Heart period time series data were converted off-line into equal time-distance sampling data. This conversion was done from the original heart periods and time-position data. (The SA was not concerned, therefore, with the above PI or other T-E analysis processing.) Data sampling was effectuated on computer software at 2 Hz for folded heart periods (26). Obtained time series data were processed by direct current elimination, high-pass digital filtering (<0.02 Hz), and Hamming window before fast Fourier transformation (1,024 points, ~8.5 min) was performed. Analyses were carried out in frequency range (0.02–0.8 Hz); lower limit (0.02 Hz) was determined according to Akselrod et al. (2); high end (0.8 Hz) was determined according to Arai et al. (3). The frequency domain was divided into two parts: (LF, 0.02–0.15 Hz) and (HF, 0.15–0.8 Hz) (22, 24, 29). Three indexes were calculated: 1) power in 0.02–0.8 Hz (ms²; total power); 2) parasympathetic nervous system (PNS) index, power in 0.15–0.8 Hz divided by total power; and 3) ratio of power (LF/HF).

**Subjects**

Experiments were performed with 12 female athletes, age 21.0 ± 0.8 (SE) yr, height 1.62 ± 0.02 m, and body mass 55.7 ± 1.0 kg. Heart rate at ventilatory threshold (VT) was determined by maximum exercise testing accomplished by cycle ergometer (33). Maximum work rates were 228 ± 9 W.
Heart rate at final stage was 180 ± 2 beats/min. Maximum oxygen consumption was 2.60 ± 0.06 l/min or 46.8 ± 1.2 ml·kg⁻¹·min⁻¹. VT was 69.1 ± 1.8% of maximum oxygen consumption, and heart rates at VT were 152 ± 3 beats/min. Informed consent was submitted in written form before the experiment from all the subjects.

Experimental Procedure

The experiment was carried out in a room maintained at constant temperature (22–25°C) for 2 h in the morning. At first, each subject sat on a chair quietly for 20 min. Exercise was performed successively on a cycle ergometer for 30 min at heart rates of VT determined as described above. Work rates were readjusted, if necessary, in the observation of heart rates. After the exercise, each subject got off the cycle and sat on the chair quietly for 70 min. For subjects to change clothes and use towels, 5 min were allowed at two time points (see Fig. 3; 20 and 45 min after the exercise session).

Data Acquisition

An electrocardiographic signal (CM5) was monitored during the whole experimental session. The signal was digitized at a sampling rate of 1,000 Hz by an analog-to-digital converter (TEAC PS-9351) and simultaneously transformed into a heart period time series on a computer (DOS/V). Detection of the QRS complex was performed on-line under an inspection on a computer display, and heart periods (R-R intervals) were calculated in precision of 1 ms. The set of software used in this data acquisition and in the following analyses was developed in our laboratory.

Standard Distributions

The physiological significance of PI distribution and its indexes, tone and entropy, was examined in standard conditions provided with pharmacological autonomic blockades. Male volunteers participated in the experiment. We show, here, data for a typical subject (age 24 yr) as an example of standard distributions.

The whole time course of a heart period in a subject under successive blockades of each autonomic pathway is shown in Fig. 1 (top). Electrocardiographic data were obtained while subjects were in a sitting position in a comfortable chair in the morning for 40 min. Autonomic block agents were intravenously injected within 4 min from the time position indicated in Fig. 1: propranolol (0.2 mg/kg), 10 min after the beginning of the experiment; atropine (0.04 mg/kg), 25 min after the beginning of the experiment. Successive differences of heart period (Fig. 1, bottom trace) were increased after sympathetic blockade (P) compared with control condition (C) and extremely decreased after the blockade of both pathways (P + A). Time courses of PI and their distributions are shown in Fig. 2. For control resting, the distribution pattern was similar to a Gaussian pattern. After sympathetic blockade, the range became wide and PI distribution was separated into two components, one in the accelerator field (solid vertical lines) and another in the inhibitor field (dotted vertical lines). Under double blockades, it was no more than a distribution. For these standard distributions, two indexes were calculated as tone [−0.13 (C), −0.33 (P), and −0.01 bit (P + A)] and entropy [4.22 (C), 4.87 (P) and 1.92 bit (P + A)].

The results could be summarized in the following principles. First, both autonomic pathways are always active in the ordinary sitting condition because β-adrenergic and cholinergic blockade agents both altered the PI distributions significantly. Second, tone changes its value in correspondence with sympathovagal balance in a definite way. In fact, sympathetic blockade made tone deeply minus; both blockades made tone nearly zero. The more balance inclined to the vagus, the more tone shifted its position to the minus direction. Third, entropy is low for low activity and high for high activity; it represents the total activity of both mediators.

Statistical Analysis

Data are expressed as means ± SE. One-way analysis of variance and Tukey’s post hoc examination were carried out for comparison among five time ranges. P < 0.05 was considered to be significant for all examinations.

RESULTS

Evolution of Heart Period

The time course of the heart period in the whole experimental session of a subject is shown in Fig. 3 (top trace). Exercise was performed by cycle ergometer during 30 min at VT level. Recovery was observed for 70 min. During exercise, heart periods were maintained almost constant at 390 ± 8 ms or 154 ± 3
beats/min, which was really equal to the heart rates at VT, $152 \pm 3$ beats/min ($P > 0.05$; cf. METHODS). Heart periods returned to the control length by degrees after the exercise.

The successive difference of the period is shown in Fig. 3, (bottom trace). Differences were large at rest, remarkably reduced during exercise, and returned to the original size progressively after the exercise. Statistical analyses were made among the time ranges (8.5 min) designated R0 (control rest; 5 min after the beginning); exercise (Ex; 35 min); first recovery (R1; 55 min); second recovery (R2; 80 min); and third recovery (R3; 105 min), respectively. Heart rates in these time ranges were $69 \pm 2$, $154 \pm 3$, $87 \pm 3$, $76 \pm 2$, and $71 \pm 2$ beats/min, respectively. Significance was detected at Ex and at R1 when compared with R0 ($P < 0.05$).

Spectral Analysis

A set of spectra obtained from the data in Fig. 3 are shown in Fig. 4. In the frequency domain, three peaks were recognized. It has been reported that respiratory rates exceeded 0.5 Hz in dynamic exercise (3); accordingly, we expected a peak to appear during exercise in the higher region of 0.5-0.8 Hz. The third peak, however, was observed at rest, contrary to our expectation. This third peak was not necessarily observed for all the subjects. It might be due to respiration characteristics of the subject, which we leave for future studies.

The remarkable result was a disappearance of spectrum during exercise. Total power in R0, $12,307 \pm 1,868$ ms$^2$, was reduced in Ex, $47 \pm 9$ ms$^2$, i.e., only 0.36% of R0. This reduction of power was already reported in many documents (3, 6, 21, 23, 25, 34). It is one of the conditions that makes it hard to carry out SA for exercise.

Spectral indexes are shown in Fig. 5. Powers were reduced to almost zero during Ex and were regained gradually in recovery (Fig. 5, top). Low power was always dominant; low and high power came back in the same way as did total power. PNS and LF/HF are shown in Fig. 5 (bottom). PNS decreased to a minimum in early recovery (R1; $P < 0.05$, compared with R0) and increased after R1 (R2 to R3). LF/HF was extremely high during Ex, but its variance was also very large. This was because total power was reduced to almost zero in Ex. As a consequence, statistical significance was not detected ($P > 0.05$) in any combinations among the five time ranges.

PI Distributions

PI time series data derived from the data in Fig. 3 are shown in Fig. 6 (top). PIs were almost within a range of $\pm 20$ at R0 and confined in an extremely narrow range during Ex. The range was regained by degrees in recovery. Histograms are depicted through probabilities (cf. METHODS) in Fig. 6 (bottom). At R0, it was nearly Gaussian. The form disappeared in Ex, in which fluctuations were restricted within a range of $\pm 2$. The original form of the distribution returned progressively in the course of recovery.
Before showing an evolution of the distribution indexes in ensemble averages, we display in Fig. 7 a whole time course of tone and entropy calculated on the data of Fig. 3. In this case, calculations were carried out for data of 2 min; time ranges were fixed to 2 min and were moved successively at 10 s all over the 120-min experimental session. Tone (Fig. 7, top trace) was definitely minus in the inhibitor field at rest; moved abruptly to plus to the accelerator field at the start of exercise; was precisely zero during exercise; fell down deeply after exercise and soon rebounded; and returned in intense fluctuations by degrees to the original minus value in recovery. Entropy (Fig. 7, bottom trace) described another evolution: −4 bits at rest, decrease to nearly 1 bit during Ex; and return to the control value in recovery.

This time course of two indexes was depicted simultaneously in T-E space in Fig. 8, with tone as ordinate and entropy as abscissa. Physiological conditions were differentiated by color: resting (R0; dark blue); starting (white); exercise (Ex; red); first recovery (R1; yellow); second recovery (R2; green); and third recovery (R3; light blue). Dark-blue points were all found in lower right portion; white points in top portion; red points in right portion; yellow points divided into two parts, one corresponding to a downshoot after Ex; green points were found between yellow and dark blue points; light-blue points were found in the same region as dark blue points. It can be easily noticed that the heart control operations followed a definite route despite furious fluctuations from the start to Ex and in the course of recovery.

Evolution of tone and entropy in ensemble average of five distributions (R0, Ex, R1, R2, and R3) is shown in Fig. 9. At R0, tone (T in Fig. 9) was $-0.13 \pm 0.02$ and entropy (E in Fig. 9) was $4.14 \pm 0.15$ bits. Travel began from R0 (dark blue), following a route in top region to Ex (red), $0.00 \pm 0.00$ (T) and $1.66 \pm 0.11$ bit (E; P < 0.05, compared with R0). From Ex to recovery (R1 to R3), it traced a curve like an exponential: red-yellow-green-light blue. R3, $-0.13 \pm 0.02$ (T) and $4.18 \pm 0.11$ bit (E), was superimposed on R0. The recovery process
is shown, in this way, as a curved trajectory like an exponential in T-E space. The physiological significance of the recovery route can be appreciated with reference to the values obtained in the standard distributions (cf. METHODS), which were marked on the figure by a plus.

DISCUSSION

The cardiac recovery process was studied through a new method, T-E analysis. Autonomic interactive modulation was expressed as a curved path in T-E space: tone was shifting deeply into the inhibitor field as entropy was increasing in recovery (Fig. 9). The physiological significance of the curved path in relation to sympathovagal modulations is discussed below.

Recovery Process in SA

Arai et al. (3) reported that power in the frequency domain is extremely reduced during exercise and returned to the control level in recovery; prevailing power in recovery was observed in the low-frequency domain (−0.1 Hz). This prevailing low power after exercise was observed by other authors as well (6, 10, 25). They speculated that the phenomenon would be a consequence of an elevated sympathetic activity outlasting cessation of exercise. On the other hand, an index for parasympathetic activity, power in the high-frequency domain (−0.25 Hz), was found to be much lower immediately after exercise when compared with resting condition (6, 23).

The time span of observation for recovery is not the same between work of the above-mentioned authors and our study: ~10 min or so in all of the above-mentioned work, except for one (48 h) (10), vs. ours (70 min). However, our results do not contradict those of these authors: powers were reduced during exercise and returned progressively to control level in recovery; prevailing power was found also in LF domain; and HF power was also reduced in the early stage of recovery (Fig. 5). It is of interest that sympathovagal modulations are described in SA as a sort of see-saw game: withdrawal of sympathetic system always follows an increase of parasympathetic activity and vice versa (19) (Fig. 5).

Recovery Process in T-E Analysis

The recovery process was described in T-E analysis through an evolution of tone and entropy (Figs. 7–9). Tone was stagnant near zero immediately after the exercise (R1) and shifted deeply into the inhibitor field after R1 (from R2 to R3; Figs. 7–9). Considering that tone was defined as a representative of balance between acceleration and inhibition, we could interpret the results as the inhibitor was superior to the accelerator at rest; two mediators were in equilibrium during exercise, or the inhibitor won back progressively in the course of recovery. On the other hand, considering that entropy was introduced for indicating a degree of activity in both mediators, we could say that their activities were in the lowest level during exercise and returned to the original level gradually in recovery (Figs. 7–9).

With reference to the principles stated with regard to the standard distributions (cf. METHODS), we could further advance the discussion. As seen in Fig. 9, the recovery route connects not only Ex (red) with R3 (light blue) but with two terminals marked by a plus sign of the standard values of the PI distributions. The recovery route is, thus, the same route that connects two extremes: from pharmacologically denervated heart to control one. It leads us to a somewhat improbable but natural proposition: autonomic activities are withdrawn in both pathways during exercise; both divisions begin to work in the process of recovery; as activity of both divisions increases, their balance point shifts deeply to the vagus side.

Savin et al. (30) investigated the heart recovery process through pharmacological blockade in humans and dogs. From the results, they considered that the sympathetic system was gradually withdrawing, whereas the parasympathetic system increased its activities in recovery; the heart rate decay process, thus, might be expressed in an exponential curve. In fact, the decay process was almost linear in the case of heart-transplant patients or congestive heart failure (3, 30). This classical work of Savin et al. (30) is now to be slightly corrected: it is not an alternation but a shift of balance between two cardiac autonomic divisions that is observed in the process of heart recovery.

However, with regard to an improbable proposition, concomitant vagal and sympathetic withdrawal during exercise, our study design does not allow a discrimination of the nature of the accelerator and inhibitor during exercise; further studies are needed to clarify this unexpected finding.

Propositions on Cardiac Autonomic Interactive Regulations

Two other propositions on the autonomic controls disclosed in our results may be stated.

The first is about a hypothesis from which we started: heart rate is intensively controlled on a beat-to-beat basis in an antagonistic way by two autonomic divisions. Although further examinations are needed to prove the validity of the hypothesis, we found support in our results. As seen in PI distributions (Figs. 2 and 6), histograms were always almost symmetrical: the accelerator and inhibitor worked reciprocally in equal power. In recovery, both mediators were increasing their activities; none of the mediators was decisively dominant; only the balance between two operators shifted slightly toward the inhibitor (Figs. 7–9). The important fact is that tone, the balance between the two operators, represented changes in accordance with vagosympathetic balance in a definite way: tone inclined to the inhibitor when autonomic balance inclined to the vagus division and vice versa (Fig. 9).

Another proposition concerns a more sophisticated interactive regulation: tone might be connected with entropy through a nonlinear functional relationship.
that is shown as a curved path in T-E space (Fig. 9); that is, tone shifts toward the inhibitor as entropy increases its value. In ordinary physiological terms heart rate variability is increased when the balance point shifts to the parasympathetic system and vice versa. In this way, we are led to a solution of a commonly observed phenomenon: during sympathetic activation, tachycardia accompanies a marked reduction in the heart period fluctuations, whereas the reverse occurs during vagal activation (32). Increasing and reducing of heart period fluctuations is thus caused not by chance but by an intrinsic regulation of heart rate control networks.

Conclusion

Levy (17) stated his view on heart rate control systems that both autonomic divisions are usually active; heart rates are controlled through antagonistic effects of both divisions on nonlinear summation. T-E analysis described a heart recovery process through new conceptions, tone and entropy, consistent with this view of Levy (17). The heart recovery process was expressed as a simple curved path in T-E space, in which tone shifted its position deeply into the inhibitor field as entropy increased. This suggests that heart rate decay is carried out not by a withdrawal of the sympathetic pathway but by vagosympathetic cooperation: both divisions are increasing their activities in reciprocal operations, shifting their balance point slightly toward the vagus in the course of heart recovery.

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