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Effects of nitroglycerin on fractal features of short-term heart rate and blood pressure variability

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Abstract
Purpose. We investigated the effect of nitroglycerin(NTG) on fractal features of short-term heart rate variability (HRV) and blood pressure variability (BPV) using coarse-graining spectral analysis (CGSA).
Method. Nine healthy young volunteers participated in this study. Five-minute recordings of electrocardiogram and blood pressure estimated by photoplethysmograph were made during stepwise NTG infusions of 0.2, 0.4, 0.8, and 1.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ under rate-controlled breathing at 0.25 Hz. CGSA broke down the total power of the time series into harmonic (low- and high-frequency) and nonharmonic (β of $1/f^{\beta}$ and %fractal) components.
Results. A statistically significant difference from the control period was observed during the maximum dose of NTG infusion, with decrease in mean blood pressure, shortening of mean R-R interval, and increase in plasma norepinephrine and epinephrine. The β in HRV increased significantly (0.89 ± 0.06 *vs.* 1.27 ± 0.13, $P < 0.05$). However, %fractal was not affected (47.9 ± 6.7 *vs.* 50.1 ± 4.0). Indicators of parasympathetic and sympathetic nervous system activity showed reduced and increased values, respectively. No change in BPV was observed for any measurement.
Conclusion. The data suggest that NTG significantly affected fractal features, as well as harmonic components, of short-term HRV. NTG had no effect on BPV, suggesting a different mechanism for genesis of $1/f^{\beta}$ fluctuation in BPV and HRV.

Key words: Nitroglycerin, $1/f^{\beta}$ fluctuation, Heart rate variability, Blood pressure variability

Introduction

Nitroglycerin (NTG) is frequently administered for the treatment of myocardial infarction, control of hypertension, and induced hypotension during anesthesia. Besides its powerful dilatation effect on the coronary arteries, NTG is also used as a physiological tool to assess arterial baroreceptor reflex sensitivity in humans [1]. NTG is known to induce reflex tachycardia due to attenuation of vagal cardiac tone followed by sympathetic activation [2]. Although there have been many investigations regarding the arterial baroreceptor reflex using NTG, the effects of NTG on heart rate variability (HRV) have not been studied closely [3,4].

Since the introduction of frequency domain analysis into HRV [5], numerous studies have shown that HRV has not only periodic components, such as low- and high-frequency, but also nonharmonic components [6]. Many investigators consider such components as noise. Kobayashi first found that in long-term HRV the time series was characterized as $1/f^{\beta}$ ($\beta \sim 1.0$) fluctuation [7] when the data were plotted as the log of spectral power *vs.* log of frequency. This was later confirmed by Saul et al. [8], and harmonic peaks around the low- and high frequency area are superimposed on a broad-band "1/f noise" [9]. Mathematically, however, it is difficult to evaluate the slope of β precisely, because the periodic components prevent the complex time series from extracting nonperiodic components. Recently a new approach has been applied to analyze $1/f^{\beta}$ fluctuation, coarse-graining spectral analysis (CGSA) [10]. CGSA evaluates harmonic and nonharmonic fluctuation of the time series separately, and several studies have revealed that $1/f^{\beta}$ nonperiodic characteristics are fractal [11] and autonomic neural mechanisms may be applicable to the genesis of fractal features of HRV [12,13]. Blood pressure variability (BPV) also has fractal characteristics [9]; however, β is slightly higher than that of β in HRV [12]. Thus, there may be a different mechanism for BPV.

We performed CGSA to HRV and BPV during infusion of NTG to assess how fractal features, as well as harmonic fluctuations, of HRV and BPV are affected in

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an altered autonomic state induced by NTG administration. Parameters derived from CGSA are %fractal and β of 1/f$^{\beta}$ as the indexes of fractal features, the ratio of integrated low-frequency power (P_{LF}) to integrated high-frequency power (P_{HF}) as sympathetic nervous system (SNS) indicator, and the ratio of P_{HF} to integrated total power (P_{Tot}) as parasympathetic nervous system (PNS) indicator. Plasma catecholamine levels are also measured during infusion of NTG.

Methods

Subjects

Nine healthy young adults (four men and five women, aged between 23 and 27 years) participated in this study. Each subject signed a consent form approved by the committee on human investigation of Kure National Hospital.

Measurements

The subjects were studied in the supine position in a quiet room. An electrocardiogram (ECG) was recorded via II leads, and bilateral antecubital vein catheters were placed for blood sampling and drug administration. Beat-to-beat arterial pressure was estimated with a photoplethysmograph (Finapres Model 2300, Ohmeda, Englewood, CO, USA) placed on the middle finger. Arterial pressure was also measured every 2.5 min with an automated oscillometric device (Pulsemate BX-5, Colin Electronics, Komaki, Aichi, Japan). Tidal volume and airway flow (taken as respiratory activity) were measured through a mouthpiece connected to a respiratory gas analyzer (RGM-5250, Ohmeda). Tidal volumes measured every 10 s were stored in the hard disk of a personal computer. All physiological measurements were archived using FM tape or electrostatic paper recorders. Blood samples (7 ml) were centrifuged immediately following withdrawal, and plasma samples were stored at −40°C until assay for catecholamines (Special Reference Laboratory, Tokyo, Japan).

Experimental protocol

The experiment began after an initial 20-min resting period, during which the subjects received infusion of physiological saline at 1 ml·min^{-1} . Saline infusion was continued throughout the period of the measurements. Then a 5-min recording was made at a fixed respiratory rate of 15 breaths·min^{-1} (the subjects started inspiration with each tone of the metronome, and the breathing rate was maintained throughout the data collection period), which was taken as the baseline control value. The stepwise infusion of NTG (0.2, 0.4, 0.8, and 1.6 μg·kg^{-1}·min^{-1}) was then conducted consequently with the same respiratory rate. Each infusion was continued for 10 min, and data were collected during the final 5-min period at each infusion rate.

Spectral analysis

Before CGSA was conducted, the stored tidal volume data were compared using repeated-measure ANOVA to confirm that the respiratory conditions were kept fairly constant during the measurements.

ECG and beat-to-beat arterial pressure wave forms were digitized at 250 Hz using signal acquisition hardware and software (CODAS, Dataq Instruments, Akron, OH, USA). Peak and valley analysis was performed to determine R-R interval, systolic pressure, and diastolic pressure, which were subsequently analyzed by the method of CGSA as described by Yamamoto [10,11]. The procedure involved 5 min beat-to-beat R-R intervals. Unequal R-R intervals were aligned sequentially to obtain equally spaced samples, the spectra of which were reported to have no significant difference from the HRV spectra for the interpolated time series [14]. Performed CGSA estimated power spectra on this time series with averages of 256-beat time shifted ensembles. From the harmonic component, integrated power at the low-frequency and high-frequency region was defined as 0.0–0.15 Hz (LF) and 0.15–0.50 Hz (HF), respectively. The ratio of HF power (P_{HF}) to total power (P_{Tot}) the and ratio of LF power (P_{LF}) to P_{HF} were used as indicators of parasympathetic nervous system (PNS) and sympathetic nervous system (SNS) activity. From the fractal component, a percentage of random fractal components to P_{Tot} (%fractal) was calculated, and the fractal component was plotted in a log-power *vs.* log-frequency plane, with the spectral exponent β estimated as the slope of the linear regression of the 1/f$^{\beta}$ plot. This linear regression was calculated for Fourier components from 2.5% of Nyquist frequency to the point corresponding to 0.3 Hz.

As for beat-to-beat values of systolic blood pressures, equally spaced time series were constructed using the mean R-R interval. CGSA was performed on this systogram with the same computer algorithm that was used for HRV.

Statistical analysis

Values were expressed as means ± SD. Data were analyzed by repeated-measure one-way analysis of variance (ANOVA). Bonferroni's *t*-test was conducted for multiple comparison when the null hypothesis was

not applicable. $P < 0.05$ was considered statistically significant.

Results

Figure 1 shows recordings of R-R intervals and the corresponding CGSA obtained from one subject during control period. In the total power spectra, when plotted in log-log scale, a distinct peak at the respiratory frequency (~0.25 Hz) was found in HRV, indicating that respiratory modulation of HRV was mainly harmonic. At an LF range lower than 0.1 Hz, some harmonic peaks were also found. When the fractal power spectra were plotted on the log-log axis, the harmonic peaks disappeared almost completely.

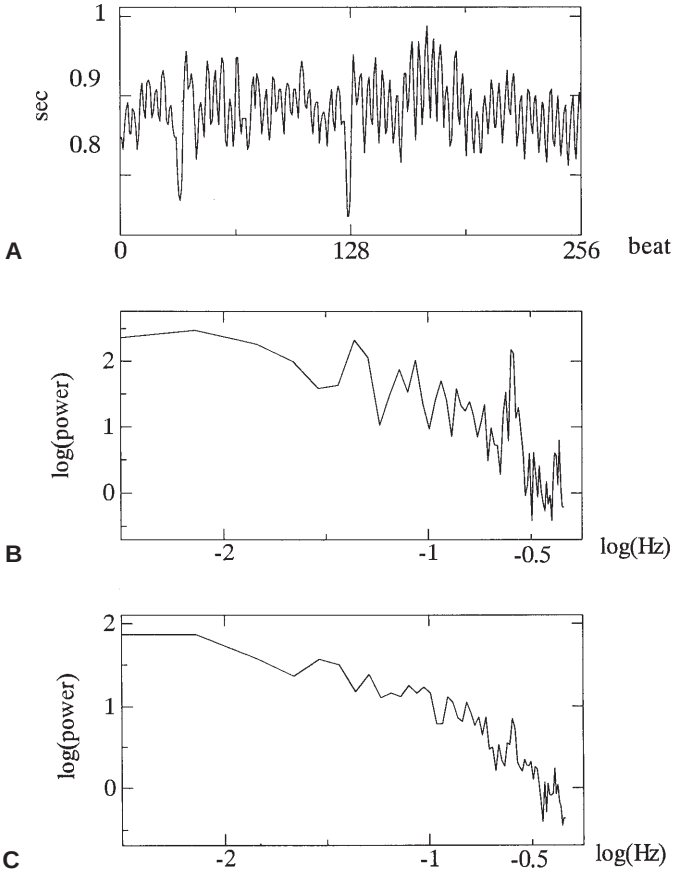

Fig. 1. R-R interval and its corresponding coarse graining spectral analysis (CGSA) from one subject. **A** Original R-R interval time series for 256 beats. **B** Total power spectra of R-R interval plotted in log(Hz) versus log(power) scale. **C** Fractal power spectra derived from CGSA

Baseline hemodynamic values are shown in Table 1. The mean R-R interval was significantly shortened from the control period during maximum NTG infusion. Systolic arterial pressure, measured by an automated oscillometric device, decreased significantly during infusion of 0.4, 0.8, and 1.6 μg·kg^{-1}·min^{-1}, whereas diastolic pressures significantly increased during infusion of 0.8 and 1.6 μg·kg^{-1}·min^{-1}. Significant increase in norepinephrine and epinephrine was observed during the maximum dose of NTG infusion.

Table 2 shows the results of statistical analysis for HRV derived from CGSA. The PNS indicator was significantly reduced during infusions of NTG, whereas the SNS indicator was significantly affected only during the 1.6 μg·kg^{-1}·min^{-1} NTG infusion period. The %fractal ranged between 55% and 60% for all measurements. The slope of β significantly increased during the maximum dose of NTG infusion.

As for BPV shown in Table 3, no statistical by significant differences were found for any of the measurements.

Discussion

In this study, we investigated fractal features of HRV and BPV by CGSA during infusions of NTG. We found that, with rate-controlled ventilation, the fractal slope of β in HRV was 0.89 ± 0.06 during control measurement and became significantly steep (1.27 ± 0.42) during infusion of 1.6 μg·kg^{-1}·min^{-1} of NTG. The fractal percentage in HRV against total power was not affected. Indicator of parasympathetic nervous system derived from the harmonic component of HRV (P_{Tot}/

Table 1. Baseline values of heart rate, blood pressure, and plasma catecholamines during measurements ($n = 9$)

		NTG (μg·kg^{-1}·min^{-1})			
Value	Control	0.2	0.4	0.8	1.6
mR-R (ms)	947 ± 27	930 ± 36	909 ± 33	876 ± 33*	836 ± 32*
SBP (mmHg)	114.4 ± 9.1	108.0 ± 8.6	104.6 ± 9.3*	103.1 ± 8.4*	102.2 ± 8.1*
DBP (mmHg)	62.0 ± 6.9	63.3 ± 8.3	65.9 ± 9.1	68.6 ± 8.9*	72.7 ± 10.1*
Nor (pg/ml)	229.2 ± 58.2	239.9 ± 71.2	243.6 ± 58.1	268.0 ± 67.8	311.9 ± 109.1*
Epi (pg/ml)	22.7 ± 9.7	24.6 ± 10.5	25.3 ± 11.8	25.1 ± 9.8	32.2 ± 18.2*

NTG, Nitroglycerin; mR-R, mean R-R interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; Nor, norepinephrine; Epi, epinephrine. Values are expressed as means ± SD.
* $P < 0.05$ *vs.* control.

Table 2. Statistical analysis of parameters for R-R interval obtained from CGSA during measurements ($n = 9$)

		NTG ($\mu g \cdot kg^{-1} \cdot min^{-1}$)			
Value	Control	0.2	0.4	0.8	1.6
PNS indicator	0.39 ± 0.06	0.23 ± 0.04*	0.17 ± 0.03*	0.15 ± 0.03*	0.16 ± 0.05*
SNS indicator	0.43 ± 0.18	0.82 ± 0.23	1.69 ± 0.71	1.73 ± 0.54	3.24 ± 0.97*
%fractal	47.9 ± 6.7	57.4 ± 3.2	57.1 ± 6.0	56.5 ± 4.1	50.1 ± 4.0
β	0.89 ± 0.06	0.96 ± 0.10	1.02 ± 0.09	1.08 ± 0.13	1.27 ± 0.13*

NTG, Nitroglycerin; PNS indicator, parasympathetic nervous system indicator (P_{HF}/P_{Tot} ratio); SNS indicator, sympathetic nervous system indicator (P_{LF}/P_{HF} ratio); Values are expressed as means ± SD.
* $P < 0.05$ *vs.* control.

Table 3. Statistical analysis of parameters for systolic blood pressure obtained from CGSA during measurements ($n = 9$)

		NTG ($\mu g \cdot kg^{-1} \cdot min^{-1}$)			
Value	Control	0.2	0.4	0.8	1.6
PNS indicator	0.06 ± 0.05	0.09 ± 0.07	0.12 ± 0.10	0.08 ± 0.05	0.10 ± 0.05
SNS indicator	3.48 ± 3.28	3.43 ± 2.69	4.05 ± 2.80	3.15 ± 1.82	3.19 ± 2.83
%fractal	80.4 ± 11.7	71.5 ± 22.1	58.1 ± 21.2	69.7 ± 15.6	66.6 ± 12.7
β	1.33 ± 0.27	1.22 ± 0.35	1.20 ± 0.48	1.21 ± 0.38	0.99 ± 0.31

NTG, Nitroglycerin; PNS indicator, parasympathetic nervous system indicator (P_{HF}/P_{Tot} ratio); SNS indicator, sympathetic nervous system indicator (P_{LF}/P_{HF} ratio); Values are expressed as means ± SD.

P_{HF} ratio) were reduced, whereas sympathetic nervous system indicator (P_{LF}/P_{HF} ratio) were increased. Furthermore, plasma catecholamine levels were significantly increased. No parameter derived from BPV showed significant changes from the control. NTG, thus, significantly affected fractal features of HRV by leading the autonomic cardiac neural balance to sympathetic dominance. Different mechanisms may thus possibly apply to fractal features in BPV.

Several studies showed that β of 1/f$^{\beta}$ in HRV is ~1.0 in the resting position [7,8,12] regardless of the data length [11], which is a slightly higher level than our present data. The lower the β, the more random is the time series at $0 < \beta < 1$. This means that the time series comes close to white noise and is more stationary [15]. This paper is the first to measure β under rate-controlled respiration, whereas all other published values were obtained under spontaneous respiration. In the first investigation on the relationship between respiration (spontaneous breathing) and the fractal features of HRV, no parameter of respiratory activity was related to β, suggesting that control of breathing is not always needed for measurement of fractal features [13]. During controlled respiration, however, respiration modulates not only heart rate but also muscle sympathetic nerve activity [16–18]. Respiratory activity influences low-frequency as well as high-frequency R-R interval power spectra [19], and power spectra are not reproducible when HRV is measured under spontaneous respiration [20]. Although the origin of 1/f$^{\beta}$ fluctuation of HRV is unknown, the high degree of complexity in HRV may be mainly mediated via the parasympathetic nervous system [11,15]. Considering that metronome breathing causes sympatho-vagal balance shift in favor of the vagal component [21,22], control of respiratory rate may affect %fractal and β in the resting position.

Regarding the effects of NTG on harmonic fluctuation of HRV using conventional frequency domain analysis, animal studies showed that NTG induced a remarkable increase in the LF component, which is consequently associated with increase in the P_{LF}/P_{HF} ratio. This may be due to sympathetic activation, because the response is completely blunted by bilateral stellectomy [3]. In humans increases in P_{LF}/P_{HF} during NTG infusion were observed repeatedly [4]. The cardiovascular response to NTG administration is primarily mediated via the arterial baroreceptor reflex, which induces cardiac sympathetic activation and cardiac vagal withdrawal. The present data showed that heart rate was accelerated as arterial pressure decreased. Plasma norepinephrine and epinephrine increased significantly at infusion of 1.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of NTG. Variables derived from harmonic components by CGSA significantly attenuated PNS and activated SNS. In frequency domain analysis of HRV, the P_{LF}/P_{HF} and P_{HF}/P_{Tot} ratios have proved highly repeatabe as indexes of sympathetic and parasympathetic nervous activity [4]. Thus, NTG infu-

sion caused autonomic neural balance towards sympathetic dominance in this study. Under such autonomic alteration, the fractal slope of β in HRV became significantly steeper (1.27 ± 0.42) than during the control period. This means that the time series became less irregular. β is highly sensitive to sympathetic activation, such as exercise, orthostatic stress, and gravitational stress [12,23,24], and our results confirm that the fractal slope β is affected by elevated catecholamines. Physiologically, control of heart rate is primarily mediated via direct innervation to the sinoatrial node by the vagal nerve, and the sympathetic nervous system modulates heart rate by changing the levels of circulating catecholamines. Our data thus suggest that elevated catecholamines may affect the fractal slope of β. Not only vagal cardiac but also sympathetic neural activity may thus give rise to 1/f$^{\beta}$ fluctuation in HRV.

No parameter derived from BPV was affected during measurements. β is 1.34 for long-term BPV [25], which is close to that observed for long-term HRV in humans [7,8]. Butler reported β for short-term BPV as 2.31 [12], which is much higher than the value in this study. This means that the time series of BPV looks like Brownian motion. The time series loses its complexity, and variability becomes smaller [14]. It is not possible to compare our data with Butler's because of several different factors. The first major difference was the respiratory condition, rate-controlled or spontaneous. Second, in the animal study, blood pressure was measured by a chronically indwelling catheter in the femoral artery. Third, the photoplethysmograph (Finapres) is able to estimate intraarterial pressure with acceptable accuracy [26]. However, servo-setting is required every 70 beats to maintain reliability. In this study servo-setting was performed according to the default setting during the measurements. Butler's measurement was performed without servo-setting for 9 min. The operation and maintenance manual of that device recommends not changing the default settings, and if the servo self-adjust setting is turned off, data reliability may be compromised [2300 Finapres Blood Pressure Monitor Operation and Maintenance Manual, User Responsibility]. To compare β for different measurements, we reanalyzed previously published data [27] in which arterial pressure was recorded directly via a catheter inserted into the left radial artery. Under rate-controlled respiration (0.25 Hz), β = 1.18 ± 0.37, %fractal = 58.1 ± 18.8 for BPV where β = 0.91 ± 0.41, %fractal = 54.2 ± 13.0 for HRV. The precise value of β for either HRV or BPV remains undetermined, since the cause of 1/f$^{\beta}$ fluctuation still remains unknown. CGSA has not been established completely as a nonlinear method for analyzing HRV [28]. Further study is needed on the methodology, neurological mechanisms, and origin of human fluctuation in 1/f.

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