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Effects of nicardipine and diltiazem on fractal features of short-term heart rate variability—application of coarse graining spectral analysis

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Abstract
Purpose. This study was designed to investigate the effects of nicardipine and diltiazem on the fractal features of short-term heart rate variability (HRV), using coarse graining spectral analysis (CGSA).
Methods. Eighteen healthy volunteers participated in this study; they were divided into two groups according to the drug administered. Five-minute electrocardiogram and arterial pressure recordings were made during stepwise infusions of either nicardipine (0.4, 0.8, 1.6, and 3.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or diltiazem (2, 4, 8, and 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$) under rate-controlled breathing at 0.25 Hz. CGSA broke down the total power of the time series into harmonic (low frequency [0.0–0.15 Hz; LF] and high frequency [0.15–0.5 Hz; HF]) and nonharmonic (fractal) components. Cardiac sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) activity indicators were evaluated as the ratios LF/HF and HF/TP (total spectral power), respectively. Fractal components were evaluated as %fractal and the spectral exponent β of $1/f^{\beta}$.
Results. Compared with control measurements, the maximum dose of nicardipine infusion caused a significant decrease in systolic arterial pressure, a significant increase in the mean heart rate, and a significant increase in plasma norepinephrine level, findings that were associated with significant increases in %fractal and β values (54.2 $\pm$ 13.3 vs 75.6 $\pm$ 9.8, and 0.86 $\pm$ 0.22 vs 1.32 $\pm$ 0.46, respectively; $P < 0.05$). PNS and SNS indicators showed decreased and increased values, respectively. Diltiazem caused a reduction in arterial pressure; however, no other parameters, including the nonharmonic components of HRV, were affected by this drug.
Conclusions. These findings strongly suggest that nicardipine suppresses vagal cardiac neural outflow and activate the SNS, an action which, subsequently, causes changes in the fractal features of HRV. Although diltiazem reduces arterial pressure, it preserves the basic neural balance of the autonomic nervous system in regard to heart rate control.

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Introduction

Nicardipine and diltiazem are widely used, not only for the treatment of cardiovascular diseases such as hypertension and coronary artery disease but also for the attenuation of cardiovascular response to tracheal intubation during anesthesia [1]. The main mechanism of their action is the blocking of the Ca^{2+} inward current through the slow Ca^{2+} channel; however, the hemodynamic effects of nicardipine and diltiazem differ in terms of their action on the autonomic nervous system. Intravenous administration of nicardipine induces an increase in heart rate owing to sympathetic activation [2–4]. As for diltiazem, several different findings have been reported; the differences may have resulted from differences in the subjects and in the methods used [2,5,6].

From the viewpoint of autonomic neural control of cardiovascular dynamics, the frequency domain analysis of heart rate variability (HRV) would be advantageous, because it could provide noninvasive evaluation of the autonomic neural balance of the heart in a number of physiological and clinical settings. It is widely accepted that the high-frequency (HF; respiratory frequency, around 0.15 to 0.50 Hz) components of HRV are associated with parasympathetic nervous system (PNS) activity, while the low-frequency (LF; around 0.10 Hz; 0.05 to 0.15 Hz) components are associated with both PNS and sympathetic nervous system (SNS) activity [7]. Numerous studies have examined the autonomic neural mechanisms of HRV, and their clinical relevance; however, the effects of Ca^{2+} antagonists on HRV have not been investigated thoroughly [8–12].

Recently, a new approach to the study of HRV was established; coarse graining spectral analysis (CGSA) [13]. Both the LF and HF components of HRV are superimposed on a broadband "$1/f^{\beta}$ noise ($\beta \sim 1.0$)" [14]. CGSA enables the evaluation of harmonic and nonharmonic fluctuations of HRV to be done separately, and several studies have revealed that $1/f^{\beta}$ nonperiodic characteristics are fractal [15]. It has been suggested that autonomic neural mechanisms may be involved in the genesis of the fractal features of HRV [16–18]. In the present study, we employed CGSA to evaluate the effects of intravenous infusions of nicardipine and diltiazem on both the harmonic fluctuations and the fractal features of HRV.

Subjects and methods

Subjects

Eighteen healthy young adults (11 men and 7 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 National Hospital Kure Medical Center.

Measurements

The subjects were studied in a quiet room, while they were in the supine position. An electrocardiogram (ECG) was recorded via leads II, and bilateral antecubital vein catheters were placed for blood sampling and drug administration. Arterial pressure was measured every 2.5 min with an automated oscillometric device (Pulsemate BX-5; Colin Electronics, Komaki, Japan). Tidal volume and airway flow (taken as respiratory activity) were measured through a mouthpiece connected to a respiratory gas analyzer (RGM-5250; Ohmeda, Englewood, CO, USA). Tidal volumes, measured every 10 s, were stored on 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 after withdrawal, and plasma samples were stored at −40°C until assayed for catecholamines (Special Reference Laboratory [SRL], Tokyo, Japan).

Experimental protocol

The subjects were divided into two groups according to the drug administered, i.e., nicardipine or diltiazem. The choice of drug was dictated by a coin toss. The experiment began after an initial 20-min resting period, during which the subjects each received an infusion of physiological saline, at $1\,ml \cdot min^{-1}$. Then a 5-min recording was made at a fixed respiratory rate of 15 $breaths \cdot min^{-1}$ (the subjects started inspiration on hearing a sound from a metronome, and the breathing rate was maintained throughout the data collection period), which was taken as the baseline control value. After the control measurements had been completed, the stepwise infusion of each drug (nicardipine, doses of 0.4, 0.8, 1.6, and $3.2\,\mu g \cdot kg^{-1} \cdot min^{-1}$, and diltiazem, doses of 2, 4, 8, and $16\,\mu g \cdot kg^{-1} \cdot min^{-1}$) was conducted. These infusion rates were selected by preliminary studies to provoke equivalent arterial pressure changes at the maximum dose of the infusion. Each infusion was continued for 10 min, and measurements were made during the final 5-min period at each infusion rate.

Spectral analysis

ECG wave form digitization (sampling rate at 250 Hz) and subsequent peak (R wave) detection was performed using signal acquisition hardware and software (CODAS; Dataq Instruments, Akron, OH, USA). The determined R-R intervals were subsequently analyzed by the CGSA method, as described by Yamamoto and Hughson [13,15]. The procedure involved 5 min beat-to-beat R-R intervals. Unequal R-R intervals were aligned sequentially to obtain equally spaced samples, in which the spectra were reported to have no significant difference from HRV spectra for the interpolated time series (the sample rate was determined from the mean R-R interval) [19]. CGSA was performed to estimate the power spectra in this time series, with averages of 256-beat time-shifted ensembles. From the harmonic component, the integrated powers at the LF and HF regions were defined as 0.0–0.15 Hz and 0.15–0.50 Hz, respectively. The ratio of HF power (P_{HF}) to total power (P_{Tot}), and the ratio of LF power (P_{LF}) to P_{HF}, were used for statistical comparisons as indicators of PNS and SNS activities. From the fractal component, the percentages of the random fractal components (%fractal) to P_{Tot} were calculated, and the fractal component was plotted on 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 the Nyquist frequency to the point corresponding to 0.3 Hz. The upper limit of the regression was extended to the end of the Fourier components (depending on the linearity of the decay beyond 0.3 Hz).

Statistical analysis

Values were expressed as means ± SD. Data were analyzed by repeated measure one-way analysis of variance (ANOVA). The least significant difference (LSD) test was conducted for multiple comparisons within a group

when the null hypothesis was not applicable. Student's *t*-test was also used for comparisons between groups. $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the baseline hemodynamic and catecholamine values during the infusions of Ca^{2+} antagonists. Compared with control measurements, systolic arterial pressure decreased significantly during infusion of the maximum dose of the Ca^{2+} antagonists, whereas diastolic arterial pressure showed no difference. A significant heart rate increase, compared with the control, was found with 3.2μg·kg^{-1}·min^{-1} nicardipine infusions, which also induced a significant increase in heart rate compared with the equivalent doses of 1.6μg·kg^{-1}·min^{-1} and 3.2μg·kg^{-1}·min^{-1} diltiazem infusions. However, the heart rate did not change from the control level during diltiazem infusions.

As for catecholamine levels, nicardipine infusion increased norepinephrine levels significantly at a dose of 3.2μg·kg^{-1}·min^{-1}, whereas diltiazem did not induce any change in norepinephrine levels during infusions.

Table 2 shows the findings of the statistical analyses for HRV derived from CGSA. All measurements were

Table 1. Baseline values for blood pressure, heart rate, and plasma catecholamines during infusions of Ca^{2+} antagonists

	Nicardipine (μg·kg^{-1}·min^{-1}) ($n = 9$)				
	Control	0.4	0.8	1.6	3.2
SAP (mmHg)	114.8 ± 9.0	111.8 ± 9.2	111.2 ± 9.2	108.9 ± 7.4	107.3 ± 7.6*
DAP (mmHg)	63.4 ± 6.7	61.9 ± 7.1	60.7 ± 5.3	59.3 ± 4.4	57.3 ± 3.5
mHR (/min)	65.7 ± 7.2	64.6 ± 8.8	67.3 ± 9.0	73.0 ± 8.3**	80.8 ± 11.5*;**
Nor (pg/ml)	215.1 ± 41.4	230.9 ± 65.9	250.8 ± 74.7	279.6 ± 71.4	334.4 ± 97.9*
Epi (pg/ml)	20.4 ± 9.9	19.0 ± 10.4	20.4 ± 11.9	21.1 ± 10.0	23.1 ± 13.1
	Diltiazem (μg·kg^{-1}·min^{-1}) ($n = 9$)				
	Control	2	4	8	16
SAP (mmHg)	119.3 ± 9.2	116.5 ± 9.2	114.6 ± 7.7	112.5 ± 6.6	109.4 ± 6.6*
DAP (mmHg)	64.9 ± 10.1	63.2 ± 9.8	60.6 ± 8.1	60.0 ± 7.2	58.8 ± 5.4
mHR (/min)	66.7 ± 7.4	65.0 ± 6.9	64.3 ± 6.6	64.2 ± 6.6	65.8 ± 6.7
Nor (pg/ml)	281.9 ± 84.0	310.9 ± 81.8	302.3 ± 85.9	317.6 ± 86.6	350.0 ± 89.8
Epi (pg/ml)	25.5 ± 7.4	23.4 ± 6.0	24.3 ± 7.3	25.0 ± 9.1	26.6 ± 8.7

* $P < 0.05$ vs control; ** $P < 0.05$ vs equivalent dose of diltiazem
Values are expressed as means ± SD
SAP, Systolic arterial pressure; DAP, diastolic arterial pressure; m-HR, mean heart rate; Nor, norepinephrine; Epi, epinephrine

Table 2. Statistical analysis of parameters of heart rate variability derived from CGSA during infusions of Ca^{2+} antagonists

	Nicardipine (μg·kg^{-1}·min^{-1}) ($n = 9$)				
	Control	0.4	0.8	1.6	3.2
SNS indicator	0.67 ± 0.34	0.65 ± 0.48	1.10 ± 0.92	1.16 ± 0.86	2.00 ± 1.57*
PNS indicator	0.29 ± 0.15	0.32 ± 0.21	0.29 ± 0.18	0.18 ± 0.11**	0.10 ± 0.05*;**
%Fractal	54.2 ± 13.3	53.1 ± 19.5	53.5 ± 18.7	67.0 ± 14.9	75.6 ± 9.8*;**
β	0.86 ± 0.22	0.82 ± 0.36	0.98 ± 0.32**	1.19 ± 0.34**	1.32 ± 0.46*;**
	Diltiazem (μg·kg^{-1}·min^{-1}) ($n = 9$)				
	Control	2	4	8	16
SNS indicator	0.58 ± 0.56	0.68 ± 0.33	0.92 ± 0.65	0.70 ± 0.33	0.83 ± 0.48
PNS indicator	0.32 ± 0.18	0.37 ± 0.12	0.43 ± 0.07	0.42 ± 0.13	0.41 ± 0.11
%Fractal	65.4 ± 16.8	60.0 ± 12.9	52.6 ± 6.5	54.1 ± 12.6	55.5 ± 10.0
β	0.61 ± 0.26	0.47 ± 0.26	0.52 ± 0.18	0.56 ± 0.25	0.52 ± 0.25

* $P < 0.05$ vs control; ** $P < 0.05$ vs equivalent dose of diltiazem
Values are expressed as means ± SD
SNS indicator, Sympathetic nervous system indicator (P_{LF}/P_{HF} ratio); PNS indicator, parasympathetic nervous system indicator (P_{HF}/P_{Tot} ratio); CGSA, coarse graining spectral analysis. See text for explanaturs of %fractal, β, P_{HF}/P_{Tot}, and P_{LF}/P_{HF}

affected during the 3.2 μg·kg^{-1}·min^{-1} infusion of nicardipine. That is, the SNS indicator, %fractal, and β were significantly increased, compared with control values, whereas the PNS indicator was significantly decreased. Significant differences from the equivalent diltiazem infusion were also found in the PNS indicator and β at 1.6 μg·kg^{-1}·min^{-1}, and in β at the maximum dose of nicardipine infusion. During diltiazem infusions, no significant differences from the control values were found for any of the measurements.

Discussion

In reviewing previous studies, we noted that findings consistently showed that the intravenous administration of nicardipine induced a marked increase in heart rate and levels of plasma norepinephrines, owing to the activation of the sympathetic nervous system, in both normotensive and hypertensive subjects [2–4]. For diltiazem, several different findings have been reported, and these differences may have resulted from differences in subjects and methods. Amodeo et al. [5] reported that immediate intravenous administration of diltiazem increased the heart rate in hypertensive patients, and this was not associated with an increase in the plasma norepinephrine level. Long-term oral administration of diltiazem, however, caused a decrease in the heart rate in both hypertensive patients and healthy volunteers [2,6]. Although this has not been thoroughly investigated, it is likely that diltiazem does not enhance sympathetic nervous system activity in humans [20]. In fact, our present findings showed no significant change in heart rate and plasma norepinephrine levels during continuous infusions of diltiazem, whereas systolic arterial pressure decreased significantly. The precise mechanisms responsible for these hemodynamic effects and the inhibited norepinephrine release during diltiazem administration shown in the present study have not been established. In rats, diltiazem has been shown to inhibit norepinephrine release from sympathetic nerve terminals and the adrenal gland through an alteration in adrenergic cardiovascular stimulation [21]. Imai et al. [22], however, reported that continuous infusion of diltiazem induced a gradual decrease in both arterial pressure and heart rate in rats, whereas it also induced activation of the sympathetic nervous system, as assessed by the correlation between systolic pressure and norepinephrine. Recently, it has been suggested that diltiazem has inhibitory effects on both prejunctional and postjunctional sympathetic transmission [23].

Regarding the effect of calcium antagonists on heart rate variability (HRV), Bekheit et al. [8] were the first to investigate HRV after myocardial infarction in patients treated with diltiazem. They observed that diltiazem reduced the LF component without significantly changing arterial pressure. Yamasaki et al. [9] also reported a decrease in the LF component, with the HF component not showing any difference, in vasospastic angina patients under conditions of rate-controlled respiration, as used in the present study. It was suggested that diltiazem may have effects only on sympathetic nervous activity and not on vagal cardiac activity, which would be advantageous for patients with ischemic heart disease [9]. In contrast, Frey et al. [10] observed that diltiazem increased the HF power spectra in patients with coronary heart disease, and they suggested that diltiazem enhanced the vagal influence on the heart. Cook et al. [11] reported another result from 24-h ECG analysis, observing that diltiazem had no effect on any measure of HRV in normal subjects. In the present study, no significant difference was found in any parameters derived from HRV during diltiazem infusions, whereas systolic arterial pressure was significantly reduced. Butler et al. [16,17] induced the arterial baroreceptor reflex using lower body negative pressure and orthostatic challenge, and observed that the SNS indicator increased whereas the PNS indicator decreased in frequency domain analysis. The difference between their observations and our findings may result from differences in the subjects and methods. However, the present findings appear to suggest that diltiazem inhibits the sympathetic activation caused by the arterial baroreceptor reflex.

As for nicardipine, Lucini et al. [12] reported that, in patients with mild hypertension, nicardipine induced a significant increase in the LF component (in normalized units), whereas the HF component was decreased. They attributed this finding to a sympathovagal balance towards sympathetic dominance. Kimura et al. [24] also observed that nicardipine induced increases in the LF component of HRV during anesthesia. The present findings were consistent with the observations reported by Lucini and Kimura. In the present study, nicardipine induced increases in the SNS indicator and decreases in the PNS indicator. Thus, it was suggested that, through the window of HRV, nicardipine activates the SNS and suppresses the PNS, in terms of neural control of the heart.

With this autonomic neural alteration, the fractal slope of β in HRV was significantly affected during nicardipine infusions, whereas none of the parameters of HRV were affected during diltiazem infusions. Butler et al. [16,17] studied the effects of sympathetic activation on the fractal dimensions of HRV, and showed that β was significantly affected during orthostatic stimulation and lower body negative pressure, which were associated with decreased PNS and increased SNS indicators, respectively. We previously reported similar observations obtained under pharma-

cological conditions. Nitroglycerin, with rate-controlled respiration, induced increases in β, and this finding was associated with increases in plasma catecholamine levels [25]. In the present study, we also observed that, during nicardipine infusions, the slope of β became steeper than the control level under the same circumstances as it did with nitroglycerin administration. However, diltiazem did not have any effect on the slope of β, and levels of plasma catecholamines remained stable with diltiazem infusion.

Yamamoto et al. [18] reported that, in subjects with normal cardiac function, the fractal components of resting HRV were primarily mediated via vagal cardiac neural activity, while the SNS played a minor role in modulating the fractal nature of HRV [15]. Changes in the modulation of the heart rate by the autonomic nervous system would affect not only the harmonic components but also the nonharmonic 1/f components of HRV. Thus, the present findings strongly suggest that nicardipine suppressed vagal cardiac neural outflow and activated the SNS, results which, subsequently, produced a change in the fractal features of HRV, whereas diltiazem preserved the basic neural balance of the autonomic nervous system in terms of heart rate control.

In this study, we controlled the respiratory rate, because it has been emphasized that control of respiration was needed when frequency domain analysis of HRV was employed [26,27]. The need for controlled respiration is based on the finding that respiratory sinus arrhythmia was predominantly affected by respiratory activity, and was suggested to be a predictor of vagal cardiac neural activity [28]. Recently, however, it was reported that the fractal features of HRV were, basically, not affected by respiratory arrhythmia [29] and the HF component of HRV did not always reflect the parasympathetic nervous activity on the heart [30]. Furthermore, it has been reported that a stressful mental test induced a significant decrease in β [31]. Thus, the voluntary control of respiration may have affected the baseline fractal features of HRV. In fact, the β value during the control period in the present study was 0.86 $\pm$ 0.22 for the nicardipine group, and 0.61 $\pm$ 0.26 for the diltiazem group, values that were slightly lower than those obtained during free respiration. The precise mechanisms that give rise to the fractal features of HRV remain unknown [32]; thus, further studies are needed to clarify the relationship between autonomic neural mechanisms and fluctuations in human HRV.

In conclusion, the effects of nicardipine and diltiazem on HRV were studied, using CGSA. Both nicardipine and diltiazem induced reductions in blood pressure, in a similar manner; however, nicardipine decreased the PNS indicator, increased the SNS indicator, and increased the fractal slope of β significantly, and these effects were associated with an increase in plasma catecholamines. Diltiazem caused no marked change in HRV, with stable catecholamine levels being maintained throughout the period of the diltiazem infusions.

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