Circadian Rhythms of Atrioventricular Conduction Properties in Chronic Atrial Fibrillation With and Without Heart Failure

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Objectives. We examined the circadian variations in atrioventricular (AV) conduction properties during atrial fibrillation (AF) by a technique based on the Lorenz plot of successive ventricular response (VR) intervals and analyzed their relations with clinical features.

Background. The VR interval in chronic AF shows circadian variation, which is attenuated in patients with an increased risk of death. Although the VR interval is determined by the dynamic processes in the AV node randomly stimulated by rapid atrial activity, the circadian variations of the AV conduction properties related to this mechanism are unknown.

Methods. In 48 patients with chronic AF, Lorenz plots were generated on overlapping sequential segments of 512 VR intervals in 24-h ambulatory electrocardiograms. For each scatter plot, the 1.0-s intercept of the lower envelope ($LE_{1.0}$) of the plot and the degree of scatter above the envelope (root mean square difference from the envelope [scattering index]) were measured for estimating AV node refractoriness and concealed AV conduction, respectively.

Results. In all patients, a significant circadian rhythm was observed for the average VR interval, $LE_{1.0}$ and scattering index, with an acrophase occurring at night. The mesor, amplitude and acrophase of $LE_{1.0}$ and the scattering index closely and independently correlated with the corresponding rhythm variables of the average VR interval (partial r^2 0.98, 0.86 and 0.68 for $LE_{1.0}$ and 0.98, 0.92 and 0.92 for scattering index). The amplitudes of these measures were lower in patients with congestive heart failure (CHF) even after adjustment for the effects of age, duration of AF, medications, left atrial diameter and blood pressure (p < 0.01 for all).

Conclusions. These results suggest that 1) both AV node refractoriness and the degree of concealed AV conduction during AF may show a circadian rhythm; 2) the circadian rhythms of these properties may independently contribute to the circadian variation of the VR interval; and 3) these circadian rhythms may be attenuated in patients with CHF.

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In patients with chronic atrial fibrillation (AF), long-term ambulatory electrocardiographic (ECG) monitoring often reveals circadian variation in the ventricular response (VR) (1). Recent studies (2,3) have reported that attenuation of this circadian variation is associated with an increased risk of death in patients with AF. During AF, the short-term variation in the VR interval appears to be highly irregular (4,5). The mechanism of this irregularity has been explained as concealed atrioventricular (AV) conduction; that is, the rapid and random atrial impulses that continuously bombard the AV node lead to summation or cancellation, or both, of wave fronts in the AV node, thereby creating a high level of disorganization of the penetrating impulses (6–8). However, the short-term variation in the VR interval in AF may not be completely

random; rather, it may have a distinct lower limit resulting from the refractoriness of the AV node that determines the shortest cycle length of successive impulses that can be conducted by the AV node (9–12). Thus, the circadian variation of the VR may be attributable, at least in part, to the circadian variations in AV conduction properties, including concealed AV conduction and AV node refractoriness. However, limited data are available on the circadian variations in these AV conduction properties during AF.

In this study, we analyzed circadian variations in AV conduction properties during chronic AF by a noninvasive technique based on the Lorenz plot of VR interval sequence (10–12). This technique revealed the underlying structure of VR interval dynamics and provided information about AV conduction during AF. The purposes of this study were to examine 1) whether the AV conduction properties assessed by this noninvasive technique show a circadian variation during chronic AF; 2) whether the circadian variations of the AV conduction properties, if they exist, explain the circadian variation in the VR interval; and 3) whether the circadian variations differ between patients with different clinical features of AF.

Abbreviations and Acronyms

AF	=	atrial fibrillation
AV	=	atrioventricular
CHF	=	congestive heart failure
ECG	=	electrocardiogram, electrocardiographic
$LE_{1.0}$	=	1.0-s intercept of the regression line on the lower envelope of the Lorenz plot of ventricular response intervals
LE slope	=	slope of the regression line on the lower envelope of the Lorenz plot of ventricular response intervals
scattering index	=	the degree of scatter above the lower envelope of the Lorenz plot of ventricular response intervals calculated as the root mean square difference of VR intervals from the regression line on the lower envelope
VR	=	ventricular response

Methods

Study patients. We studied the ambulatory 24-h ECGs of 48 patients with chronic AF (mean age $\pm$ SD 67 $\pm$ 12 years [range 42 to 84]). Data were excluded if the ambulatory ECG showed 1) periods of artifacts or noise for >10% of the total monitoring time, 2) frequent ventricular ectopic beats that comprised >10% of the total ventricular beats, 3) chronic bundle branch block, or 4) atrial tachyarrhythmias other than AF, even transiently. The procedures of this study were in accordance with the ethical guidelines of Nagoya City University Medical School.

The duration of AF ranged from 1 month to >20 years (mean 6.1 $\pm$ 4.4 years, Table 1). All except 9 of the 48 patients had associated diseases, including coronary artery disease, systemic hypertension, dilated cardiomyopathy, valvular heart disease and hyperthyroidism. All but 3 patients were receiving cardiovascular medications; 35 were receiving AV node blocking drugs (digoxin or calcium channel antagonists, or both), but none were receiving beta-adrenergic blocking agents or class Ia, Ic or III antiarrhythmic drugs. The patients were classified into two groups according to the presence of clinical symptoms of chronic heart failure (CHF) of New York Heart Association class II or greater at the time of ambulatory ECG monitoring.

Data collection. Ambulatory ECGs were recorded with use of a portable tape recorder (DMC-3253, Nihon Koden, Tokyo, Japan) for ≥24 h during usual daily activities. In six patients, a second ambulatory ECG was recorded 12 to 82 days (mean $\pm$ SD 37 $\pm$ 25) after the first recording under similar clinical conditions (functional class and medications). The data in these six patients were used to evaluate the reproducibility of measurements.

The tapes were played back with an ECG scanner (DMC-4100, Nihon Koden), at a rate of 240 times real time and digitized to 12-bit data at a sampling frequency of 128 Hz. All QRS complexes were detected and labeled automatically. The results of automatic analysis were completely reviewed and any errors in R wave detection and QRS labeling (wide or normal)

Table 1. Clinical Characteristics of Study Patients

	All Patients (n = 48)	CHF− (n = 30)	CHF+ (n = 18)
Age (yr)	67 ± 12	64 ± 13	71 ± 10
Men	34 (71%)	20 (67%)	14 (78%)
Duration of AF (yr)*	6.1 ± 4.4	4.9 ± 4.8	8.3 ± 3.6†
Associated disease			
None (lone AF)	9 (19%)	9 (30%)	0 (0%)†
Coronary artery disease	3 (6%)	1 (3%)	2 (11%)
Systemic hypertension	7 (15%)	5 (17%)	2 (11%)
Dilated cardiomyopathy	2 (4%)	1 (3%)	1 (6%)
Valvular disease	26 (54%)	14 (47%)	12 (67%)
Hyperthyroidism	2 (4%)	1 (3%)	1 (6%)
Medications			
None	3 (6%)	3 (10%)	0 (0%)
Digoxin	33 (69%)	19 (63%)	14 (78%)
Calcium antagonist	9 (19%)	4 (13%)	5 (28%)
ACE inhibitor	11 (23%)	3 (10%)	8 (44%)†
Diuretic drugs	16 (33%)	11 (37%)	5 (28%)
Vasodilator	6 (13%)	2 (7%)	4 (22%)†
Warfarin	16 (33%)	13 (43%)	3 (17%)
Mexiletine	2 (4%)	0 (0%)	2 (11%)
LA diam (cm)†	4.7 ± 0.5	4.3 ± 0.5	5.3 ± 0.4†
Systolic BP (mm Hg)	134 ± 20	140 ± 21	124 ± 17†
Diastolic BP (mm Hg)	75 ± 9	77 ± 10	72 ± 8

*Durations >20 years were counted as 20 years. †$p < 0.05$ versus patients without congestive heart failure (CHF−). Data are presented as mean value $\pm$ SD or number (%) of patients. ACE = angiotensin-converting enzyme; AF = atrial fibrillation; BP = blood pressure; CHF+ = patients with congestive heart failure (New York Heart Association class II or greater); LA diam = left atrial diameter measured by echocardiography.

were edited manually. The labels of each QRS complex and the preceding RR interval were transferred to a personal computer (P5-100, Gateway 2000).

To examine the circadian variations, 24-h RR interval time series were divided into 288 overlapping segments of 512 consecutive RR intervals, so that a new segment began every 5 min. If the RR interval sequence in a segment was interrupted by a period of artifact or noise that continued for >3 s or if a segment included ≥52 ventricular ectopic beats (≥10%), the segment was excluded. For each analyzable segment, the mean of all AV conducted RR intervals (VR interval) was calculated as the average VR interval and was used to evaluate the circadian variation in the VR interval.

Lorenz plot analysis of VR interval dynamics. Lorenz plots were generated for the VR interval sequence in each segment according to the previously reported method (10,11); that is, each VR interval was plotted as the value on the vertical axis against the immediately preceding VR interval as the value on the horizontal axis. Before evaluating VR interval dynamics, the pattern of Lorenz plots was inspected to distinguish AF from atrial flutter and other supraventricular tachycardias with apparently irregular RR intervals (10) and to differentiate between ventricular ectopic beats and aberrant ventricular conduction (13). The Lorenz plots of VR intervals in AF showed diffuse scatter within a sector form (Fig. 1). In contrast, atrial flutter and supraventricular tachycardia showed lattice-
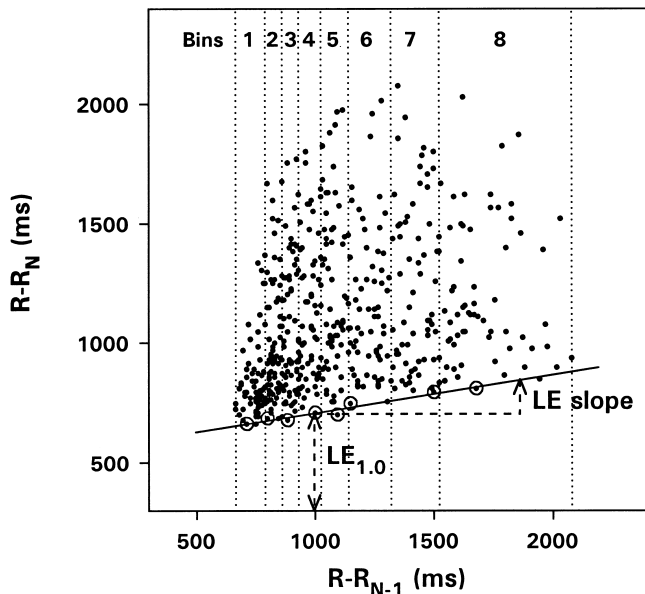
Figure 1. Lorenz plots of 512 successive RR intervals in AF and linear regression of the lower envelope of the plots. **Dotted vertical lines** indicate the separations between bins, each of which includes 64 points of the plots. **Circled points** indicate the minimal values for individual bins. The **solid line** indicates the regression line on the minimal values. R-R_N = nth RR interval; R-R_{N-1} = (n−1)th RR interval.

Figure 2. Schematic representation of the variables that characterize a circadian rhythm in a chronobiologic analysis performed by the method of least square cosine curve fitting. Acrophase = time of peak estimated rhythm; mesor = midline estimating statistics of rhythm.

like clusters on the plot (10), although patients who showed such patterns even transiently were not included in the study group. Also, the VR intervals with aberrant ventricular conduction appeared on the lower envelope of the plots of the VR intervals without aberrant ventricular conduction, whereas the distribution of the RR intervals of ventricular ectopic beats was not related to the envelope.

In the Lorenz plot of VR intervals during AF, the VR intervals occurring after a particular length of preceding VR intervals show a distribution with a distinct lower limit. Thus, the set of the minimal values of VR intervals for different lengths of preceding VR intervals forms a distinct line—that is, the lower envelope—above which longer VR intervals for each preceding VR interval show wide scatter (Fig. 1). To quantify this characteristic structure, the following three measures were calculated: 1) slope of the regression line on the lower envelope (LE slope); 2) 1.0-s intercept of the regression line on the lower envelope ($LE_{1.0}$); and 3) the degree of scatter above the lower envelope calculated as the root mean square difference of VR intervals from the regression line on the lower envelope (scattering index).

The linear regression of the lower envelope was performed semiautomatically as follows: 1) The horizontal axis (preceding VR interval) was divided into eight consecutive bins so that each bin included 64 points of data; 2) in each bin, the minimal value of the subsequent VR interval was determined; 3) the eight minimal values thus obtained were linearly regressed on the average preceding VR interval calculated for each bin; and 4) the regression line on the scattergram for each segment was inspected on the computer display by an investigator who,
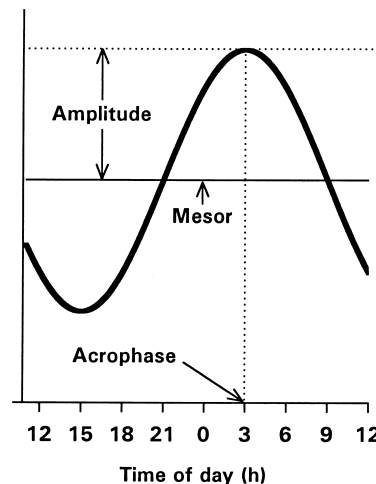
without knowledge of the patients' clinical features, excluded the segments that did not reveal a linear lower envelope in the scattergram. In this analysis, we based the division of the consecutive bins on the number of points rather than on prospectively defined RR intervals so that the shortest possible VR interval would appear with the same probability for all bins. Among all tapes, the median and range of the number of segments that met all criteria (artifacts, noise, number of ventricular ectopic beats and shape of the scattergram) were 285 (99%) and 213 to 288 (74% to 100%), respectively.

Analysis of circadian rhythmicity. To evaluate the circadian rhythmicity of the variations in the average VR interval, LE slope, $LE_{1.0}$ and scattering index, we used an algorithm for least square cosine-curve fitting (14) that is applicable to time series with defective data points. The algorithm estimated the following four variables that characterize circadian rhythmicity: 1) significance of rhythm, 2) midline estimating statistics of rhythm (mesor), 3) amplitude, and 4) time of peak estimated rhythm (acrophase) (Fig. 2). A circadian rhythm was considered to be present when the significance of rhythm showed a p value < 0.05.

Statistical analysis. The Statistical Analysis System program package (SAS Institute) was used. Statistical differences in mean values and frequencies were evaluated by paired *t* tests and chi-square tests with the Yates correction. Correlations between two variables were evaluated by the Pearson product-moment correlation coefficient. Multivariate correlations were evaluated by the SAS regression procedure. To compare mean values between two groups that differed in covariates, analysis of covariance in terms of the SAS general linear model was used to adjust for the effects of the covariates on the group means. Intraindividual reproducibility of each measure over time was examined by the intraclass correlation coefficient for one-way random effects analysis of variance with defining subjects as the random factor (15) and by the coefficient of
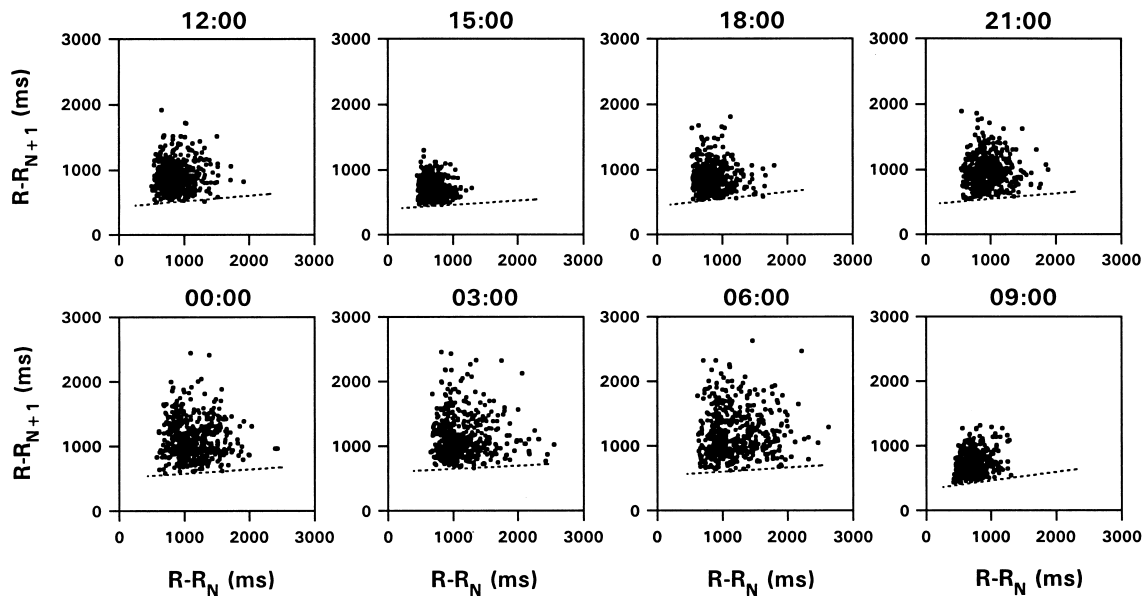
Figure 3. Lorenz plots of 512 successive RR intervals at different times of day (shown above each panel) in a patient with chronic AF without CHF. The **dashed line** in each panel indicates the regression line on the lower envelope of each scattergram. Both the position of the lower envelope and the degree of scatter above the lower envelope show diurnal variations. $R\text{-}R_N$ = nth RR interval; $R\text{-}R_{N+1}$ = (n + 1)th RR interval.

repeatability of Bland and Altman (16), which estimates the limit for a true change that is distinguishable from random errors between repeated measurements. Data are presented as mean value ± SD except for the regression parameters in multiple regression models and the group means adjusted for the effects of covariates, which are presented as least square mean value ± SEM. A p value <0.05 was considered significant.

Results

Circadian rhythms in measures of Lorenz plot. Figure 3 shows Lorenz plots of the 512 RR intervals at eight time points during 24-h ECG recording in a patient with chronic AF without CHF. At night, an upward shift of the lower envelope of the Lorenz plot (dashed line) and an increase in the degree of scatter above the envelope are observed. Figure 4 shows the 24-h variations of the average VR interval, LE slope, $LE_{1.0}$ and scattering index obtained from the same ECG recording at a time resolution of 5 min.

In all 24-h recordings, significant circadian rhythms were observed for the average VR interval, $LE_{1.0}$ and scattering index (p < 0.001 for all measures for all tapes) with the acrophase at 23:37 to 04:40 h, 23:28 to 04:55 h and 23:10 to 04:23 h, respectively. We detected in 30 patients (63%) a significant circadian rhythmicity of the LE slope in which no consistent distribution of acrophase was observed (mean ± SD 23:46 h ± 477 min; range 12:16 to 11:23 h). Therefore, only the 24-h average (mean LE slope) was evaluated for the LE slope in the subsequent analyses.

Relation to the circadian rhythm of the VR interval. The mean LE slope correlated negatively with the mesor and amplitude of the average VR interval (Table 2), indicating that the LE slope was steeper in patients with a shorter average VR interval and a weaker circadian rhythmicity of the average VR interval. In contrast, the mesor, amplitude and acrophase of the

$LE_{1.0}$ closely correlated with those of the average VR interval (r = 0.92, 0.82 and 0.94, respectively). Similar correlations of the circadian rhythm variables were also observed between the scattering index and the average VR interval (r = 0.89, 0.89 and 0.99, respectively). The circadian rhythm variables of $LE_{1.0}$ and the scattering index showed internal correlations (r = 0.65, 0.51 and 0.89 for the mesor, amplitude and acrophase, respectively), which might result in a spurious correlation. However, the partial correlation coefficient showed that the correlations in the rhythm variables both between $LE_{1.0}$ and the average VR interval and between the scattering index and the average VR interval were significant and independent of each other (Table 3).

Relations with clinical features. The circadian rhythmicities of the average VR interval, $LE_{1.0}$ and scattering index appeared attenuated in patients with AF and CHF (Fig. 5). However, the patients with and without CHF differed in duration of AF, medications used, left atrial diameter and blood pressure (Table 1). Also, the circadian rhythm variables of the average VR interval, $LE_{1.0}$ and scattering index and mean LE slope showed significant correlations with some of these clinical features (Table 4). Therefore, we compared the two patient groups after adjustment for the effects of these covariates (age, duration of AF, medications, left atrial diameter and systolic and diastolic blood pressure). The results revealed that the amplitude of the average VR interval was attenuated in patients with CHF compared with that in patients without CHF (p < 0.001, Fig. 6). The amplitudes of the
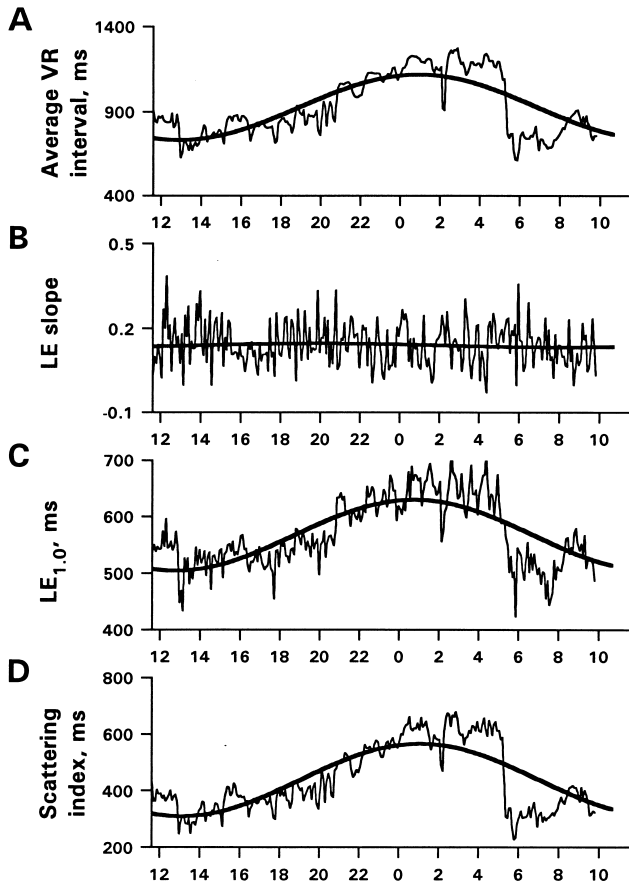
Figure 4. Circadian variations in the average VR interval and measures of the Lorenz plot in a patient with chronic AF without CHF. **Thick solid lines** indicate the least square cosine curves fitted to the circadian variation of individual variables. The time resolution is 5 min for all plots.

$LE_{1.0}$ and scattering index were also lower in patients with than in those without CHF (p < 0.001 for both). Additionally, the mean LE slope was steeper in patients with than in those without CHF (adjusted least square mean ± SEM, 0.18 ± 0.01 vs. 0.12 ± 0.01, p < 0.001).

The differences in the mesor and acrophase of the average VR interval, $LE_{1.0}$ and scattering index between patients with and without CHF were not significant after the adjustment. Also, in these multivariate models, the effects of the covariates, including medications used, were no longer significant for any variables. Similarly, analysis of covariance adjusted for the same covariates revealed no difference in any variable based on gender or the presence of associated disease, except that the mean LE slope was less steep in patients with lone AF than in those with associated disease (adjusted least square mean ± SEM 0.11 ± 0.02 vs. 0.16 ± 0.01, p = 0.015).

Reproducibility of measures. All variables measured in this study showed good reproducibility in the six patients with repeat analyses (Table 5). There was no significant difference in the mean values of any variables between time 1 and time 2. The intraclass correlation coefficients and the coefficients of

Table 2. Relation of Circadian Rhythm Variables Between Average Ventricular Response Interval and Lorenz Plot Measures

AV Conduction Property	Average VR Interval		
	Mesor	Amplitude	Acrophase
Mean LE slope	−0.53*	−0.44*	−0.08
$LE_{1.0}$			
Mesor	0.92*	0.42*	−0.09
Amplitude	0.62*	0.82*	0.27
Acrophase	−0.10	0.39*	0.94*
Scattering index			
Mesor	0.89*	0.54*	0.09
Amplitude	0.33*	0.89*	0.49*
Acrophase	0.05	0.46*	0.99*

*Significant correlation coefficient (p < 0.05). Values presented are correlation coefficients. LE slope = slope of the regression line on the lower envelope of the Lorenz plot of ventricular response intervals; $LE_{1.0}$ = 1.0-s intercept of the regression line on the lower envelope of the Lorenz plot; scattering index = degree of scatter above the lower envelope of the Lorenz plot calculated as root mean square difference of ventricular response (VR) intervals from the regression line on the lower envelope.

repeatability showed excellent agreement between the repeat measurements for all variables.

Discussion

Major findings. We observed significant, reproducible circadian rhythms in new noninvasive measures of AV conduction properties derived from Lorenz plot analysis of VR interval dynamics during AF, that is, the $LE_{1.0}$ and the scattering index. The circadian rhythm variables (mesor, amplitude and acrophase) of these measures closely and independently correlated with the corresponding variables of circadian variation in the VR interval. The quantitative method used in this study seems useful for characterizing the autonomic and other mechanisms underlying the circadian variation of VR during AF.

Measures of Lorenz plot and electrophysiologic properties of the AV node. Several studies (10–12) reported the relation between the lower envelope of the Lorenz plot of the VR

Table 3. Regression Analysis of Circadian Rhythm Variables of Average Ventricular Response Interval With Those for Lorenz Plot Measures

Dependent Variable	Independent Variable	Parameter*	p Value†	Partial r^2
Mesor	Intercept	−170.7 ± 11.0	0.0001	
	$LE_{1.0}$	1.14 ± 0.03	0.0001	0.984
	Scattering index	0.99 ± 0.03	0.0001	0.976
Amplitude	Intercept	3.30 ± 4.50	0.469	
	$LE_{1.0}$	1.16 ± 0.08	0.0001	0.862
	Scattering index	0.98 ± 0.05	0.0001	0.916
Acrophase	Intercept	0.05 ± 0.04	0.207	
	$LE_{1.0}$	0.25 ± 0.03	0.0001	0.679
	Scattering index	0.69 ± 0.04	0.0001	0.919

*Regression parameter ± SE of the parameter. †p value for null hypothesis that the regression parameter is zero. Abbreviations as in Table 2.
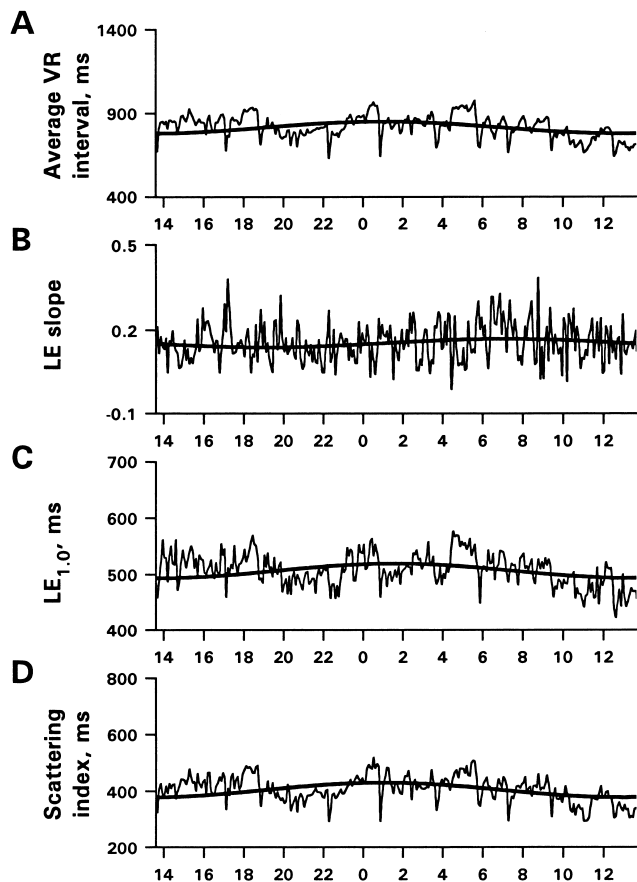
Figure 5. Circadian variations in the average VR interval and measures of the Lorenz plot in a patient with AF and CHF. **Thick solid lines** indicate the least square cosine curves fitted to the circadian variation of individual variables.

interval during AF and the cycle length–dependent function of the functional refractory period of the AV node. Studies in dogs (9–11) reported that the length of the minimal VR interval during AF was proportional to the functional refrac-

tory period determined by the conventional method with atrial pacing; the minimal VR interval was approximately equal to the functional refractory period when the latter was short, but it was longer than the functional refractory period when the latter was long (11). Another study in dogs (17) showed that the cycle length–dependent shortening of the functional refractory period was induced maximally by only one short cycle, and one normal basic cycle was sufficient to dissipate the effect. These data suggest that the variations in the envelope of the Lorenz plot that reflect cycle length–dependent changes in the minimal VR interval during AF may be attributable to variations in AV node refractoriness; more specifically, the intercept ($LE_{1.0}$) and slope (LE slope) of the envelope of the Lorenz plot during AF may be related to the functional refractory period of the AV node and its dependence on cycle length, respectively, although these relations may be lost when the functional refractory period is long.

In contrast, the degree of scatter above the lower envelope of Lorenz plot (scattering index) may be related to the electrophysiologic phenomenon known as concealed conduction. Although the short-term VR irregularity during AF may originate primarily from irregularity in atrial activity (4), the mechanism more directly responsible for the irregularity is believed to be concealed conduction, that is, incomplete penetration of the impulses through the AV node due to rapid and random inputs from the adjacent atrial tissue (6–8,18). If the shortest VR interval can be thought to correspond to AV conduction with no or minimal concealed impulses, the degree of scatter above the envelope may be a marker of the degree of concealed AV conduction.

Circadian variations in measures of Lorenz plot. In an earlier study, Suzuki et al.(12) applied Lorenz plot analysis to the VR interval segments selected from ambulatory ECG recordings in patients with AF. They observed an upward shift of the lower envelope during the night, which we confirmed in the present study. In their study, Suzuki et al. generated each Lorenz plot for 1-h segments (3,600 to 4,000 VR intervals), a

Table 4. Relations Between Clinical Features of Atrial Fibrillation and Circadian Rhythm Variables of Average Ventricular Response Interval and Lorenz Plot Measures

	Age	AF Duration	LA Diam	Systolic BP	Diastolic BP
Average VR interval					
Mesor	−0.22	−0.16	−0.05	0.44*	−0.01
Amplitude	−0.48*	−0.32*	−0.49*	0.32*	0.13
Acrophase	−0.23	−0.04	0.18	0.02	0.22
Mean LE slope	−0.01	−0.01	0.54*	−0.42*	−0.45*
$LE_{1.0}$					
Mesor	−0.16	−0.11	0.13	0.38*	−0.13
Amplitude	−0.25	−0.28	−0.35*	0.28	−0.02
Acrophase	−0.19	0.14	0.25	0.01	0.22
Scattering index					
Mesor	−0.23	−0.20	−0.18	0.45*	0.15
Amplitude	−0.48*	−0.35*	−0.75*	0.27	0.25
Acrophase	−0.23	−0.01	0.15	0.03	0.21

*Significant correlation coefficient (p < 0.05). Values presented are correlation coefficients. Abbreviations as in Tables 1 and 2.
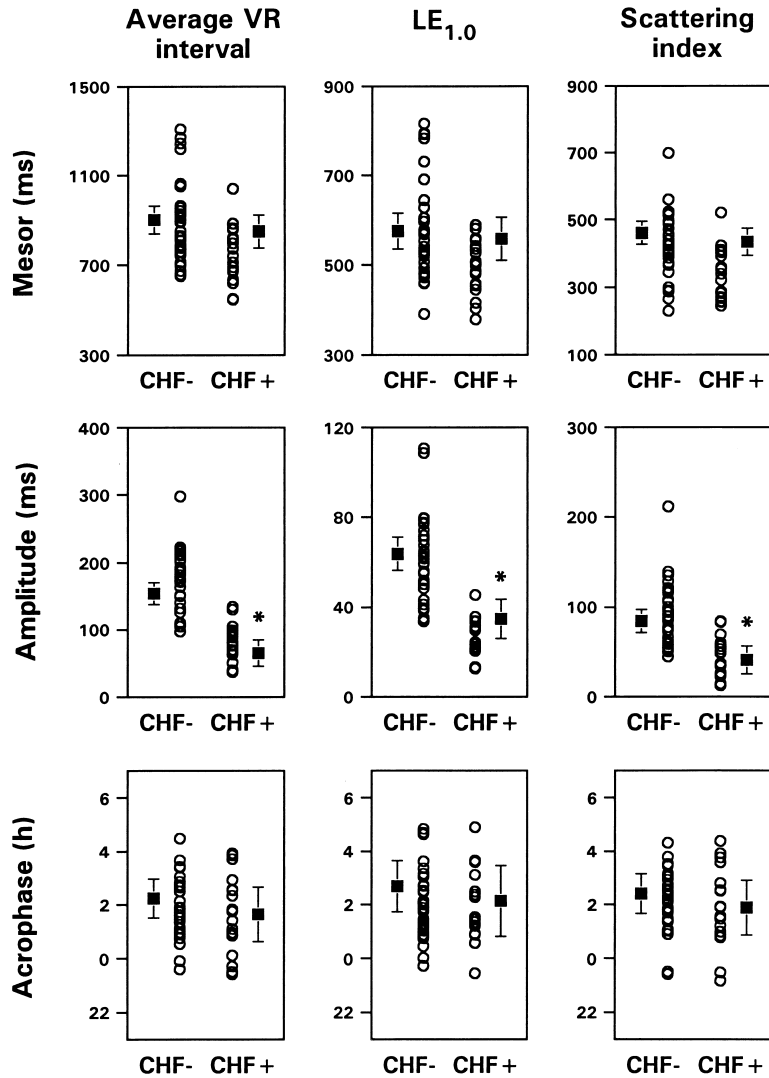
Figure 6. Comparison of circadian rhythm variables for the average VR interval and measures of the Lorenz plot in patients with (CHF+) and without (CHF−) CHF. **Open circles** indicate the raw data of the variables in individual patients. **Closed squares** and **error bars** indicate the least square mean ± SEM adjusted for the effects of age, duration of AF, medications, left atrial diameter and systolic and diastolic blood pressures. *Least square means are significantly different from the value for CHF− (p < 0.002).

segment length far longer than that used in our present study (512 intervals). In a recent study of the power spectral structure of 24-h VR interval variation during AF (5), we observed the 1/f noise-like characteristics suggestive of a fractal-like fluctuation in the VR interval spectrum below 0.005 Hz; above the frequency it showed the characteristics of white noise. This finding suggests that even VR fluctuations within several minutes could include important information concerning their regulation.

Although our results provide no direct evidence, the circadian variation in the $LE_{1.0}$ is most likely mediated by autonomic neural modulation of electrophysiologic properties of the AV node. Using sequential bedside electrophysiologic testing, Cinca et al. (19) demonstrated that the effective refractory period of the AV node also shows a distinct circadian rhythm with an acrophase during sleep. The velocity of AV conduction is decelerated by vagal stimulation and accelerated by sympathetic stimulation, and the autonomic

neural activity regulating AV conduction has been reported (20–22) to be parallel to that regulating sinoatrial rate. More directly, Van den Berg et al. (23) reported that methylatropine reduced the minimal RR interval during AF, suggesting that the vagal stimulation may prolong AV node refractoriness during AF. Additionally, the acrophase of the $LE_{1.0}$ that we observed is consistent with vagal augmentation and sympathetic attenuation, which are known to prevail at night through studies of autonomic regulation of the sinoatrial rate (24).

In the present study, we also observed a distinct circadian variation in the scattering index, suggesting that the degree of concealed AV conduction may also show a circadian variation. The circadian variation in the degree of concealment may be mediated primarily by the autonomic neural modulations of the atria. It has been established (25,26) that vagal activity markedly shortens atrial refractoriness, thereby reducing the wave length of the atrial f wave and increasing fibrillatory activity. An increased number of circulating wavelets in the

Table 5. Intraindividual Reproducibility of Circadian Rhythm Variables of Average Ventricular Response Interval and Lorenz Plot Measures

	Time 1	Time 2	ICC	p Value*	CR
Average VR interval					
Mesor (ms)	906 ± 252	871 ± 231	0.964	< 0.001	123
Amplitude (ms)	159 ± 59	145 ± 52	0.960	< 0.001	50
Acrophase (h $\pm$ min)	0216 ± 50	0209 ± 34	0.999	< 0.001	123
Mean LE slope	0.14 ± 0.02	0.14 ± 0.01	0.999	< 0.001	0.03
$LE_{1.0}$					
Mesor (ms)	596 ± 201	551 ± 161	0.879	0.002	175
Amplitude (ms)	58 ± 33	50 ± 25	0.973	< 0.001	24
Acrophase (h $\pm$ min)	0219 ± 51	0224 ± 34	0.995	< 0.001	114
Scattering index					
Mesor (ms)	411 ± 114	385 ± 93	0.871	0.002	104
Amplitude (ms)	73 ± 33	80 ± 38	0.966	< 0.001	24
Acrophase (h $\pm$ min)	0220 ± 47	0228 ± 26	0.996	< 0.001	110

*p value for the significance of ICC. Data for Time 1 and Time 2 are presented as mean value $\pm$ SD. CR = coefficient of repeatability; ICC = intraclass correlation coefficient; other abbreviations are as in Table 2.

atria enhances the concealed conduction in the AV node (6,7,27). Van den Berg et al. (23), in the study cited earlier, reported that the maximal VR interval during AF was also reduced by methylatropine, suggesting that vagal stimulation increases the degree of concealment. These facts support the view that the nocturnal increase in the scattering index is mediated by augmented vagal activity at night. Because the refractoriness of the atrium is also shortened with its expansion (28,29), the increase in venous return caused by the supine position might also contribute to the nocturnal increase.

Relations to circadian variation in VR. The VR interval in AF has been reported (1–3) to show distinct circadian variation with nocturnal lengthening. In a recent study, Stein et al. (2) reported that reduction of circadian variation in the VR interval was associated with a combined risk of death or need for valve surgery during a follow-up period of 9.1 years in patients with AF with nonischemic mitral regurgitation. Also, Frey et al. (3) reported in patients with AF and advanced CHF an association between decreased VR circadian variation and 12-month deterioration (death or listing for urgent heart transplantation). In these earlier studies (1–3), a change in AV node refractoriness induced by the autonomic nervous system was suggested as a mechanism for both the circadian variation of VR and its attenuation among high risk patients; however, there has been no direct evidence for this hypothesis.

Our present findings obtained by a noninvasive technique seem to support this hypothesis. However, our observations further suggest that a distinct circadian rhythm may exist not only in AV node refractoriness, but also in the degree of concealed AV conduction, and that each may contribute independently to the circadian variation in VR.

Limitations and clinical implications. The patients in the present study were heterogeneous in age, gender, duration of AF and associated diseases. Because the measurements were performed while the patients were taking their regular medications, we cannot exclude possible effects of selection bias; for

example, AV node blocking drugs were more likely to be prescribed for patients with shorter VR intervals and may have shifted the AV node refractoriness and VR interval to clinically more preferable levels. Therefore, our findings concerning the relations with clinical features should be considered preliminary.

Despite these limitations, our observations that patients with AF and CHF showed a reduction in the circadian rhythmicity of the average VR interval, $LE_{1.0}$ and scattering index even after adjustment for other clinical features may be of clinical importance. Several earlier studies (30,31) reported a marked reduction or absence of circadian rhythm of the autonomic indexes of heart rate variability in patients with CHF and sinus rhythm. Thus, the attenuated circadian rhythmicity of the average VR interval and the AV conduction properties observed in patients with AF and CHF may also reflect the reduced circadian rhythmicity in autonomic neural control. Additionally, our observations of a steeper 24-h mean LE slope in patients with CHF may be attributable at least in part to reduced vagal activity on the AV node, because vagal stimulation has been reported (32) to decrease the cycle length dependence of AV node refractoriness. These data suggest that it may be possible to obtain information concerning altered autonomic control of the VR interval in patients with AF and CHF with the noninvasive technique used in this study.

Conclusions. We examined the circadian variations in the properties of AV conduction during AF by a new noninvasive technique of sequential Lorenz plot of VR intervals. The results suggest that 1) both AV node refractoriness and the degree of concealed AV conduction during AF may show a circadian rhythm; 2) the circadian rhythms of these properties may contribute independently to the circadian variation of the VR interval; and 3) these circadian rhythms may be attenuated in patients with CHF. Our technique of analysis of ambulatory ECG recordings may provide a useful probe into the auto-

nomic and other mechanisms underlying circadian variation of VR in patients with chronic AF.

References

1. Raeder EA. Circadian fluctuations in ventricular response to atrial fibrillation. Am J Cardiol 1990;66:1013–6.

2. Stein KM, Borer JS, Hochreiter C, Devereux RB, Kligfield P. Variability of the ventricular response in atrial fibrillation and prognosis in chronic nonischemic mitral regurgitation. Am J Cardiol 1994;74:906–11.

3. Frey B, Heinz G, Binder T, et al. Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart failure. Am Heart J 1995;129:58–65.

4. Bootsma BK, Hoelen AJ, Strackee J, Meijler FL. Analysis of R-R intervals in patients with atrial fibrillation at rest and during exercise. Circulation 1970;41:783–94.

5. Hayano J, Yamasaki F, Sakata S, Okada A, Mukai S, Fujinami T. Spectral characteristics of ventricular response to atrial fibrillation. Am J Physiol Heart Circ Physiol. In press.

6. Langendorf R, Pick A, Katz LN. Ventricular response in atrial fibrillation: role of concealed conduction in the AV junction. Circulation 1965;32:69–75.

7. Moore EN. Observations on concealed conduction in atrial fibrillation. Circ Res 1967;21:201–8.

8. Yamada K, Okajima M, Hori K, et al. On the genesis of the absolute ventricular arrhythmia associated with atrial fibrillation. Circ Res 1968;22:707–15.

9. Billette J, Nadeau RA, Roberge F. Relation between the minimum RR interval during atrial fibrillation and the functional refractory period of the AV junction. Cardiovasc Res 1974;8:347–51.

10. Anan T, Sunagawa K, Araki H, Nakamura M. Arrhythmia analysis by successive RR plotting. J Electrocardiol 1990;23:243–8.

11. Suyama AC, Sunagawa K, Hayashida K, Sugimachi M, Nakamura M. Identification of the rate-dependent functional refractory period of the atrioventricular node in simulated atrial fibrillation. Am Heart J 1991;121:820–6.

12. Suzuki Y, Akaishi M, Yoshikawa T, Mitamura T, Ogawa S. Evaluation of the AV nodal conduction in patients with atrial fibrillation using Lorenz-plot method. Jpn J Electrocardiol 1996;16:723–32.

13. Suyama AC, Sunagawa K, Sugimachi M, Anan T, Egashira K, Takeshita A. Differentiation between aberrant ventricular conduction and ventricular ectopy in atrial fibrillation using RR interval scattergram. Circulation 1993;88:2307–14.

14. Sasaki T. Biological rhythm. Bull Inst Const Med 1977;27 Suppl:68–75.

15. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979;86:420–8.

16. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307–10.

17. Billette J. Short time constant for rate-dependent changes of atrioventricular conduction in dogs. Am J Physiol Heart Circ Physiol 1981;241:H26–33.

18. Moe GK, Abildskov JA. Observations on the ventricular dysrhythmia associated with atrial fibrillation in the dog heart. Circ Res 1964;14:447–60.

19. Cinca J, Moya A, Bardaji A, Rius J, Soler-Soler J. Circadian variations of electrical properties of the heart. Ann NY Acad Sci 1990;601:222–33.

20. Irisawa H, Caldwell WM, Wilson MF. Neural regulation of atrioventricular conduction. Jpn J Physiol 1971;21:15–25.

21. Wallick DW, Martin PJ, Masuda Y, Levy MN. Effects of autonomic activity and changes in heart rate on atrioventricular conduction. Am J Physiol Heart Circ Physiol 1982;243:H523–7.

22. O'Toole MF, Wurster RD, Phillips JG, Randall WC. Parallel baroreceptor control of sinoatrial rate and atrioventricular conduction. Am J Physiol Heart Circ Physiol 1984;246:H149–53.

23. Van den Berg MP, Crijns HJGM, Haaksma J, Brouwer J, Lie KI. Analysis of vagal effects on ventricular rhythm in patients with atrial fibrillation. Clin Sci 1994;86:531–5.

24. Furlan R, Guzzetti S, Crivellaro W, et al. Continuous 24-hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects. Circulation 1990;81:537–47.

25. Ninomiya I. Direct evidence of nonuniform distribution of vagal effects on dog atria. Circ Res 1966;19:576–83.

26. Alessi R, Nusynowitz M, Abildskov JA, Moe GK. Nonuniform distribution of vagal effects on the atrial refractory period. Am J Physiol 1958;194:406–10.

27. Chorro FJ, Kirchhof CJHJ, Brugada J, Allessie MA. Ventricular response during irregular atrial pacing and atrial fibrillation. Am J Physiol Heart Circ Physiol 1990;259:H1015–21.

28. Birnbaum L, Weiner A, Farah A. Mechanisms in the production of atrial fibrillation during asphyxia. Am Heart J 1962;63:676–87.

29. Kaseda S, Zipes DP. Contraction-excitation feedback in the atria: a cause of changes in refractoriness. J Am Coll Cardiol 1988;11:1327–36.

30. Casolo G, Balli E, Fazi A, Gori C, Freni A, Gensini G. Twenty-four-hour spectral analysis of heart rate variability in congestive heart failure secondary to coronary artery disease. Am J Cardiol 1991;67:1154–8.

31. Panina G, Khot UN, Nunziata E, Cody RJ, Binkley PF. Assessment of autonomic tone over a 24-hour period in patients with congestive heart failure: relation between mean heart rate and measures of heart rate variability. Am Heart J 1995;129:748–53.

32. Nayebpour M, Talajic M, Villemaire C, Nattel S. Vagal modulation of the rate-dependent properties of the atrioventricular node. Circ Res 1990;67:1152–66.