JACC Vol. 12, No. 3
September 1988:656–61

Spontaneous Variability and Circadian Distribution of Ectopic Activity in Patients With Malignant Ventricular Arrhythmia

ERNST A. RAEDER, MD, FACC, STEFAN H. HOHNLOSER, THOMAS B. GRABOYS, MD, FACC, PHILIP J. PODRID, MD, FACC, STEPHEN LAMPERT, MD, FACC, BERNARD LOWN, MD, FACC

Boston, Massachusetts and Stony Brook, New York

Day to day variability of ventricular ectopic activity was analyzed in 45 patients with a history of malignant ventricular tachyarrhythmias who underwent two successive 24 h periods of ambulatory electrocardiographic (ECG) monitoring in the absence of antiarrhythmic drugs; 26 were male and 19 female, with a mean age of 56 years (range 15 to 76). The total number of single ventricular premature beats, couplets and ventricular tachycardia beats and runs on days 1 and 2 demonstrated a consistent overall correlation ($r = 0.76$ to 0.84). Individual variability was evaluated by regression analysis with determination of 95% confidence limits.

The minimal decrease in arrhythmia density necessary to distinguish true drug effect from spontaneous variability was 64% for single ventricular premature beats, 83% for couplets, 90% for ventricular tachycardia runs and 93% for ventricular tachycardia beats. To meet the criteria for arrhythmia aggravation, the arrhythmia density had to increase by 400, 877, 1,500 and 2,400%, respectively. Multivariate analysis disclosed an inverse relation between day to day arrhythmia variability and baseline arrhythmia density and age. Variability was more pronounced in patients with coronary artery disease but was not influenced by the type of presenting arrhythmia or left ventricular function.

The diurnal distribution of arrhythmias and heart rate followed a distinct circadian pattern. These data indicate that, despite good group reproducibility, spontaneous arrhythmia variability in individuals is substantial, necessitating standards to define both drug effect and arrhythmia aggravation.

(J Am Coll Cardiol 1988;12:656–61)

A fundamental difficulty in interpreting biologic data lies in their spontaneous variability. This variability may be a manifestation of physiologic processes such as feedback regulation, circadian rhythmicity or random fluctuations. Although much progress has recently been made in understanding the electrophysiologic mechanisms of cardiac arrhythmias, statistical aspects of arrhythmia variability have received comparatively little attention. Previous investigations (1–4) have defined confidence intervals identifying true arrhythmia suppression in populations with relatively benign ventricular arrhythmia, but little information is available in subjects at risk for sudden death. Indeed, it is precisely this population in whom guidelines for determining antiarrhythmic drug efficacy need to be defined. Moreover, even fewer statistical guidelines are available regarding aggravation of arrhythmia (5,6).

The present study addresses this issue in patients with a high density of malignant ventricular tachyarrhythmias and develops criteria for antiarrhythmic as well as proarrhythmic responses. In addition, the distribution of ventricular arrhythmias and heart rate is examined for circadian patterns.

Methods

Study patients. The study population comprised 45 patients with a history of recurrent life-threatening ventricular tachyarrhythmias that were refractory to conventional antiarrhythmic drugs. As part of an antiarrhythmic drug trial, these patients underwent two control 24 h ambulatory elec-

From the Cardiovascular Research Laboratories, Department of Nutrition, Harvard University School of Public Health and the Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts. This study was supported in part by the Rappaport International Program of Cardiology, Boston, Massachusetts. Dr. Hohnloser was a fellow of the Fritz Thyssen Foundation, Cologne, West Germany.

Manuscript received July 6, 1987; revised manuscript received March 23, 1988, accepted April 8, 1988.

Address for reprints: Ernst A. Raeder, MD, Cardiology Division, Health Sciences Center T-17-020, State University of New York, Stony Brook, New York 11794.

©1988 by the American College of Cardiology

0735-1097/88/$3.50

trocardiographic (ECG) recordings, which form the basis of the present investigation. To be eligible, patients had to exhibit salvos of ventricular tachycardia (≥3 consecutive ventricular premature beats) in at least one of the two recordings. Of the 45 patients, 26 were male and 19 female; the mean age was 56 years (range 15 to 76). Coronary artery disease was diagnosed in 23 patients, cardiomyopathy in 8, valvular heart disease in 4 and congenital heart disease in 1. In nine individuals, no structural heart disease was found. Eight patients presented with a history of ventricular fibrillation not secondary to acute myocardial infarction and 37 with ventricular tachycardia. In 20 of the latter 37 patients, ventricular tachycardia was sustained and accompanied by syncope whereas the remaining 17 patients had nonsustained ventricular tachycardia with hemodynamic compromise.

Ambulatory electrocardiographic monitoring. Two consecutive 24 h Holter ECG recordings were obtained ≥48 h after all antiarrhythmic drugs had been discontinued. The tapes were analyzed by Cardio Data Systems with the use of full disclosure methodology. Stringent quality control procedures, including blinded insertion of standard tapes with a sampling frequency of approximately 2%, were implemented to ensure the accuracy and reproducibility of readings. With the use of these procedures, the accuracy of high speed analysis was 96.6% for total ventricular premature beats, 91.6% for couplets and 96.7% for ventricular tachycardia beats. The reproducibility for these variables among different analysts, or the same analyst at different times, was 92.6, 94.4 and 99.3%, respectively. The mean recording duration was 21.4 ± 3.3 and 21.9 ± 2.1 h, respectively, for the first and the second day.

For each hour, the following data were printed out: low, mean and high heart rate; total ventricular premature beats; single ventricular premature beats; couplets; ventricular tachycardia beats; ventricular tachycardia runs and time analyzed. In addition, the percentage of monitoring hours containing couplets and ventricular tachycardia was calculated.

Analysis of left ventricular function. Left ventricular ejection fraction was determined by radionuclide ventriculography with the use of the gated equilibrium technique. Global ejection fraction was calculated from the time-activity curve obtained from 200 to 400 cardiac cycles. In patients with frequent ventricular premature beats, data acquisition was accomplished with the use of a list mode format in which only sinus beats preceded by another sinus beat were analyzed (7).

Statistical analysis. The arrhythmia frequency of each hour was normalized to 60 min based on the actual analysis time and then totaled to 24 h. To correct for skewed distributions and unequal variances, arrhythmia frequencies were transformed to their natural logarithm (ln [1 + frequency]). Individual day-to-day variability was assessed by regression analysis with monitor recording 2 as the dependent variable (8). Using the upper and lower 95% confidence intervals of predicted values, we calculated the minimal change in arrhythmia density required to distinguish true drug effects from spontaneous variability by:

$$\text{Arrhythmia aggravation} = \frac{\text{Day}_1 + \text{CL}_U}{\text{Day}_1 \times 100}$$

$$\text{Antiarrhythmic drug effect} = \frac{\text{Day}_1 - \text{CL}_L}{\text{Day}_1 \times 100},$$

where CL_U = upper 95% confidence limits and, CL_L = lower 95% confidence limits.

The independent influence of several clinical variables was examined by a stepwise regression procedure where the coefficient of variation of the two recordings served as a measure of overall variability. In this model, the coefficient of variation served as the dependent variable whereas age, left ventricular ejection fraction, presenting arrhythmia, sex, underlying heart disease, arrhythmia density and heart rate were entered as independent variables. To determine whether diurnal fluctuations exhibit correlations that could be attributed to periodicity, we computed autocorrelograms for each Holter recording. The relation of heart rate to ventricular ectopic density was examined by cross-correlation (9). Unless stated otherwise, data are expressed as medians and statistical significance is assumed if $p < 0.05$.

Table 1. Variability of Ventricular Arrhythmias Between Two 24 h Holter ECG Recordings in 45 Patients

	Monitor 1	Monitor 2	r Value ± 95% Confidence Limits
Single VPBs*	8,400	9,799	0.84 ± 0.18†
Couplets*	795	1,111	0.81 ± 0.15†
VT runs*	32	50	0.80 ± 0.14†
VT beats*	110	163	0.76 ± 0.11†
% couplet hours‡	84	87	0.76 ± 0.11†
% VT hours‡	51	52	0.81 ± 0.14†

*Median; †$p < 0.0001$; ‡mean. VPBs = ventricular premature beats; VT = ventricular tachycardia.

Results

Arrhythmia density (Table 1). In the 45 patients, the hourly frequency of single ventricular premature beats was 350 and 408, of couplets 33.1 and 46.3 and of ventricular tachycardia episodes 1.3 and 2.1 for the two recordings, respectively. There was a distinct diurnal distribution of arrhythmia density. At approximately 10 PM, ventricular ectopic activity began to subside reaching a trough at 5 AM. Between 6 AM and 7AM, ectopic activity again increased peaking between 10 AM and noon. This biphasic behavior was remarkably similar in both ambulatory recordings (Fig. 1). Autocorrelation revealed significant positive first-order

JACC Vol. 12, No. 3
September 1988:656–61

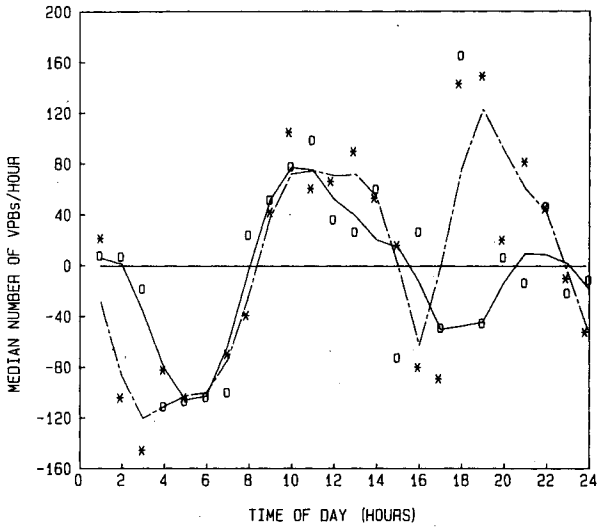


Figure 1. Diurnal variation of ventricular premature beats (VPBs) for pooled data of 45 patients. Ordinate represents deviation of hourly arrhythmia from day's mean. Open circles and solid line = day 1; stars and dashed line = day 2.

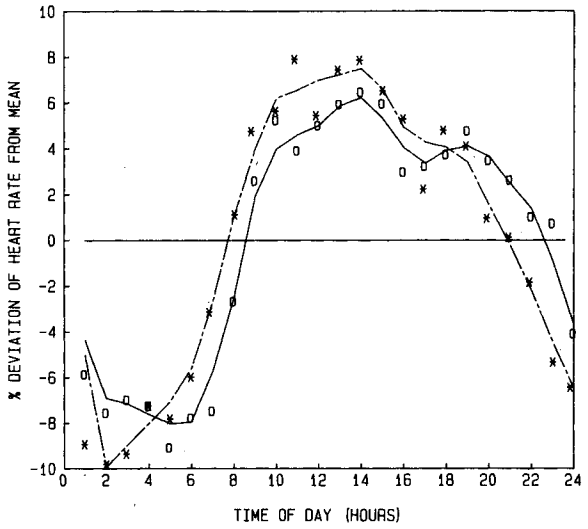


Figure 2. Diurnal variation of heart rate in 45 patients. Symbols as in Figure 1.

autocorrelation coefficients in 49 (54%) of the 90 recordings. Higher order coefficients in the 90 recordings were less frequently significant (second-order, 23 [26%]; third-order, 8 [9%]; fourth-order, 4 [4%]; fifth-order, 2 [2%]).

Heart rate exhibited a similar pattern that was consistent for both recordings (Fig. 2). The hourly medians of heart rate and ventricular ectopic activity showed a significant correlation for both days (day 1: $r = 0.57 \pm 0.14$ [95% confidence limit], $p = 0.0024$; day 2: $r = 0.68 \pm 0.08$, $p = 0.0003$). Analysis of individual Holter recordings by crosscorrelation of heart rate and ventricular ectopic activity revealed a mean zero-order cross-correlation coefficient of 0.54 for both days (range on day 1, −0.83 to 0.89; day 2, −0.55 to 0.90).

Day-to-day variability of arrhythmia (Table 2). Group comparisons revealed good reproducibility between the two ambulatory recordings with correlation coefficients between 0.76 and 0.84. By contrast, linear regression analysis of individual data showed substantial day-to-day variability of ventricular ectopic activity (Fig. 3). Based on the 95% confidence limits, the minimal decrease in arrhythmia density required to identify a true drug effect ranged from 63.5% for single ventricular premature beats to 92.6% for ventricular tachycardia beats (Table 2A). When the percentage of monitoring hours containing couplets or ventricular tachycardia was used to define efficacy, less arrhythmia reduction was necessary to exclude spontaneous variability. An increase ranging from 400% (single ventricular ectopic beats) to 2,400% (ventricular tachycardia beats) density was necessary to distinguish spontaneous variability from genuine arrhythmia enhancement (Table 2B).

Relation between clinical variables and day-to-day variability of arrhythmias (Table 3). To assess the influence of clinical variables on spontaneous variability, age, sex, underlying heart disease, presenting arrhythmia, baseline arrhythmia density and left ventricular function were correlated with the coefficients of variation of various arrhythmia categories. Stepwise regression analysis disclosed an inverse relation between the coefficient of variation and both the baseline arrhythmia density and age. The presence of coronary artery disease was associated with more marked day-to-day variability of single ventricular premature beats and ventricular tachycardia beats whereas left ventricular function and the type of presenting arrhythmia exerted no independent influence on spontaneous variability.

Discussion

Day-to-day variation and criteria for a drug effect. Several previous investigations (1,2,4,5,10–13) have documented that ventricular arrhythmias occur with substantial, seemingly random variations. The general applicability of these results is uncertain, however, because they were obtained mainly in patients with benign arrhythmias not requiring therapy and because of differences in arrhythmia frequency and study design. Furthermore, many of these studies were limited by their focus on arrhythmia suppression without addressing the possibility of proarrhythmic effects. The present investigation shows that the day-to-day reproducibility of arrhythmias in patients with a history of life threatening arrhythmias and high density of ventricular ectopic activity on ambulatory ECG monitoring is good when group data are compared (Table 1). By contrast, when the effect of an intervention is evaluated in individuals, comparisons must allow for the considerable day-to-day variability found in these patients. The minimal suppression of arrhythmia

Table 2. Day-to-Day Variability of Ventricular Arrhythmia

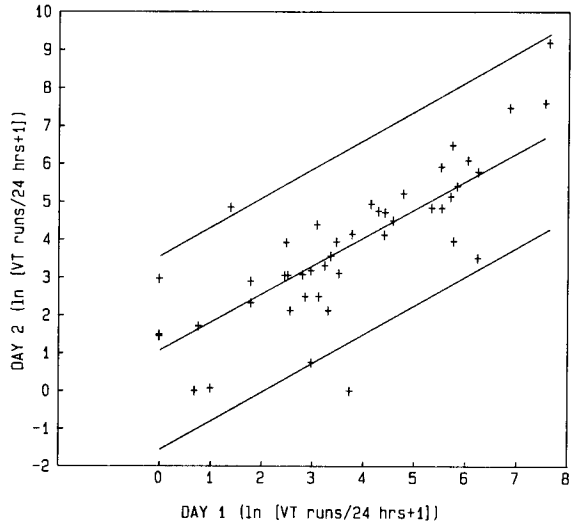
	Minimum % Decrease (median)	Range	25th Percentile	75th Percentile
A. Criteria for True Drug Effect Based on 95% Confidence Limits				
Single VPBs	65.0	45.8 to 74.4	57.5	69.9
Couplets	84.0	68.7 to 92.7	78.6	87.8
Couplet hours	29.3	29.3 to 46.3	29.3	30.3
VT beats	93.5	77.9 to 98.5	91.2	96.7
VT episodes	89.8	79.1 to 96.5	97.2	93.8
VT hours	70.0	53.5 to 100.00	53.5	97.9
B. Criteria for Arrhythmia Aggravation Based on 95% Confidence Limits				
Single VPBs	415	337 to 641	369	481
Couplets	877	521 to 1,988	706	1,173
Couplet hours	231	229 to 481	229	245
VT beats	2,394	766 to 10,931	1,342	3,172
VT episodes	1,506	689 to 3,613	986	1,878
VT hours	270	227 to 1,500	234	331

Abbreviations as in Table 1.

required for a true drug effect in this high risk population is comparable with that of patients with less serious ventricular arrhythmias. However, as a consequence of the nonlinear relation between baseline ventricular tachycardia density and minimal arrhythmia suppression, comparatively less reduction is necessary for <300 ventricular tachycardia episodes on day 1 (Fig. 4). A similar finding was reported by Pratt et al. (3).

When one uses the percentage of hours containing couplets of ventricular tachycardia instead of the hourly arrhythmia counts, the criteria for a drug effect are less stringent (Table 2A). For example, although the number of hourly ventricular tachycardia episodes needs to be reduced by 89.5% to demonstrate efficacy, the percentage of hours containing ventricular tachycardia episodes has to decrease by only 70%. However, it is not clear whether this decrease is helpful because the reduction may be more difficult to achieve.

Figure 3. Linear regression analysis of day-to-day variability of ventricular tachycardia (VT) runs on day 1 and day 2 and two-tailed 95% confidence limits.



Criteria for aggravation. The expanding armamentarium of powerful antiarrhythmic agents and the increasing number of patients with serious ventricular arrhythmias coming to treatment has heightened awareness of drug induced aggravation of arrhythmia (14). To date, the criteria used to define this complication have often been arbitrary (6,14). Our investigation uses a statistical approach and establishes confidence limits for various categories of ventricular ectopic activity (Table 2B). It is important to note that the minimal increase defining aggravation declines sharply as the density of ventricular tachycardia increases, remaining essentially flat for >300 ventricular tachycardia episodes per 24 h on day 1 (Fig. 5). Furthermore, a minimum of 35 episodes per 24 h must be present on day 2 to permit reliable detection of arrhythmia aggravation (Fig. 3). Therefore, to the extent that it is based on the frequency of ventricular

Table 3. Factors Related to Spontaneous Variability of Malignant Ventricular Arrhythmias in 45 Patients

	Single VPBs	Couplets	VT Beats	VT Episodes
VEA Density	−0.0001	−0.0002	−0.0001	−0.0001
Age	−0.0782	NS	−0.0008	−0.031
CAD	0.0376	NS	0.0948	NS
Male gender	−0.021	NS	NS	NS
Heart rate	NS	0.0141	NS	NS

CAD = coronary artery disease; VEA = ventricular ectopic activity; other abbreviations as in Table 1.

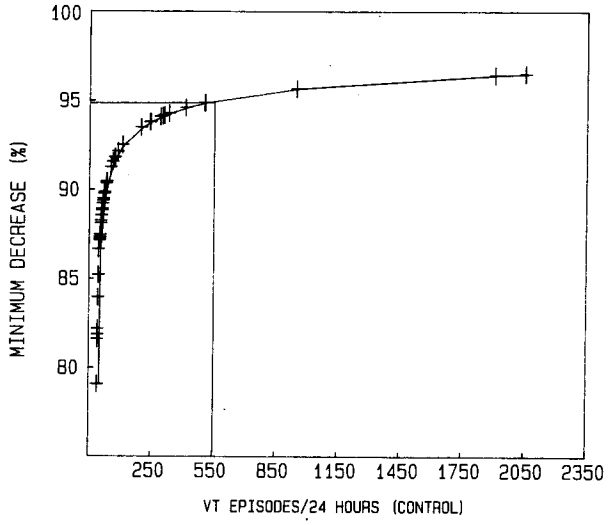


Figure 4. Minimal arrhythmia suppression as a function of ventricular tachycardia (VT) prevalence at baseline. Note that at higher ventricular tachycardia frequencies, the required reduction of ectopic activity levels off at approximately 96%.

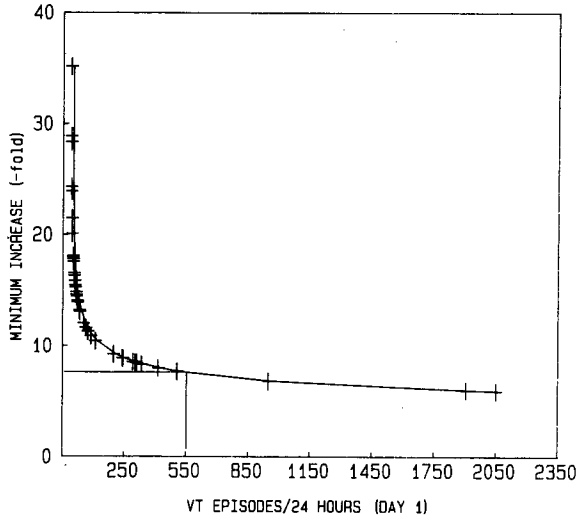


Figure 5. Minimal increase in ventricular tachycardia (VT) density as a function of ventricular tachycardia prevalence at baseline. With >100 ventricular tachycardia events at baseline, the necessary increase in arrhythmia density is approximately tenfold.

tachycardia episodes, the incidence of arrhythmia aggravation may have to be reassessed to reflect these constraints.

Difference between clinical subsets. Pratt et al. (3) recently reported that the spontaneous variability of arrhythmias differs among certain clinical subsets of patients. Those with coronary artery disease exhibited significantly greater variability of ventricular premature beats than patients without coronary artery disease whereas left ventricular function did not appear to influence variability. Although our results agree with these findings, they contrast with regard to baseline arrhythmia density. Multivariate regression analysis disclosed an inverse relation between ventricular ectopic activity during day 1 and each of the arrhythmia categories analyzed. In addition, arrhythmia variability decreased with age and was more pronounced in female patients (Table 3).

Circadian variation. There are conflicting reports concerning the diurnal distribution of ventricular ectopic activity. Although some authors found no relation between ectopic activity and sleep-wake cycles (4,15–17) or an increase during sleep (18,19), our observations as well as those of others (2,20–23) demonstrate the presence of circadian periodicity. This finding is even more persuasive in light of the remarkably similar pattern evident during the two monitoring periods. Autocorrelation analysis of individual recordings disclosed significant first-order coefficients in 54% of recordings. This indicates that the arrhythmia density of a given hour influences the succeeding or even later hours, reflecting a waxing and waning of arrhythmogenesis. The mechanisms underlying the described diurnal variations remain largely unexplored. Fluctuations in sympathetic or

Table 4. Criteria for Drug Efficacy and Arrhythmia Aggravation

	Baseline					Minimal Reduction (%)			Minimal Increase (%)		
Author/Reference	No. of Pts	Interval (days)	VPBs/h	Couplets/h	VT/h	VPBs	Couplets	VT	VPBs	Couplets	VT
Morganroth et al. (4)	15	1	37 to 1,801	—	—	83	—	—	—	—	—
Michelson and Morganroth (2)	20	1	>30	20/20 pts	14/20 pts	—	75	65	—	—	—
Sami et al. (1)	21	14	48	0.2*		65	85*		—	—	—
Morganroth and Horowitz et al. (6)	—	—	—	—	—	—	—	—	3 to 10 = fold	—	—
Pratt et al. (3)	110	1	663	43	19	78	83	77	—	—	—
Pratt et al. (11)	26	17 months	580	20	—	50†	65†	83†	—	—	—
Pratt et al. (5)	88	8	103	1.9	7.1	95	88	—	1,780	217	—
Toivonen (10)	20	4 days to 9 months	777	44*		65 to 100	78 to >100*		—	—	—

*Repetitive VPBs; †observed spontaneous reduction; Pts = patients. Other abbreviations as in Table 1.

parasympathetic tone are possibly involved as suggested by the circadian pattern of heart rate. This mechanism is also suggested by a recent report by Zimmermann et al. (24) who found a positive correlation between the heart rate preceding an episode of ventricular tachycardia and its length. They interpreted this correlation as adrenergic dependence. More research is needed to clarify the role of the autonomic nervous system in spontaneous ventricular arrhythmia.

Regardless of the mechanisms, recent observations on the diurnal distribution of in-hospital cardiorespiratory arrest (25) and out of hospital sudden cardiac death (26) provide an intriguing correlate to our findings. Eltringham and Dobson (25) reviewed the records of 218 patients with in-hospital cardiac arrest and noted two peak periods (13:00 to 15:00 h and 18:00 to 21:00 h) during which 34% of all incidents occurred. Muller et al. (26) surveyed all cases of sudden cardiac death reported in Massachusetts for the year 1983 and found a preponderance of events in the late morning hours with a peak just before noon. At present, it is not entirely clear whether these observations represent a true diurnal pattern or whether confounding factors such as selection bias play a role.

Conclusions. Our study demonstrates that patients with a high density of malignant arrhythmias exhibit substantial day-to-day variability. Therefore, confidence limits must be observed in assessing the effect of therapeutic interventions. There appears to be a circadian pattern of ventricular ectopic activity that correlates well with heart rate. The mechanism of diurnal fluctuations and the potential role of the autonomic nervous system require further investigation.

References

1. Sami M, Kraemer H, Harrison DC, Houston N, Shimasaki C, DeBusk RF. A new method of evaluating antiarrhythmic drug efficacy. Circulation 1980;62:1172–9.
2. Michelson EL, Morganroth J. Spontaneous variability of complex ventricular arrhythmias detected by long-term electrocardiographic recording. Circulation 1980;61:690–5.
3. Pratt CM, Slymen DJ, Wierman AM, et al. Spontaneous variability of ventricular arrhythmias: consecutive ambulatory electrocardiographic recordings of ventricular tachycardia. Am J Cardiol 1985;56:67–72.
4. Morganroth J, Michelson E, Horowitz L, Josephson M, Pearlman A, Dunkman W. Limitations of long-term electrocardiographic monitoring to assess ventricular ectopic frequency. Circulation 1978;58:408–14.
5. Pratt CM, Theroux P, Slymen D, et al. Spontaneous variability of ventricular arrhythmias in patients at risk for sudden death after acute myocardial infarction: consecutive ambulatory electrocardiogram recordings of 88 patients. Am J Cardiol 1987;59:278–83.
6. Morganroth J, Horowitz LN. Flecainide: its proarrhythmic effect and expected changes on the surface electrocardiogram. Am J Cardiol 1984;53:89B–94B.
7. Polak JF, Podrid PJ, Lown B, Holman BL. Ventricular postextrasystolic potentiation in the dog: a study using list mode radionuclide ventriculography. Invest Radiol 1983;18:530–5.
8. SAS Institute Inc. SAS User's Guide: Statistics. Cary, NC, 1982.
9. Chatfield C. The Analysis of Time Series. New York: Chapman and Hall, 1984:23.
10. Toivonen L. Spontaneous variability in the frequency of ventricular premature complexes over prolonged intervals and implications for antiarrhythmic treatment. Am J Cardiol 1987;60:608–12.
11. Pratt CM, Delclos G, Wierman AM, et al. The changing base line of complex ventricular arrhythmias. N Engl J Med 1985;313:1444–9.
12. Winkle RA, Gradman AH, Fitzgerald JW, Bell PA. Antiarrhythmic drug effect assessed from ventricular arrhythmia reduction in the ambulatory electrocardiogram and treadmill test: comparison of propranolol, procainamide and quinidine. Am J Cardiol 1978;42:473–80.
13. Shapiro W, Canada WB, Lee G, et al. Comparison of two methods of analyzing frequency of ventricular arrhythmias. Am Heart J 1982;104:874–5.
14. Velebit V, Podrid P, Lown B, Cohen BH, Graboys TB. Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. Circulation 1982;65:886–94.
15. Smith R, Johnson L, Rothfeld D, Zir L, Tharp B. Sleep and cardiac arrhythmias. Arch Intern Med 1972;130:751–3.
16. Morrison G, Kumar E, Portal R, Aber C. Cardiac arrhythmias 48 hours before, during, and 48 hours after discharge from hospital following acute myocardial infarction. Br Heart J 1981;45:500–11.
17. Orr W, Stahl MR, Whitsett T, Langevin E. Physiological sleep patterns and cardiac arrhythmias. Am Heart J 1979;97:128–9.
18. Lown B, Wolf M. Approaches to sudden death from coronary heart disease. Circulation 1971;44:130–42.
19. Flick M, Block J. Nocturnal vs diurnal cardiac arrhythmias in patients with chronic obstructive pulmonary disease. Chest 1979;75:8–11.
20. Lown B, Tykocinski M, Garfein A, Brooks P. Sleep and ventricular premature beats. Circulation 1973;48:691–701.
21. Canada WB, Woodward W, Lee G, et al. Circulation rhythm of hourly ventricular arrhythmia frequency in man. Angiology 1983;34:274–82.
22. Pickering T, Goulding L, Cobern B. Diurnal variations in ventricular ectopic beats and heart rate. Cardiovasc Med 1977;2:1013–5.
23. Sensi S, Capani F, Lucente M, Coppola E. Circadian rhythm of ventricular ectopy (Letter). Chest 1980;77:580.
24. Zimmermann M, Maisonblanche P, Cauchemez B, Leclerq J, Coumel P. Determinants of the spontaneous ectopic activity in repetitive monomorphic idiopathic ventricular tachycardia. J Am Coll Cardiol 1986;7:1219–27.
25. Eltringham RJ, Dobson MB. Cardiorespiratory arrest—a diurnal variation (Letter)? Br J Anaesth 1979;51:72.
26. Muller JE, Ludmer PL, Willich SN, et al. Circadian variation in the frequency of sudden cardiac death. Circulation 1987;75:131–8.