Antiarrhythmic Drug Effect Mimicked by Spontaneous Variability of Ventricular Ectopy

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SUMMARY **Twenty patients with frequent ventricular ectopic beats had a 5½ hour ECG rhythm strip recorded. Individual patients showed a marked spontaneous variability from one half-hour to the next in the total number of ectopic beats (−99% to +1100%) and the occurrence of pairs or salvos. Although no patient received antiarrhythmic drugs, some patients showed a spontaneous change in arrhythmia which mimicked either drug suppression or drug-induced worsening of arrhythmias. If an antiarrhythmic drug had been given to these patients after the first half-hour, 65% would have been termed "drug responders," using the criteria of 50% reduction in ectopic beats and elimination of pairs or salvos during any half-hour period in the subsequent three hours. Spontaneous variability in ventricular ectopic beats causes serious problems when using ECG monitoring to evaluate antiarrhythmic drug response in individual patients. The arrhythmias averaged for the entire group remained stable during the recording period. Evaluating antiarrhythmic drugs by examining group response rather than individual patient response minimizes the effect of spontaneous variability.**

THE EVALUATION of antiarrhythmic drug efficacy is perplexing and difficult. When arrhythmias recur and are associated with symptoms, or are sustained with or without symptoms, drug efficacy can be determined by evaluating clinical response.[1] Documenting antiarrhythmic effect is more difficult in patients with asymptomatic ventricular ectopic activity. Before treating such patients, one must weigh the risks of the arrhythmia and the expected rate of occurrence of drug side effects. For many patients and drugs, the antiarrhythmic drug dose should be determined by measuring plasma drug concentration and subsequently adjusting the drug dose to achieve generally accepted therapeutic concentrations.[2-4] However, some patients' arrhythmias may not be responsive to a given drug, or may be suppressed by either unusually low or very high plasma drug concentrations.[5] Therefore, a method of directly assessing antiarrhythmic effect in each patient seems desirable. Recently, ECG recordings of several hours' duration[6] have been combined with the administration of single large oral doses of antiarrhythmic drugs and used as a method for evaluating antiarrhythmic drug efficacy in individual patients.[7, 8] The study reported in this paper determines the spontaneous variability in ventricular ectopic activity during a 5½ hour period and examines the implication of this variability for evaluating antiarrhythmic therapy in individual patients and populations.

Methods

The study population was 20 patients who were referred to Stanford University Medical Center for evaluation of cardiac arrhythmias. The criterion for inclusion in this study was a known history of frequent ventricular ectopic activity averaging at least one premature ventricular beat per minute during the 5½ hour monitoring period. There were 13 men and seven women in the study, ranging in age from 30 to 68 years. Ten patients had coronary artery disease documented by a coronary arteriogram demonstrating greater than 70% narrowing in a major coronary vessel, or a previous myocardial infarction, or both. Four patients had mitral valve prolapse, one had cardiomyopathy, and five had no clinical evidence for cardiac disease other than the arrhythmias. Previous workup of the latter five patients included normal coronary arteriograms, left ventricular angiograms, and echocardiograms. Thirteen of the 20 patients had experienced episodes of ventricular tachycardia, either as brief 3–10 beat paroxysms or, in four of the 13 patients, as sustained episodes requiring immediate therapy. In addition to these 13 patients, two patients had experienced previous cardiac arrest due to documented ventricular fibrillation. One of these patients had ventricular fibrillation on two separate occasions.

The ECG data for this study were obtained while each patient was hospitalized. The purpose of this hospitalization was the evaluation of antiarrhythmic therapy and the data collected for this study served as a part of a control against which to measure antiarrhythmic drug effects. Sixteen of the 20 patients were hospitalized in the Stanford General Clinical Research Center. Because of the severity of their previous arrhythmias, four were hospitalized in an intermediate care, continuously telemetry-monitored cardiac unit. All antiarrhythmic drugs were discontinued at least five half-lives prior to the recording of the ECG data in this study. No patient had significant abnormalities of hepatic or renal function. All patients had undergone previous cardiac monitoring and most had previously worn ambulatory ECG recording equipment.

All patients had a restful sleep the night before the study. At approximately 8:00 a.m., after a light breakfast, all patients began continuous ECG monitoring using an Avionics ambulatory ECG recorder. During the study, patients were permitted ambulation limited to their rooms and the hallway adjacent to the room. For the 16 patients in the Clinical Research Center, a relaxed atmosphere was provided that was free of many of the usual stresses of a hospital environment.

The first 5½ hours of the continuous rhythm strip recorded on the ambulatory ECG were analyzed in detail. The total number of ventricular ectopic beats in each minute was determined using a digital computer system.[9] Manual checks verified the accuracy of these counts for all patients. To identify and quantify all episodes of ventricular pairs (two consecutive ectopic beats) or salvos (three or more con-

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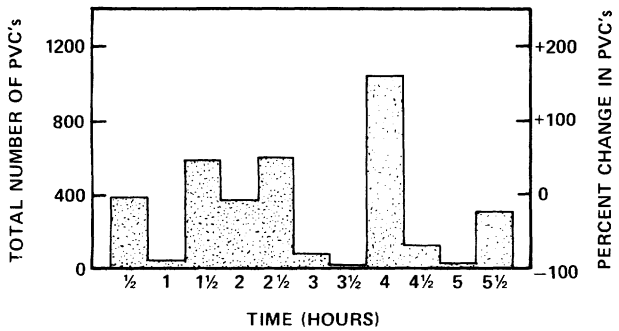

FIGURE 1. *Total number of ventricular ectopic beats (PVCs) during each half-hour period for a patient with considerable spontaneous variability. Percent change compared with the first half-hour (control) is given on the right vertical axis. A similar format is used in figures 2–4.*

secutive ventricular ectopic beats), the entire 5½ hour ECG rhythm strip was printed and analyzed by visual inspection for all pairs and episodes of ventricular tachycardia. Each patient's rhythm strip was divided into half-hour blocks for arrhythmia data analysis. The initial half-hour was termed the control period and the 10 subsequent half-hour blocks were termed the test period. The total number of ventricular ectopic beats and the number of episodes of pairs and salvos were determined for each of the half-hour blocks (Appendix I). For each patient each half-hour period during the 5-hour test was compared with the half-hour control period for the percent change in total number of ventricular ectopic beats. In addition, it was determined how many half-hour periods contained two consecutive ventricular ectopic beats (pairs) or ventricular tachycardia (three or more ventricular ectopic beats in a row). This method of data analysis simulates conditions of short term antiarrhythmic drug testing with one half-hour of control ECG data and subsequent observation of ECG rhythm for several hours.[7, 10] However, in the present study no drug was administered after the control period.

To document that each patient's activity level was reasonably constant during each half-hour, the mean heart rate for each half-hour was determined. The mean heart rate for the entire 5½ hours for all patients was 77.1 ± 7.34. The mean individual patient coefficient of variation in heart rates was only 8.6 ± 3.5%. This stability of heart rate suggests that activity level and cardiovascular stress were relatively

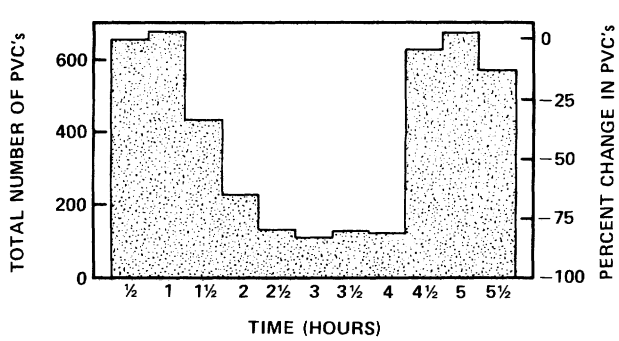

FIGURE 2. *A patient whose spontaneous variation in PVCs mimicked an antiarrhythmic drug response with a return to control arrhythmia levels.*

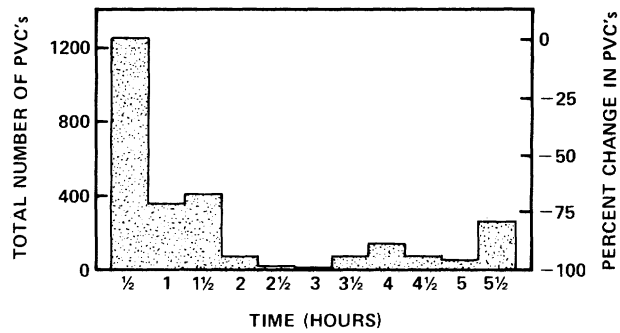

FIGURE 3. *A patient whose spontaneous variability in PVCs mimicked a sustained drug response.*

constant throughout the test period, and changes in these parameters do not account for the observed variation in ventricular ectopic beats.

The statistical evaluation of the total number of ectopic beats in each half-hour compared with control for the group of 20 patients was performed using the Wilcoxon rank sum nonparametric statistical technique.

Results

Variability of the Total Number of Ectopic Beats

Each patient experienced a large spontaneous variation in the total number of ventricular ectopic beats from one half-hour period to the next. When compared with the control half-hour period, these variations ranged from a 99% decline to an 1100% increase during a single half-hour period. For many patients the total number of ventricular ectopic beats fluctuated considerably from one half-hour to the next (fig. 1). However, other patients showed a transient (fig. 2) or sustained (figs. 3 and 4) decline or increase (fig. 5) compared with control and thus mimicked anticipated drug effect or drug worsening of arrhythmias.

Figure 6 illustrates the percent change in total number of ventricular ectopic beats for each half-hour period compared with the control half-hour period for the entire group of 20 patients. Although individual patients showed considerable spontaneous variability, for the group as a whole there was no statistically significant difference in premature ventricular contraction counts for any one half-hour period compared with the control period. This lack of group variability is explained by the fact that, for any given half-hour period,

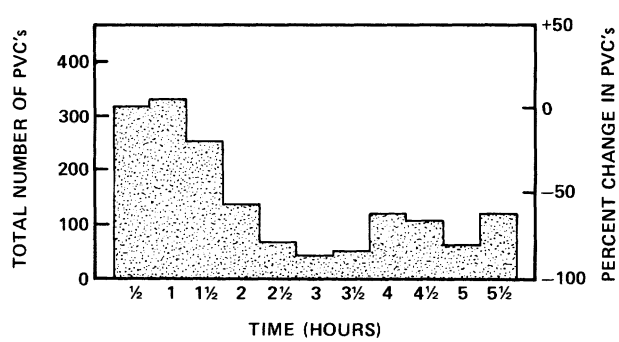

FIGURE 4. *Another patient whose spontaneous variation in PVCs mimicked a drug response.*

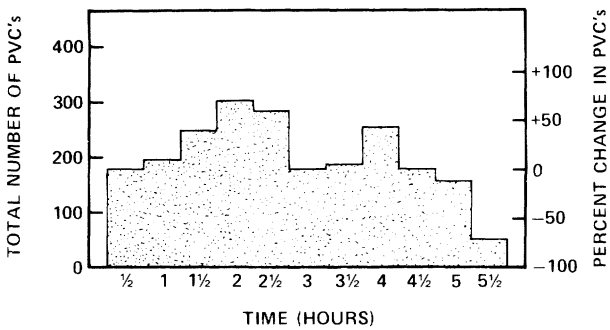

FIGURE 5. *A patient whose spontaneous variation in PVCs mimicked a drug-induced worsening of arrhythmias.*

as many patients showed a spontaneous increase as showed a spontaneous decrease in the total number of ectopic beats. The stability of the group over the five-hour period suggests that there were no systematic trends related to diurnal arrhythmia variation, protocol design, or other factors which might have altered ectopic beat frequency.

Variability of the Occurrence of Pairs and Salvos

Fifteen patients demonstrated paired ectopic beats during the 5½ hour study. Ten of these 15 patients had paired premature ventricular contractions during the control half-hour recording period. Five patients manifested this rhythm for the first time during the subsequent 5-hour period. Table 1 shows the number of half-hour periods containing ventricular pairs for the 15 patients who exhibited pairs. If detection of pairs were perfectly reproducible, each patient with pairs should have had 11 half-hour periods containing pairs. However, the data suggest that for many patients with pairs the occurrence varied greatly from one half-hour period to the next. In fact, only three patients showed pairs in each of the 11 half-hour periods.

Five patients demonstrated salvos of ectopic beats during the 5½ hour study. Two of these five patients had this rhythm during the control half-hour recording and three additional patients showed it for the first time during the subsequent five hours. The number of half-hour periods containing salvos is given in table 1 for the five patients with salvos. As is the case for pairs, the appearance of salvos was highly variable; they occurred during each of the 11 half-hour segments in only one patient.

Measuring Antiarrhythmic Effects in Individual Patients

This spontaneous variation in ventricular ectopic beat frequency would have had considerable impact on the evaluation of antiarrhythmic therapy in many of these individual patients. If a single large dose of an antiarrhythmic drug had been given at the end of the half-hour control, and if one looked for antiarrhythmic effect during the subsequent three hours (the expected time of peak drug plasma concentration), what would have been the conclusions? During the three hours after the control period, 14 of the 20 patients demonstrated a 50% or greater ventricular ectopic beat reduction during at least one half-hour compared with control. Thus, if one defined antiarrhythmic drug responders as those patients with 50% or greater reduction in ectopic beat frequency during a half-hour period, 70% of the patients in this no-drug study would have been classified as responders. Requiring a greater percentage reduction in ectopic beats during a half-hour period provides only a modest improvement (table 2). Twelve of the 20 patients experienced 60% reduction and seven experienced 80% reduction during at least one half-hour period. Three patients demonstrated at least 90% spontaneous reduction in premature ventricular contractions compared with control during one half-hour period of the first three hours of the test period. No patient had complete suppression for a half-hour period. Simultaneous consideration of complex ventricular arrhythmias did not improve the situation. Considering drug responders as those patients with a 50% reduction in ventricular ectopic beats and elimination of pairs or ventricular tachycardia during the same half-hour period, if these complex rhythms were present during the control period,[7] 13 of the 20 patients would have been classified as drug responders.

Because for many patients there was great variability in premature ventricular contraction frequency from one half-hour period to the next, and one might expect antiarrhythmic drug effect to be sustained beyond one half-hour, the data were re-analyzed, requiring that each level of ec-

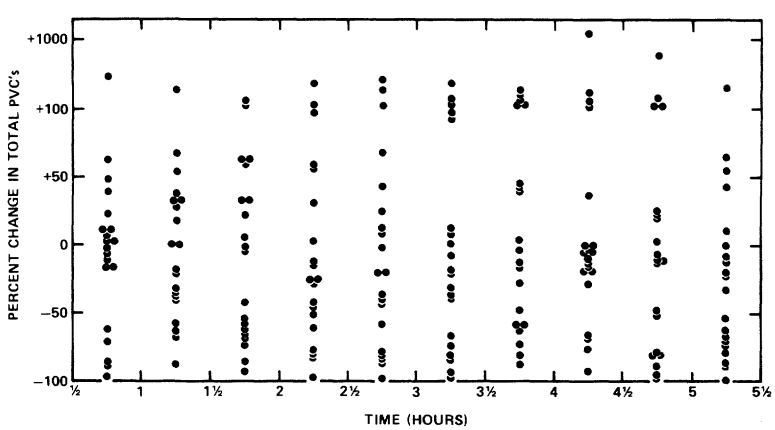

FIGURE 6. *The percent change in total number of ventricular ectopic beats (PVCs) for all patients for each half-hour of the test compared with the total number of PVCs during the control half-hour period.*

TABLE 1. *The Number of Half-hour Periods Containing Pairs and Salvos*

Number of half-hour periods	Number of patients*	
	Pairs	Salvos
1 of 11	2	0
2 of 11	2	1
3 of 11	1	0
4 of 11	0	1
5 of 11	1	0
7 of 11	0	1
8 of 11	2	0
10 of 11	4	1
11 of 11	3	1

*Those patients having pairs or salvos during these half-hour periods.

topic beat reduction be maintained for either two or three consecutive half-hour periods during the first three hours after control (table 2). Eight of 20 patients showed 50% premature ventricular contraction reduction that was maintained for two consecutive half-hour periods, and 5 of 20 patients showed 50% reduction that was sustained for three consecutive half-hour periods compared with the control period. Only one patient demonstrated 90% premature ventricular contraction reduction that was sustained for one hour or longer, compared with the control period. This was a patient with sustained bigeminy during the half-hour control period and only occasional premature ventricular contractions during the subsequent five hours. Only by requiring complete ventricular ectopic beat suppression for one half-hour, or nearly complete ventricular ectopic beat suppression (i.e., greater than 90% decline) to be maintained for at least two or three consecutive half-hour periods, is the effect of spontaneous variability reduced to a reasonable level.

Discussion

In recent years, technology has evolved which permits recording and evaluating lengthy ECG strips.[6, 9] It is possible to qualitatively and quantitatively grade arrhythmias, and to use ECG recordings to assess the response to antiarrhythmic drugs or other therapeutic and diagnostic interventions. Using these types of data there are two general types of study design which may be used to evaluate antiarrhythmic drug efficacy. One type of study evaluates drug efficacy in one group of patients and compares the data with data obtained in an appropriately matched and *separate* group of untreated patients.[11-13] This type of study design frequently randomizes patients to drug *or* placebo.[14-19] Such a study design eliminates problems with spontaneous arrhythmia variation in individual patients and spontaneous variation which might occur over time for the entire group,

TABLE 2. *Maximum Reduction in Total Number of Ventricular Ectopic Beats during the First Three Hours of the Test Period as a Percent of Control (N = 20)*

Level of reduction (%)	½ hour	1 hour	1½ hours
>50	14	8	5
>60	12	8	4
>70	8	6	4
>80	7	6	2
>90	3	1	1

such as a spontaneous fall in arrhythmias for all patients after an acute myocardial infarction.

The second general type of study design uses each patient as his own control. A large number of drug studies have followed this design.[7, 8, 10, 20-31] It is more difficult to control for spontaneous variation in arrhythmias using this type of study. The present study indicates that any drug or intervention (or as in the present study, a nonintervention) could result in a group of patients with a reduction in arrhythmias, a group of patients with no effect on arrhythmias, and a group of patients with apparent increase in arrhythmias. However, rather than being due to the drug or intervention itself, these groupings might only be due to spontaneous variation in the arrhythmias.

Antiarrhythmic drug studies which use each patient as his own control can avoid this problem by determining group effect rather than responses in individual patients. Such an approach assumes that there are as many patients in whom arrhythmia frequencies are increasing as there are those in whom they are spontaneously decreasing, and therefore one must demonstrate that average arrhythmia frequency for the entire group has not changed over the course of the study. The problems with long-term group trends can be minimized by a cross-over study design. An alternative to group data analysis is to analyze control data for individual patients in order to statistically define levels of arrhythmia decline which are not likely to be due to spontaneous variability alone.

The above comments relate primarily to antiarrhythmic drug trials. However, in the everyday practice of medicine physicians must determine whether or not a given patient is responding to an antiarrhythmic drug. This situation closely parallels the type of drug study where each patient serves as his own control. Baseline ECG recordings of varying length are obtained before drug administration or other intervention and are then continued or repeated after drugs are given. One assumes that the difference in the two ECG recordings is the result of the drug or intervention. If fewer ventricular ectopic beats are seen, one may be inclined to conclude that the drug or intervention has resulted in this reduction. Similarly, if more frequent ventricular ectopic activity or more severe grades of ventricular ectopic beats are seen, one may be inclined to conclude that the drug or intervention is exacerbating the rhythm disturbance.[7, 10, 28] However, the present study illustrates the errors inherent in such reasoning caused by the marked spontaneous variability of ventricular ectopic activity. When evaluating drug effects in patients one must set standards by which it is reasonably certain that one is measuring drug response rather than spontaneous arrhythmia reduction. The data in the present study suggest that for individual patients, by requiring complete disappearance of ectopic beats for a half-hour period or at least 90% suppression in ventricular ectopic beat activity that was maintained for at least one hour, we could be reasonably certain of measuring drug effect, rather than observing spontaneous variation in ventricular beat frequencies.

The findings of this study must not be extrapolated to patients with only infrequent or sporadic ventricular ectopic beats. Our patients were known to have frequent ventricular ectopic beats, and these beats averaged at least one per

minute over the course of the study. Patients with infrequent ventricular ectopic beats might tend to show even more variability than was observed in our patients with frequent ectopic beats, thus making antiarrhythmic drug evaluation even more difficult and less reliable.

One might ask whether longer control ECG recording periods and more recordings during therapy might improve the ability to separate less than nearly complete antiarrhythmic drug effect from spontaneous variation. Within the clinically relevant constraints of the availability of resources, this appears doubtful. In a recent study evaluating therapy with quinidine, propranolol or procainamide, we performed two control 24-hour ambulatory ECGs and maximal exercise treadmill tests one month apart.[32] In that study, as in the present study, there was so much spontaneous variability in ventricular ectopic beats that delineation of individual antiarrhythmic drug responders was difficult. Thus, even if 24 hours of ECG data are obtained prior to administering the drug and 24 hours of ECG reading is repeated while the patient is taking the drug, the problem of marked spontaneous variation in ventricular ectopic activity which may mimic or obscure drug effect remains. In that study, however, spontaneous declines in arrhythmias exceeding 90% were uncommon, suggesting that nearly complete arrhythmia suppression can usually separate drug response from spontaneous variation.

While researchers performing antiarrhythmic drug evaluation can determine drug effectiveness by evaluating group drug effect, the clinician charged with the therapy of an individual patient may be left with a sense of confusion. For the present it appears that he must document complete or nearly complete and sustained arrhythmia suppression to be certain he is measuring antiarrhythmic drug effect in a particular patient.

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APPENDIX I. *Total Ventricular Ectopic Beats and Presence of Pairs or Ventricular Tachycardia during Each Half-hour*

Patient		Time (hr) 0–½	½–1	1–1½	1½–2	2–2½	2½–3	3–3½	3½–4	4–4½	4½–5	5–5½
#1	Total PVCs	47	281	47	122	230	262	233	160	587	409	215
	Pairs	0	+	0	0	0	0	0	0	0	0	0
	VT	0	0	0	0	0	0	0	0	0	0	0
#2	Total PVCs	68	56	24	23	70	54	225	271	232	84	68
	Pairs	0	0	0	0	+	+	0	+	0	+	+
	VT	0	0	0	0	0	0	0	+	+	0	0
#3	Total PVCs	843	867	1129	1114	1083	1054	919	880	732	726	774
	Pairs	+	0	+	+	+	+	+	+	+	+	+
	VT	0	0	0	0	0	0	0	0	0	0	0
#4	Total PVCs	307	455	193	114	261	442	197	161	304	377	141
	Pairs	+	+	+	0	+	0	0	+	+	+	+
	VT	0	0	0	0	0	0	0	0	0	0	0
#5	Total PVCs	86	95	36	12	15	18	22	23	21	18	9
	Pairs	0	+	0	0	0	0	0	0	0	0	0
	VT	0	0	0	0	0	0	0	0	0	0	0
#6	Total PVCs	274	227	264	70	107	113	252	113	223	239	225
	Pairs	+	+	+	+	+	+	+	+	+	+	+
	VT	+	+	+	+	+	+	+	+	+	+	+
#7	Total PVCs	192	25	23	203	141	153	370	269	137	20	58
	Pairs	+	0	0	0	+	0	0	0	0	0	0
	VT	0	0	0	0	0	0	0	0	0	0	0
#8	Total PVCs	404	377	674	914	895	901	966	866	1072	844	629
	Pairs	+	+	+	+	+	+	+	+	+	+	+
	VT	0	0	0	+	−	+	+	+	0	0	0
#9	Total PVCs	652	675	437	227	128	109	124	122	626	671	569
	Pairs	+	+	+	+	+	+	0	+	+	+	+
	VT	0	0	0	0	0	0	0	0	0	0	0
#10	Total PVCs	319	330	254	137	68	42	48	120	107	60	119
	Pairs	0	0	0	0	0	0	+	+	0	+	0
	VT	0	0	0	0	0	0	0	0	0	0	0
#11	Total PVCs	1248	358	403	71	18	7	71	142	87	53	261
	Pairs	+	+	+	+	0	+	+	+	+	+	+
	VT	+	+	+	+	0	+	+	+	+	+	+
#12	Total PVCs	119	106	77	53	68	77	93	104	108	149	91
	Pairs	+	+	+	0	+	+	+	+	+	+	+
	VT	0	0	0	0	0	0	0	0	0	0	0
#13	Total PVCs	179	192	246	302	285	176	181	261	172	158	49
	Pairs	+	+	+	+	+	+	+	+	+	+	+
	VT	0	+	+	+	+	0	+	+	+	0	0
#14	Total PVCs	296	326	237	169	144	180	184	215	253	142	199
	Pairs	0	0	0	0	0	0	+	0	+	0	0
	VT	0	0	0	0	0	0	0	0	0	0	0
#15	Total PVCs	43	1	188	69	24	47	49	62	59	94	71
	Pairs	0	0	0	0	0	0	0	0	0	0	0
	VT	0	0	0	0	0	0	0	0	0	0	0
#16	Total PVCs	359	502	459	441	312	206	295	344	291	339	396
	Pairs	0	0	0	0	0	0	0	0	0	0	0
	VT	0	0	0	0	0	0	0	0	0	0	0
#17	Total PVCs	187	304	247	181	139	213	62	67	183	36	1
	Pairs	0	0	0	0	0	0	0	0	0	0	0
	VT	0	0	0	0	0	0	0	0	0	0	0
#18	Total PVCs	119	146	140	200	156	426	235	260	251	62	15
	Pairs	0	0	0	0	0	0	0	0	0	0	0
	VT	0	0	0	0	0	0	0	0	0	0	0
#19	Total PVCs	383	40	591	376	602	75	9	1020	119	10	303
	Pairs	0	0	0	0	0	0	0	0	0	0	0
	VT	0	0	0	0	0	0	0	0	0	0	0
#20	Total PVCs	32	12	19	41	63	54	22	27	32	88	46
	Pairs	+	0	0	+	+	+	+	+	+	+	+
	VT	0	0	0	0	0	0	0	0	0	0	0

Abbreviations: PVC = premature ventricular contraction; VT = ventricular tachycardia; + = present; 0 = absent.