dependent of the carotid baroreflex. Phenylephrine and nitroglycerin affect venous compliance and venous return to the heart, in addition to their effects on the peripheral arterial tree. Neck suction or pressure may change venous return from the head or may influence aortic baroreceptors in a direction opposed to the presumed effect on carotid baroreceptors. When the obtained results from different studies using different measurement techniques are discrepant, and when, as in our study, the obtained results in the same subjects vary with the measurement technique, these operational definitions of baroreflex sensitivity become meaningless. We therefore caution clinical investigators against drawing inferences about overall baroreflex function on the basis of a single measurement technique.

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The Relationship Between Ventricular Ectopic Beat Frequency and Heart Rate

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SUMMARY We examined the relationship between the frequency of premature ventricle complexes (PVCs) and underlying heart rate in 24 patients with frequent PVCs using 24-hour ambulatory ECG recordings. Plots of PVC frequency vs heart rate were made at 1-beat/min intervals for all heart rates that were recorded for at least 5 minutes of the 24 hours. Heart rates during 24 hours ranged from 56 ± 10.0 to 102.2 ± 15.4 beats/min. Twenty-three of the 24 patients had a distinct relationship between PVC frequency and heart rate. Patterns included an approximate log-linear increase in PVCs at higher heart rates in 12 patients, a log-linear decrease (overdrive suppression) in one patient, flat curves in three patients, and a complex relationship (e.g., more PVCs at low rates and suppression at high rates) in seven patients. Patterns were reproducible in 21 of the 24 patients on repeat ambulatory ECG monitorings done 1 day to 2 months later. We conclude that most patients with frequent PVCs have a characteristic relationship between PVC frequency and heart rate over the range of heart rates achieved during routine daily activity. The most frequent relationship is a marked increase in PVC frequency with increasing heart rate. These observations may in part explain such phenomena as "spontaneous" variability of PVC frequency, sleep suppression of PVCs and suppression of PVCs by β-blocking drugs.

A DIRECT RELATIONSHIP between ventricular ectopic beat frequency and heart rate has been reported in animal studies.1,2 Similarly, most clinicians have observed patients in whom ventricular arrhythmias seem related to underlying heart rate. Examples are the emergence of ventricular escape beats in patients with sinus bradycardia or complete atrioventricular block and exercise-induced or overdrive suppression of ventricular arrhythmias. These observations are usually made over short recording periods and at heart rates higher or lower than those achieved during most ordinary daily activities. The present study is a report of the relationship between the occurrence of ventricular ectopic beats and underlying heart rate in a group of ambulatory patients with frequent ventricular ectopic beats. The analysis of long periods of ECG recordings using computer techniques allowed us to uncover rela-
tionships between frequency of premature ventricular complexes (PVCs) and heart rate that are not readily appreciated in many patients by examining the data from standard ECG strips.

Methods

Twenty-four-hour, two-channel ambulatory ECG recordings were analyzed from 24 patients at Stanford Medical Center. Patients were randomly selected from those with frequent chronic ventricular ectopic beats referred for participation in antiarrhythmic drug protocols. To be included in this report, patients had to have more than one PVC per minute averaged over 24 hours on an initial ambulatory ECG recording and to have a second 24-hour ECG monitoring available for analysis. Both recordings were done after discontinuing all antiarrhythmic drugs for at least 5 half-lives.

Ambulatory ECG analysis was performed using the Stanford computerized system.3,4 This system provides identification of all PVCs recorded on a 24-hour recording. Each beat is classified as supraventricular or ventricular in origin. Ventricular ectopic beats are those with wide QRS complexes and no preceding P wave. The accuracy of ventricular ectopic beat counts are verified by selecting random minutes during each recording and by selecting a representative sampling of minutes containing arrhythmias. During these selected minutes, beat-by-beat annotation of each QRS complex is obtained. All digitized ECG data are stored on a random access disc or on magnetic tape for easy retrieval and review of data. Fortran programming permits easy implementation of new data analysis algorithms.

We generated tabular and graphic information concerning the frequency of ventricular ectopic beats as a function of heart rate. In this algorithm, the average heart rate is established for each minute during the 24 hours by averaging all RR intervals during each minute. The number of PVCs is also tabulated for each minute. The number of minutes at each heart rate (in 1-beat/min increments) is determined, as well as the total number of PVCs in these minutes. The number of PVCs per 15 minutes is calculated for each heart rate according to the formula (number of PVCs in all minutes at a given heart rate/the number of minutes at a given heart rate) × 15. The number of PVCs per 15 minutes can be thought of as the number of PVCs that occur for each 15 minutes spent at any given heart rate. Heart rates recorded for less than 5 minutes of the 24 hours were not analyzed. Patients with interpolated PVCs were excluded from analysis because they would have an artifactual increase in heart rate at high PVC frequencies. Data were plotted as the log of the number of PVCs per 15 minutes as a function of heart rate. The graphs were inspected visually to estimate the relationship between PVC frequency and heart rate for each patient. The second 24-hour ambulatory ECG monitoring was compared with the initial recording to determine if patterns were reproducible over time.

Results

Patients

Twenty-four ambulatory ECG recordings from 24 patients (18 males and six females, average age 60.3 ± 10.5 years, range 36–76 years) were studied. Thirteen patients had coronary artery disease, eight of whom had a previous myocardial infarction and six of whom had previous coronary bypass grafting. Three patients each had atypical chest pain and primary myocardial disease, two had apparently normal hearts and one patient each had mitral valve prolapse, sleep apnea syndrome and paroxysmal, nonsustained ventricular tachycardia.

PVC Frequency and Minimum and Maximum Heart Rates

The median PVC frequency on the initial ambulatory ECG recordings was 8672 per 24 hours (range 1499–60,477 per 24 hours). The lowest heart rate recorded for at least 5 minutes during the 24-hour recording was 56.2 ± 10.0 beats/min (range 37–72 beats/min) and the highest heart rate recorded for at least 5 minutes was 102.2 ± 15.4 beats/min (range 61–122 beats/min). On the second ambulatory ECG recording, the median number of PVCs was 10,976 per 24 hours (range of 3029–50,307 per 24 hours), and low and high heart rates were not significantly different from the initial recording, averaging 58.8 ± 8.8 beats/min (range 40–80 beats/min) and 100.0 ± 12.0 beats/min (range 68–121 beats/min).

Relationship Between PVC Frequency and Heart Rate

Twenty-three of the 24 patients showed a distinct relationship between PVC frequency and heart rate. While there were almost as many patterns of this relationship as there were patients, the relationships were classified into broad categories. Twelve patients showed a positive correlation between PVC frequency and heart rate (fig. 1–3). The slopes of this relationship varied from only slightly to markedly positive. Some subjects with a positive slope showed a tendency toward slight flattening of the curves at higher heart rates (fig. 3). Seven patients showed a complex relationship between PVC frequency and heart rate. Overall, most subjects with complex patterns tended to have more PVCs at higher heart rates. Some of these patients had reproducible dips or notches in their relationships and others had an increasing PVC frequency at lower heart rates, a flat relationship at intermediate heart rates and overdrive suppression (a negative correlation between PVC frequency and heart rate) at the highest heart rates achieved (fig. 4). Three patients showed a relatively flat curve at all heart rates, indicating equal numbers of PVCs at each heart rate. One patient had a predominantly negative pattern, showing fewer PVCs at higher heart rates (fig. 5). Only one subject had no apparent relationship between PVC frequency and heart rate. There was no correlation between type of underlying heart disease and pattern of the relationship between PVC frequency and heart rate.
Reproducibility

Repeat ambulatory ECG monitorings were carried out 1 day to 2 months after the initial recording (figs. 1–5). Of the 23 patients showing a relationship between PVC frequency and heart rate on the initial recording, 21 showed reproducibility of this pattern on the repeat monitoring. In a qualitative sense, this reproducibility was judged excellent in 11 patients, good in five patients and fair in five patients. Reproducibility did not seem to be a function of number of days between recordings. The graphic pattern was reproducible, but in some patients, the PVC frequency–heart rate curve shifted slightly upward or downward or to the right or left from one recording to the next.

Discussion

This study shows a remarkable correlation between ventricular ectopic beat frequency and underlying heart rate in patients with frequent PVCs. The majority of patients have a relationship between PVC frequency and heart rate that is characteristic for that patient and is reproducible over time. Heart rate–dependent ventricular ectopy has been described in dogs after acute coronary artery ligation. Chadda et al.\(^2\) showed more ventricular ectopic beats at rapid and slow heart rates and could demonstrate an "optimal antiarrhythmic heart rate." Han et al.\(^3\) also found that the heart rate is an important determinant of PVC frequency in dogs subjected to ischemic, physiologic or electrical stress. Data in man on this subject are limited. Zipes and Knoebel\(^5\) reported two subjects with recent myocardial infarction in whom atropine-induced tachycardia was associated with an increase in ventricular ectopy. Most clinicians have seen patients in whom ventricular ectopy was either induced or suppressed by exercise. Although such patients are known to exist, one of the more remarkable findings in our study was that a high percentage of patients with frequent PVCs had definite and reproducible relationships between PVC frequency and underlying heart rate. This observation was clearly related to the availability of computer analysis of 24-hour electrocardiographic strips that enabled detection of subtle or complex relationships between
PVC frequency and heart rate. These relationships were detected even though no attempt was made to evaluate the relationship between PVC frequency and heart rate for each PVC morphology. Some of the complex patterns may have resolved into the sum of a number of simpler relationships if such a separation had been made. The heart rates achieved during these ambulatory ECG monitorings are considerably below those achieved during a routine exercise treadmill test. Some of our patients with a positive relationship between PVC frequency and heart rate might have shown overdrive suppression had they achieved heart rates during everyday activity similar to those during exercise testing.

Potential Mechanisms

These observations do not permit statements about the mechanism of the observed relationship between PVC frequency and heart rate, or that they are cause and effect. However, one may speculate on the reasons...
for such a relationship. The most common pattern was an increase in PVC frequency with heart rate; thus, one explanation could be increased ischemia at higher heart rates. This does not seem likely because a positive relationship was not confined to patients with coronary artery disease, and some patients with coronary artery disease had complex or even negative relationships between PVC frequency and heart rate. We examined PVC frequency per unit time; thus, one might expect a linear increase of PVC frequency as a function of heart rate if the PVC frequency per 1000 QRS complexes remained constant for all heart rates. However, the striking log-linear increases as well as the complex patterns in many patients could not be explained by the increase in the total number of QRS complexes as heart increased. At faster heart rates, there may be increasing conduction delay, which could cause reentrant ventricular ectopic beats. The higher sympathetic drive associated with periods of increased heart rate might accentuate phase 4 diastolic depolarization and permit the more frequent emergence of ventricular ectopic beats due to enhanced automaticity. Calcium channel-dependent afterdepolarizations are most prominent at higher cardiac rates and this might also be an explanation for more ectopy at higher heart rates in some patients. Weiss et al. suggested that increases in parasympathetic tone resulted in suppression of PVCs in many subjects. However, they did not use cardiac pacing to maintain a constant heart rate; thus, one cannot exclude the possibility that the reduction in ventricular ectopic beats occurred because of the slowing of heart rate rather than a direct vagal effect on ventricular myocardium. Moe et al. demonstrated that the electrotonic influence of changes in underlying heart rate on a parasystolic focus may cause changes in the discharge pattern of that focus. This can result in complex relationships between PVC frequency and underlying heart rate. A reduction in ventricular ectopic beats at increased heart rates may be explained on the basis of a decrease in the temporal dispersion of refractoriness at higher heart rates, which diminishes the likelihood of reentry or as simple overdrive suppression of an ectopic focus. Thus, regardless of the mechanism of genesis of the ventricular ectopic beats (reentry, parasystole, delayed afterdepolarizations or enhanced automaticity), there are a number of reasons.

**Figure 4.** The relationship between frequency of premature ventricular complexes (PVCs) and heart rate in a 68-year-old male. This patient demonstrated a complex relationship between PVC frequency and heart rate. At heart rates of 55–80 beats/min, there was a striking increase in ventricular ectopic beat frequency, whereas at heart rates above approximately 90 beats/min, there was a reduction in PVC frequency. The pattern was reproducible over 9 days.
to anticipate that a relationship should exist between heart rate and PVC frequency.

Implications for Spontaneous Variation of Ventricular Ectopic Beats

The relationships between PVC frequency and heart rate described in this study might account for a part of the spontaneous variability in PVC frequencies previously reported.\textsuperscript{10,11} Although we did not examine this issue directly, several patients' graphic outputs of PVC frequency and heart rate over time clearly suggested that this is the case: What appears to be spontaneous variation in PVC frequency over time could clearly be shown to be associated with changes in underlying heart rate (fig. 6). However, the findings in the present report can only partially account for the spontaneous variation in ventricular ectopic beats. Although the overall pattern of the relationship between PVC frequency and heart rate were reproducible from one recording to the next in most of our patients, in some instances the curves were shifted slightly upward or downward or to the right or left, suggesting an influence of the autonomic nervous system or other factors. Because the vertical axis in our graphic outputs is a logarithmic scale, slight shifts in the curve upward or downward results in striking differences in ventricular ectopic beat frequency even if heart rate is held constant from one 24-hour period to the next.

Implications for Sleep Suppression of Ventricular Ectopic Beats

Many subjects with ventricular ectopic beats have fewer arrhythmias during sleep.\textsuperscript{12,13} Although increases in parasympathetic tone have been postulated to account for these changes, for many patients sleep suppression or enhancement of ventricular ectopic beats may merely be an extension of the relationship between PVC frequency and heart rate that occurs also while that subject is awake (fig. 6). Pickering et al.,\textsuperscript{14} who studied the sleep suppression of PVCs in 12 pa-
The relationship between "spontaneous" variation of frequency premature ventricular complexes (PVCs) and changes in heart rate. These data are from a 62-year-old male with coronary artery disease. This patient's PVC frequency vs heart rate plot was similar to that of the patient shown in figure 1, i.e., a steep, log-linear increase in PVC frequency at increasing heart rates. The parallel changes in heart rate and PVC frequency suggest that the changes in PVC frequency are not spontaneous, but are due to changes in heart rate. At night there is a marked reduction of PVC frequency that might be termed "sleep" suppression. However, there is a similar fall in PVC frequency at 11 a.m. to 1 p.m., when the patient is awake but has a slow heart rate similar to that during sleep.

Implications for Studying Antiarrhythmic Drugs

Computer analysis of ambulatory ECG recordings as described in this study may provide new techniques of assessing and potentially predicting response to antiarrhythmic drugs. The findings that the majority of subjects have an increase in PVC frequency as a function of heart rate during 24-hour ambulatory ECG recordings may in part explain the findings that the majority of patients have a reduction in ventricular ectopic beats when treated with β-blocking agents.\(^\text{15,16}\) The documentation of fewer PVCs at higher heart rates might help to identify patients whose arrhythmias would be worsened by β-blocking drugs or might be suppressed by overdrive pacing. The evaluation of PVC frequency as a function of heart rate may provide a new and powerful tool for understanding the mechanism of action of and predicting response to antiarrhythmic agents.

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