A New Method for Evaluating Antiarrhythmic Drug Efficacy

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SUMMARY To develop standards for distinguishing antiarrhythmic drug effect from spontaneous variability of premature ventricular complexes (PVCs), 21 males (mean age 56 ± 8 years) with chronic ischemic heart disease and PVCs underwent symptom-limited treadmill exercise testing and 24-hour ambulatory monitoring before and after 2 weeks of placebo medication. Linear regression analysis was used to describe the relationship between baseline and placebo PVC frequency for various indexes of ventricular ectopic activity and to establish 95% and 99% one-tailed confidence intervals for this relationship within the group of 21 patients. The lower limit of baseline PVC frequency for which the procedure could distinguish a placebo from a true drug response, termed the “sensitivity threshold,” was an average frequency of 2.2 PVCs/hour for ambulatory electrocardiographic monitoring and 1.2 PVCs/min for treadmill exercise testing. All patients exceeded the sensitivity threshold on baseline ambulatory ECGs, but only 38% of patients did so on baseline treadmill exercise tests. To establish antiarrhythmic efficacy with 95% confidence, the minimal percent reduction of PVCs between baseline and placebo visits was 68% for treadmill exercise testing and 65% for ambulatory electrocardiography. Although these standards were developed in patients with chronic ischemic heart disease, the model can be used to establish antiarrhythmic drug efficacy in any patient group.

CONSIDERABLE controversy exists as to the optimal method for assessing an antiarrhythmic drug response. Some investigators favor exercise testing and others favor ambulatory ECG recording. Among the latter, controversy still exists as to the optimal duration of control and posttreatment ECG recording and the degree of reduction of premature ventricular complexes (PVCs) necessary to demonstrate drug efficacy.

The problem is even more perplexing for the clinician in applying the standards used by clinical investigators to assess drug efficacy in group studies for patient treatment. The demonstration of drug efficacy in a patient requires that the change in PVC frequency effected by the drug is substantially greater than that which could be ascribed to spontaneous variability alone. Standards to distinguish drug efficacy from spontaneous variability can be established for groups of clinically comparable patients. These standards permit the rational assessment of antiarrhythmic drug efficacy in individual patients.

In this study we used a statistical model based on linear regression analysis to establish the limits of spontaneous variability in a group of patients with chronic ischemic heart disease and asymptomatic PVCs. This model provides the clinician with objective standards for determining whether a true antiarrhythmic drug response is present. Based on this model, we also compared various indexes of ventricular ectopic activity on ambulatory ECG and treadmill exercise testing with respect to their usefulness in assessing antiarrhythmic drug efficacy.

Methods

Patients

Our patients were 21 males, mean age 56 ± 8 years, who were referred to Stanford University Medical Center. Seventeen patients had a history of documented myocardial infarction longer than 3 months before the study, three had angina pectoris and one patient had no documented evidence of cardiac disease except for frequent PVCs. All patients had previously demonstrated PVCs either at rest or during exercise at least once. To qualify for this study, patients had to have an average of at least six PVCs per hour on a 24-hour ambulatory ECG. We believed that patients with a lower PVC frequency would probably not warrant antiarrhythmic therapy, based on the findings of Moss and Akiyama and Hinkle et al. that sudden coronary death was related to the presence of higher PVC frequencies in their patients (>20 per hour and >10 per thousand beats, respectively). Antiarrhythmic drugs were discontinued at least a week before entry into the study, but other medications were continued without change. Severely symptomatic patients and those who we believed could not safely discontinue antiarrhythmic medication for at least 2 weeks were not considered for the study.

Study Protocol

On the first outpatient visit (baseline), patients were interviewed and examined by a physician and informed consent was obtained. Patients then had a treadmill exercise test and a 24-hour ambulatory ECG. After the ambulatory ECG was recorded, placebo tablets were given at the rate of one tablet every 6 hours for 2 weeks. Exercise tests and am-
Ambulatory ECGs were repeated during the fourteenth day of placebo (placebo evaluation).

Exercise Testing

Exercise tests were performed at the same time of day on the two visits, at least 2 hours after eating or smoking. Exercise was performed on a motor-driven treadmill using the Bruce protocol. Tests were symptom-limited and were supervised by a physician and a nurse. The work load was increased every 3 minutes until the appearance of any of the following end points: (1) limiting symptoms of chest pain, dyspnea, fatigue, leg cramps or dizziness; (2) hypotension, i.e., a decrease in systolic blood pressure of 10 mm Hg or more from the peak value obtained earlier during exercise; and (3) ventricular tachycardia, i.e., three or more consecutive PVCs. Twelve-lead ECGs were recorded at rest, at the end of each 3-minute stage of exercise, and at the end of each of 8 minutes of recovery. At the same time, a trained technician recorded minute-by-minute PVCs observed on a three-channel oscilloscope. Ventricular ectopic activity was considered absent when no PVCs occurred during exercise or recovery. Ventricular ectopic activity was further classified as "complex" when patients demonstrated bigeminy or repetitive PVCs (two or more consecutive PVCs).

Ambulatory Electrocardiographic Recording

Ambulatory ECGs were recorded with a two-channel Avionics 445 recorder using modified lead II and V6 systems. The tapes were analyzed by Cardio-Dynamics Laboratories, Inc., Los Angeles, California, using the Dyna-gram IIIB Holter ECG Analysis System.26 Accuracy of the system was previously evaluated in 32 patients with ventricular ectopic activity by means of randomly selected 30-minute recordings in which PVC counts on the Dyna-gram IIIB Analyzer were compared to manual counts. The mean sensitivity of this system was 99.7 ± 0.7% and the mean specificity was 99.7 ± 0.9%.27 Recordings began 3 minutes before treadmill exercise and continued for the next 24 hours. The average duration of recording on baseline evaluation was 20.5 ± 4 hours, and on placebo, 20.8 ± 4 hours. Printout of the results included an hour-by-hour calculation of (1) the average heart rate, (2) the number of isolated PVCs and their morphology, (3) the frequency of repetitive PVCs (two or more consecutive PVCs) or (4) the frequency of PVCs/1000 beats. The report also included the average frequency of PVCs/hour of monitoring and the average frequency of PVCs/1000 beats. An example of each "family" of PVCs and of pairs and runs was also obtained on each recording.

Data Analysis

To apply parametric statistical methods to distributions of PVC counts that are generally skewed, log (PVC frequency + 1) was used in place of frequency in all analyses. This transformation is used both to stabilize the variance and to normalize the distributions. Mean values for baseline and placebo measurements were compared using paired t tests. Reproducibility of individual responses between baseline and placebo were measured using the product-moment correlation coefficient. Reproducibility of the presence or absence of complex PVCs on treadmill exercise was assessed using the kappa coefficient.28

To distinguish antiarrhythmic drug efficacy from spontaneous variability of PVCs, linear regression analysis was used to describe the relationship between baseline and placebo PVC frequency for various indexes of ventricular ectopic activity and to establish 95% and 99% one-tailed confidence intervals for this relationship.29 Specifically, the slope and intercept of linear regression were estimated and confidence intervals were computed for the expected placebo response given a specific baseline PVC frequency level. Figure 1 illustrates this analysis for the average PVC frequency/hour on ambulatory electrocardiographic recordings.

In principle, to distinguish a true drug response from a placebo response (spontaneous variability) at the 0.05 or 0.01 level of significance, the single point that describes the placebo and post-drug responses must fall below the 95% or 99% confidence limits. If the baseline frequency is very low, even 100% PVC suppression cannot be distinguished from spontaneous variability at a given level of confidence. The lower

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Linear regression analysis with 95% and 99% confidence intervals of variability for baseline vs placebo measurements of average premature ventricular complex (PVC) frequency/hour of ambulatory ECG recording. Analysis was performed on the log (PVC frequency + 1). The corresponding absolute values are shown on the opposing scales. The 95% and 99% confidence lines represent the one-tailed lower confidence intervals for individual data points. The sensitivity threshold is the point at which the 95% or 99% confidence line crosses the baseline of PVC frequency. Baseline frequencies below the sensitivity threshold may vary by as much as 100% between baseline and placebo recordings and cannot be used to evaluate antiarrhythmic drug efficacy.
limit for which the procedure can distinguish a placebo from a true drug response is termed the "sensitivity threshold" and represents a point at which the 95% or 99% confidence line crosses the baseline axis (fig. 1). The results have been expressed in terms of log (PVC frequency +1) and in terms of absolute PVC frequency. From these results we determined the percent reduction of PVC frequency necessary to establish drug efficacy at a given confidence level

$$\frac{x - \hat{y}}{x} \times 100$$

where x = the baseline PVC frequency and \( \hat{y} \) = the lower confidence limit of the corresponding placebo response.

For example, if \( x = 9 \) PVCs/hour, the corresponding point on the 95% confidence line (\( \hat{y} 95 \)) is 2.39 and the percent reduction necessary to establish drug efficacy with 95% confidence is \( 9 - 2.39/9 = 73\% \). This percent reduction in PVC frequency is almost 100% at the sensitivity threshold and stabilizes at a minimal level (minimal percent reduction) as the baseline PVC frequency increases.

### Results

Average PVC frequency on baseline and placebo evaluations for individual patients is depicted in table 1. The range of PVC frequency on baseline ambulatory ECGs was wide — 6–1134 PVCs/hour. Treadmill exercise testing failed to elicit PVCs in patients 3, 7, 9 and 16 at baseline, all of whom demonstrated frequent PVCs on ambulatory ECGs. Ambulatory electrocardiography was also superior to treadmill exercise testing in detecting repetitive PVCs: of 14 patients who demonstrated one or more episodes of repetitive PVCs on baseline ambulatory ECGs, only three did so with treadmill exercise testing (table 1).

Figure 2 shows the mean frequencies for the various indexes of ventricular ectopic activity. Measurements obtained on baseline and placebo evaluations were not significantly different when the entire group of 21 patients were considered.

Quantitative indexes of ventricular ectopic activity detected by ambulatory electrocardiography and treadmill exercise testing were found to be highly reproducible (table 2). On ambulatory ECGs, the most reproducible of these indexes was the average PVC frequency per hour (\( r = 0.94, p < 0.0005 \)).

### Table 1. Results of Ambulatory Electrocardiograms and Treadmill Exercise Tests Before and After Two Weeks of Placebo

<table>
<thead>
<tr>
<th>Pt</th>
<th>AE: avg PVCs/hr</th>
<th>AE: avg repetitive* PVCs/hr</th>
<th>TM: avg PVCs/min†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Placebo</td>
<td>Baseline</td>
</tr>
<tr>
<td>1</td>
<td>144</td>
<td>258</td>
<td>2.6</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>48</td>
<td>1.1</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>12</td>
<td>0.2</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>18</td>
<td>0</td>
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<tr>
<td>7</td>
<td>60</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>17</td>
<td>9</td>
<td>0.5</td>
</tr>
<tr>
<td>9</td>
<td>55</td>
<td>96</td>
<td>0.2</td>
</tr>
<tr>
<td>10</td>
<td>324</td>
<td>354</td>
<td>0.2</td>
</tr>
<tr>
<td>11</td>
<td>73</td>
<td>84</td>
<td>0.1</td>
</tr>
<tr>
<td>12</td>
<td>78</td>
<td>48</td>
<td>0.2</td>
</tr>
<tr>
<td>13</td>
<td>6</td>
<td>6</td>
<td>0.2</td>
</tr>
<tr>
<td>14</td>
<td>8</td>
<td>X</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>204</td>
<td>450</td>
<td>0.1</td>
</tr>
<tr>
<td>16</td>
<td>210</td>
<td>54</td>
<td>2.4</td>
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<tr>
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<td>12</td>
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<td>0</td>
</tr>
<tr>
<td>18</td>
<td>258</td>
<td>324</td>
<td>1.2</td>
</tr>
<tr>
<td>19</td>
<td>1134</td>
<td>618</td>
<td>184.80</td>
</tr>
<tr>
<td>20</td>
<td>24</td>
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</tr>
<tr>
<td>21</td>
<td>43</td>
<td>44</td>
<td>0.1</td>
</tr>
<tr>
<td>Median</td>
<td>48</td>
<td>48</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Two or more consecutive PVCs.
†Exercise and 8 minutes recovery.
‡Patient also demonstrated repetitive PVCs.

Abbreviations: PVC = premature ventricular complex; X = recordings technically inadequate.
most reproducible index of ventricular ectopic activity on treadmill exercise testing was the average PVC frequency/min during exercise or recovery ($r = 0.86$, $p < 0.0005$). Other indexes of ventricular ectopic activity on ambulatory ECGs and treadmill exercise tests were generally less reproducible and therefore less helpful in evaluating antiarrhythmic drug efficacy. They had wider confidence intervals and hence, higher sensitivity thresholds, and a greater percent reduction in basal values was required to establish drug efficacy with 95% or 99% confidence (table 2). Only the average and peak PVC frequencies/hour on ambulatory electrocardiography had sensitivity thresholds that were exceeded by all patients. Other indexes of ventricular ectopic activity on ambulatory ECGs or on treadmill exercise tests permitted evaluation of only a minority of patients. Only 10% of our patients exceeded the 95% sensitivity threshold of 2.6 repetitive PVCs/hour on ambulatory ECGs necessary to evaluate drug efficacy using this index of ventricular ectopic activity.

The percent reduction in PVC frequency necessary to establish drug efficacy, i.e., to distinguish true drug response from spontaneous PVC variability, varied with the baseline PVC frequency. Table 3 depicts the relationship between the baseline PVC frequency and the percent reduction in PVCs required to establish antiarrhythmic drug efficacy with 95% confidence. The minimal percent reduction for ambulatory electrocardiography and treadmill exercise testing was not significantly different (65% and 68%, respectively). The baseline PVC frequency corresponding to these minimal percent reductions was 30 or more PVCs/hour on ambulatory electrocardiography and nine or more PVCs/min on treadmill exercise tests. The minimal percent reduction in PVCs necessary to establish antiarrhythmic efficacy was higher for other indexes of ventricular ectopic activity (table 2).

Complex PVCs, i.e. presence vs absence, on treadmill exercise testing were poorly reproducible (kappa 0.22, NS) when baseline and placebo tests were compared.

**Discussion**

In patients with asymptomatic ventricular ectopic activity, the assessment of antiarrhythmic efficacy re-

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**Figure 2.** Group means and standard deviations for various indexes of ventricular ectopic activity on ambulatory electrocardiography and treadmill exercise testing. Baseline and placebo measurements were not significantly different at the 0.05 level. Statistical analyses were performed on the log (premature ventricular complex [PVC] frequency + 1). The corresponding absolute values are shown on the opposing scale.

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**Table 2. Indexes of Ventricular Ectopic Activity Used for the Assessment of Antiarrhythmic Drug Efficacy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient of repro (r)</th>
<th>Sensitivity threshold*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>95%</td>
</tr>
<tr>
<td>24 hour AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg PVCs/hour</td>
<td>0.94</td>
<td>2.2</td>
</tr>
<tr>
<td>Avg PVCs/1000 beats</td>
<td>0.92</td>
<td>2.2</td>
</tr>
<tr>
<td>Peak PVCs/hour</td>
<td>0.76</td>
<td>4.3</td>
</tr>
<tr>
<td>Avg repetitive PVCs/hour</td>
<td>0.84</td>
<td>2.6</td>
</tr>
<tr>
<td>Treadmill exercise testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg PVCs/min</td>
<td>0.86</td>
<td>1.2</td>
</tr>
<tr>
<td>Peak PVCs/min</td>
<td>0.66</td>
<td>4.1</td>
</tr>
</tbody>
</table>

*Minimal baseline (control) PVC frequency required to evaluate antiarrhythmic drug efficacy at a given confidence level. At this threshold 100% suppression of PVCs is required to distinguish drug efficacy from spontaneous variability.
†Percent of patients demonstrating a baseline PVC frequency above the sensitivity threshold.
‡Minimal percent reduction of PVC frequency from baseline required to establish drug efficacy at the given confidence level.
§Confidence level.

Abbreviations: repro = reproducibility; AE = ambulatory electrocardiography; PVC = premature ventricular complex.
TABLE 3. Relationship of Baseline Premature Ventricular Complex (PVC) Frequency to the Percent Reduction in PVCs Required to Establish Antiarrhythmic Efficacy with 95% Confidence

<table>
<thead>
<tr>
<th>AE avg PVCs/hour</th>
<th>TM avg PVCs/min</th>
<th>PVC reduction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.2†</td>
<td>&lt; 1.2†</td>
<td>—</td>
</tr>
<tr>
<td>2.2-3.0</td>
<td>1.2-1.5</td>
<td>100 to 90%</td>
</tr>
<tr>
<td>3.0-5.5</td>
<td>1.5-2.5</td>
<td>90 to 80%</td>
</tr>
<tr>
<td>5.5-11</td>
<td>2.5-5.5</td>
<td>80 to 70%</td>
</tr>
<tr>
<td>11-20</td>
<td>5.5-9</td>
<td>70 to 68%</td>
</tr>
<tr>
<td>—</td>
<td>9 or more</td>
<td>68%‡</td>
</tr>
<tr>
<td>20-30</td>
<td>—</td>
<td>65 to 68%</td>
</tr>
<tr>
<td>30 or more</td>
<td></td>
<td>65%§</td>
</tr>
</tbody>
</table>

*Percent reduction from baseline PVC frequency necessary to establish drug efficacy with 95% confidence.
†Sensitivity threshold: frequency below which an antiarrhythmic drug response cannot be assessed with 95% confidence.
‡Minimal percent reduction for TM average PVCs/min.
§Minimal percent reduction for AE average PVCs/hour.
Abbreviations: PVC = premature ventricular complex; AE = 24-hour ambulatory electrocardiography; TM = treadmill exercise testing.

requires objective criteria. Because individual patients may show large degrees of spontaneous PVC variability, it is difficult for the clinician to distinguish true drug response from spontaneous reduction in PVC frequency. The problem has been compounded by conflicting views concerning the choice of methods for such an assessment.

We attempted to simulate a clinical situation in which the efficacy of an oral antiarrhythmic drug could be evaluated in the patient with asymptomatic ventricular ectopic activity. Such a patient would have a baseline evaluation with exercise testing and/or a 24-hour ambulatory ECG and a repeat evaluation 2 weeks later while receiving the antiarrhythmic medication to be evaluated. The 2-week interval would ensure that (1) steady-state plasma concentrations of the antiarrhythmic drug had been achieved; (2) washout of previous antiarrhythmic medication had occurred; (3) the patient’s short-term tolerance to the medication had been reasonably assessed; (4) the patient’s day-to-day routine had not been significantly altered; and (5) changes in the patient’s disease state, which might occur during longer intervals, had been avoided.

Using these guidelines, we have tested the reproducibility of PVC responses to treadmill exercise and 24-hour ambulatory ECG monitoring to establish standards for the assessment of antiarrhythmic therapy in patients with asymptomatic ventricular ectopic activity. Patients were given placebo to assess the possible psychologic effects of an oral medication on the spontaneous variability of ventricular ectopic activity. We found PVC frequency to be highly reproducible with 24-hour ambulatory electrocardiography and treadmill exercise testing. Among indexes of ventricular ectopic activity on ambulatory electrocardiography, the average frequency of PVCs/hour was the most reproducible (r = 0.94, p < 0.0005). It had the lowest sensitivity threshold (2.2 and 4 PVCs/hour for the 95% and 99% confidence levels, respectively), and required the lowest minimal percent reduction in PVC frequency to establish drug efficacy at the 95% and 99% confidence levels (65% and 77%, respectively). Less reproducible indexes of ventricular ectopic activity on ambulatory ECGs had higher sensitivity thresholds. Antiarrhythmic drug efficacy can be evaluated only in patients whose baseline PVC frequency exceeds this threshold. For example, if the average PVC frequency/1000 beats were used instead of the average PVCs/hour, antiarrhythmic drug response could have been evaluated at the 95% confidence level only in the 81% of our population exceeding the baseline threshold frequency of 2.2 PVCs/1000 beats, whereas 100% of patients could have been evaluated using the lower threshold frequency of 2.2 PVCs/hour (table 2). Further, when a less reproducible index of ventricular ectopic activity is used to evaluate drug efficacy, a greater percent reduction in PVCs is necessary to establish drug efficacy at a given confidence level. For example, at the 95% confidence level, the minimal percent reduction in peak PVC frequency/hour is 80%, vs 65% minimal percent reduction for the average PVC frequency/hour. Indexes of ventricular ectopic activity that require a large percent reduction of PVCs for evaluation of antiarrhythmic efficacy are less practical than those that require a smaller percent reduction.

The average frequency of PVCs/min during exercise or recovery was also found to be the most reproducible of the two quantitative indexes of ventricular ectopic activity on treadmill exercise testing (table 2). The sensitivity threshold and the minimal percent reduction of PVCs required to establish drug efficacy at the 95% confidence interval were both lower for average frequency/min of treadmill induced PVCs than for peak PVC frequency/min (1.2/min and 68% vs 4.1/min and 89%, respectively [table 3]). Complex PVCs on treadmill exercise testing were poorly reproducible and could not be used to assess drug efficacy.

Treadmill exercise testing was less effective than ambulatory electrocardiography in assessing antiarrhythmic drug efficacy: fewer than 40% of our patients exceeded the baseline threshold frequency of PVCs required to evaluate antiarrhythmic drug efficacy. On the other hand, in patients who exceeded this threshold frequency of PVCs on exercise testing, the reduction in average frequency of PVCs/hour required to demonstrate drug efficacy was similar to that of ambulatory electrocardiography, 68% vs 65%, respectively. This suggests that treadmill exercise testing can be used in lieu of ambulatory electrocardiography for evaluating antiarrhythmic drug efficacy in patients with higher frequencies of PVCs, i.e. more than 1.2 average PVCs/min during exercise or recovery.

The percent reduction of PVCs required to establish drug efficacy in this study is less than that recently
FIGURE 3. Comparison of results derived from the study of Morganroth et al.\textsuperscript{10} and from the present study with respect to the percent reduction in baseline average premature ventricular complex (PVC) frequency/hour on ambulatory electrocardiography necessary to establish drug efficacy with 95\% confidence. (A) The uppermost (interrupted) line represents the author's reported goal of 83\% reduction in baseline PVC frequency. The lower two lines represent our reanalysis of the data of Morganroth et al. using analysis of variance (ANOVA) for two-tailed and one-tailed 95\% confidence levels of significance. The minimal percent reduction necessary to establish drug efficacy with two-tailed 95\% confidence and with one-tailed 95\% confidence is 73\% and 65\%, respectively. (B) Regression analysis was used to determine the percent reduction in baseline PVC frequency required to establish drug efficacy with 95\% confidence (one-tailed). In both types of analyses, 100\% reduction is necessary to demonstrate drug efficacy for low PVC frequencies. The sensitivity threshold of 2.2 PVCs/hour in panel B establishes the baseline frequency at which 100\% reduction is necessary to demonstrate drug efficacy. In patients with lower baseline PVC frequencies, true drug efficacy cannot be distinguished from spontaneous variability with 95\% confidence. Regression analysis and analysis of variance yielded the same minimal percent reduction in baseline average PVCs/hour: 65\% for one-tailed 95\% confidence.

reported.\textsuperscript{8,10} Several reasons for this discrepancy should be considered:

Lack of Homogeneity of Patient Groups

Patients with coronary artery disease and ventricular arrhythmia may have different degrees of variability than those with mitral valve prolapse or cardiomyopathy. We evaluated a relatively homogeneous group of patients with coronary artery disease, most of whom had a history of myocardial infarction. Our standards for antiarrhythmic drug efficacy are therefore most directly applicable to clinically similar patients.

Unstable Clinical State of Patients

The frequency of PVCs tends to be less reproducible soon after myocardial infarction than at a later phase of convalescence.\textsuperscript{28} To ensure that our patients were in a clinically stable state, we excluded those with a history of unstable angina pectoris or myocardial infarction less than 3 months old. Furthermore, we tested patients within 2 weeks, an interval short enough to avoid changes in PVC frequency attributable to changes in clinical state alone.

Spontaneous Variability of Arrhythmia

Numerous studies have demonstrated marked hourly variations in the frequency of PVCs on ambulatory electrocardiographic recordings,\textsuperscript{8,10} a phenomenon also observed in the present study. Therefore, different segments of the same day should probably not be used to evaluate the response to antiarrhythmic medication. For example, an 8-hour segment from a given day should not be used as a baseline measurement for the next 8-hour segment, but rather for the same 8-hour segment of another day. We, as well as others,\textsuperscript{1,8,10} recommend that at least 24 hours of ambulatory electrocardiographic recording be used as a control period to antiarrhythmic drug efficacy. This duration of recording circumvents the problem of diurnal variation and is logistically feasible with regard to expense, time and patient inconvenience.

The Effects of Hospitalization

Several recent reports of antiarrhythmic drug efficacy have studied hospitalized patients.\textsuperscript{8,10} However, hospitalization itself may significantly decrease PVC frequency, exaggerating "spontaneous variability" that occurs from day to day. This fact must be considered when drug trials are conducted under circumstances different from those encountered by patients in their day-to-day activities. The complicating effects of hospitalization were avoided altogether in the present study.

Differences in Statistical Analysis

Morganroth et al.\textsuperscript{10} recently reported that a reduction of 83\% of the average PVC frequency per hour on
24-hour ambulatory ECGs was necessary to establish antiarrhythmic drug efficacy with 95% confidence. We believe this analysis suffers several statistical shortcomings: The authors have used a repeated measures analysis of variance to calculate day-to-day and hour-to-hour variability of PVC frequency in a sample of 15 patients tested by consecutive 24-hour ECGs. This type of analysis is based on the assumption of independent errors. Data collected as these were, in consecutive 1-hour periods, are unlikely to satisfy this assumption. Further, the authors claim to have used a pure model II or “random-effects” model in their analysis. However, the choice of hour and day periods was not randomly selected, so a “mixed model” would have been more appropriate. Another statistical shortcoming in the analysis of Morganroth et al. was the choice of a two-tailed approximate confidence interval rather than an exact one-tailed one, when the hypothesis of interest appears to be one-tailed: Is there a significant decrease in PVC frequency? Morganroth et al. also obtained confidence intervals for mean natural logarithm (ln) (PVC frequency + 1). However, the mean ln (PVC frequency + 1) is not the same as ln (mean PVC frequency + 1). These confidence intervals cannot be directly translated into absolute PVC frequencies as the authors have done. In our statistical approach, we obtained confidence intervals on ln (PVC frequency + 1) of individual measurements but not on the means.

We reanalyzed the data from Morganroth et al. using a mixed-model analysis of variance on 24-hour PVC frequencies, verifying the assumption of equal variances in this case and using exact one-tailed 95% confidence intervals. The results of this analysis differ from those reported by the authors. For example, we found the minimal percent reduction required to establish drug efficacy at the 95% one-tailed confidence level to be 65%, not 83% (fig. 3). On the other hand, our analysis of the data of Morganroth et al. coincides remarkably with the results of our own data with respect to the minimal percent reduction of average PVC frequency/hour on 24-hour ambulatory ECGs i.e., 65%, required to demonstrate antiarrhythmic drug efficacy at the 95% confidence level. This similarity of the two studies supports the validity of the model we have used. It also suggests that patients with diseases other than coronary artery disease, those who have high PVC frequencies, and those who are tested at intervals shorter than 2 weeks may show similar degrees of spontaneous variability. This broadens the applicability of the standards derived from our patients.

Acknowledgment

We thank Richard Ryan, Ph.D., Evansville, Indiana, for his support and help. We are also indebted to Cay Fotopoulos and Linda Raby for recording exercise tests, to Cardio-Dynamics Laboratories, Los Angeles, California, for analysis of ambulatory ECG recordings, to Arlisa Ferrara for computer assistance and to Dorothy Potter and Cathy Cassidy for manuscript typing.

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Effects of Acebutolol on Chronic Stable Angina Pectoris

A Placebo-controlled, Double-blind, Randomized Crossover Study

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RICHARD J. KATZ, M.D., REBECCA BORTZ, B.S., JOHN S. GOTTDIENER, M.D.,
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SUMMARY We evaluated the effects of acebutolol, a cardioselective $\beta$-adrenergic blocking agent, on the anginal pattern and exercise tolerance in 44 patients with chronic stable angina. There were 43 males and one female, with a mean age of 57 years (range 48-73 years).

The study consisted of an initial 4-week, single-blind placebo control phase, followed by a 3-week, single-blind dose-titration phase using increasing doses of acebutolol and by two 5-week double-blind phases that included randomization to acebutolol or placebo and crossover. A 1-week withdrawal schedule followed each treatment phase. All patients kept a diary of anginal frequency and nitroglycerin consumption. Capsule counts of returned medication were made at each visit. Exercise treadmill tests were performed at entry into the study and on the final day of each of the four phases.

Acebutolol produced a significant decrease in the frequency of angina attacks, consumption of nitroglycerin and exercise capacity. Resting and peak exercise values were significantly reduced. Heart rates were reduced by 16% and 18%, respectively ($p < 0.002$) and rate-pressure products by 17% and 30%, respectively ($p < 0.002$). At effective antianginal dosages, acebutolol had no significant adverse effects on pulmonary functions. No clinical side effects of acebutolol necessitated drug discontinuance.

Acebutolol is a well-tolerated $\beta$-blocking drug that significantly reduces spontaneous anginal frequency, decreases consumption of nitroglycerin and increases exercise capacity in patients with chronic stable angina. It is a useful therapeutic addition to the group of $\beta$-adrenergic blocking agents. Further, its lack of deleterious effects on the bronchial smooth muscle suggests that acebutolol may be safely used in patients in whom angina is associated with obstructive pulmonary disease.

THE THERAPEUTIC EFFICACY of propranolol hydrochloride, a noncardioselective $\beta$-adrenergic blocking agent, for the treatment of ischemic heart disease and symptomatic angina pectoris has been shown.$^{14}$ However, the adverse effects on bronchial$^{5,6}$ and vascular smooth muscle constriction$^{7,8}$ that accompany noncardioselective $\beta$-blockade have stimulated interest in identifying more cardioselective $\beta$-blocking agents. Cardioselective $\beta$ blockade may be associated with improved exercise capacity$^{6,10}$ and a lower risk of inducing glucose intolerance compared with noncardioselective blockade.$^{11,12}$ Acebutolol, unlike propranolol, has been shown to be cardioselective.$^{13-21}$ It also possesses mild intrinsic sympathomimetic activity,$^{12,18}$ posing a theoretical limitation to its antianginal effects; therefore, careful clinical testing to assess acebutolol for its overall effects in the treatment of angina is crucial.

Studies of this new agent for the treatment of angina pectoris$^{22-28}$ have been limited by a failure to adhere to all of the widely accepted standards for the evaluation of antianginal drugs, including documentation of disease in patients with frequent anginal pain, diaries for recording anginal pain and nitroglycerin consumption, randomization procedures with placebo-controlled, double-blind design, large homogeneous sample sizes and, especially, multistage exercise stress testing.$^{29-33}$ The present study was undertaken to investigate the effects of oral acebutolol...
A new method for evaluating antiarrhythmic drug efficacy.
M Sami, H Kraemer, D C Harrison, N Houston, C Shimasaki and R F DeBusk

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