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Editorial Comment

The Variability of Spontaneous Ventricular Arrhythmias in the Year After Myocardial Infarction*

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The present study. In this issue of the Journal, Pratt et al. (1) use data from the Cardiac Arrhythmia Pilot Study (CAPS) placebo group to evaluate spontaneous variability in the frequency of ventricular premature depolarizations and in the occurrence of nonsustained ventricular tachycardia in the year after myocardial infarction. When applying the CAPS findings, one should always recall that the CAPS patient sample was selected for time after myocardial infarction, age, ventricular premature depolarization frequency and left ventricular ejection fraction. The 100 patients in the placebo group had frequent continuous 24 h recordings during 1 year of follow-up. The variability in ventricular premature depolarization frequency among recordings was substantial enough for nearly 50% of the patients to satisfy the CAPS criteria for antiarrhythmic efficacy at least once, and for >10% of them to exhibit an apparent proarrhythmic effect (a ≥10-fold increase in ventricular premature depolarization frequency) at least once by the end of dosing. Mere inspection of the data indicates the futility of using the presence of nonsustained ventricular tachycardia, a low frequency event, to judge antiarrhythmic efficacy or a proarrhythmic effect.

Some of the possible sources of variability in the frequency of ventricular arrhythmias in the year after myocardial infarction reported by Pratt et al. (1) include 1) regression to the mean; 2) systematic trend in frequency or repetitiveness over time caused by healing of the infarct; 3) placebo effect; and 4) fluctuations in ischemia, electrolyte balance and drug treatment. We have discussed sources of variability in ventricular premature depolarization frequency elsewhere (2); the hypothesis that the decrease in frequency between the baseline and the first treatment evaluation tape is substantially due to regression to the mean is a reasonable one. We compared ventricular premature depolarization frequency in two 24 h continuous ECG recordings made 3 months apart in the placebo group of the Multicenter Diltiazem Post-Infarction Trial and found that the frequency of ventricular premature depolarizations doubled in the bottom quartile of the frequency distribution but halved in the top quartile (3). This marked and symmetric change in ventricular premature depolarization frequency is strong evidence for regression to the mean and supports the hypothesis of Pratt et al. (1).

Several studies (3,4) in representative postinfarction patient samples showed that ventricular premature depolarization frequency increases from 1 or 2 weeks after the infarction to approximately 3 months and then fluctuates about a relatively stable mean value. This pattern was not evident in the CAPS sample, which was limited to the upper quintile of the ventricular premature depolarization frequency distribution. Pratt et al. (1) assert that the frequency of ventricular premature depolarization decreased significantly ($p = 0.04$) *from* 3 *to* 12 *months after the beginning* of the trial. The significance of the decline may be overstated because of the failure to adjust the significance level for the multiplicity of tests that were performed (5). When the Bonferroni adjustment is applied (5), the decline from 3 to 12 months becomes of borderline significance at best.

The decrease in ventricular premature depolarization frequency during the 1st week of placebo treatment might be attributed to a placebo effect. However, we have examined a number of samples and have not been able to demonstrate a significant placebo effect on the frequency of ventricular arrhythmias. Regression to the mean is a better explanation.

Pratt et al. have the impression that the variability of ventricular premature depolarization frequency is higher in the year after myocardial infarction than at other times or in groups other than postinfarction patients. This hypothesis has not been proved, but it is reasonable considering the instability of the course of illness in the year after myocardial infarction, a period associated with especially high rates of mortality, reinfarction and other events (6).

Therapeutic implications. Pratt et al. (1) discuss how variability in the rates of ventricular arrhythmias makes interpretation of antiarrhythmic responses difficult after myocardial infarction. They suggest that longer recordings before and after starting antiarrhythmic drug treatment would improve the classification of responses as antiarrhythmic or proarrhythmic, but they also point out the logistic and fiscal constraints on such an approach. By restricting the approach to a single 24 h electrocardiographic (ECG) recording before treatment and a single recording after treatment,

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one could change the criteria for efficacy and proarrhythmia so that there were fewer false positive results. However, such changes would carry with them a substantial price. The price for a more stringent criterion for efficacy would be a substantial increase in the prevalence of cardiac and noncardiac toxicity, assuming that failure to achieve efficacy would result in an increased dose of the drug. The therapeutic ratio of antiarrhythmic drugs with class 1 action is not high, placing severe limits on flexibility in dosing. It really is not practical to require 70% to 80% arrhythmia suppression to classify a response as antiarrhythmic.

Using criteria similar to those of Pratt et al. (1) in a large placebo-treated group, we found a false positive proarrhythmia rate of about 2% (3). This rate could be reduced by changing the criteria but the price would be an increase in the false negative rate, that is, the rate of failure to detect patients whose arrhythmia was, in fact, aggravated by treatment. In our view, this would be unacceptable.

In contrast to the difficulties in evaluating patients, it is easy to detect and quantify antiarrhythmic action by using responses to a range of doses even in small groups of patients. If a large study showed a positive correlation between arrhythmia suppression and improved survival after infarction, then despite regression to the mean, a 70% to 80% reduction would be a reasonable criterion of antiarrhythmic action to use in individual patients receiving prophylactic treatment.

Conclusions. In light of the difficulties discussed by Pratt et al. (1), it is apparent that ventricular arrhythmias in the year after myocardial infarction are better indicators of mortality risk than of antiarrhythmic drug efficacy. They resemble left ventricular ejection fraction and the signal-averaged ECG in this respect. The Cardiac Arrhythmia Suppression Trial (CAST) results also suggest that suppression of ventricular arrhythmias after myocardial infarction with encainide or flecainide selects a low risk group if treatment is not continued after the initial titration for arrhythmia suppression.

Finally, it should be emphasized that CAST (7) and other studies (8,9) have shown that patients with ventricular arrhythmias after myocardial infarction, but with no or only minimal symptoms, should not be treated with any antiarrhythmic drug with class I action until one of these drugs is shown to improve survival significantly. This recommendation avoids altogether the need to deal with the complex issues with which the CAPS data on arrhythmia variability confront us.

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