Complex Ventricular Arrhythmias

To the Editor:

In a recent article on spontaneous variability of complex ventricular arrhythmias, Michelson and Morganroth (Circulation 61: 690, 1980) calculated that if one control 24-hour monitoring period is compared with one 24-hour treatment period, a 65% reduction in the mean hourly frequency of ventricular tachycardia and a 75% reduction in the mean hourly frequency of couplets is required to show a statistically significant therapeutic effect in an individual patient. For ventricular ectopic beats, however, an 83% reduction is required.1

We have evaluated the spontaneous variability of complex ventricular arrhythmias in 45 clinically stable patients by means of three consecutive 24-hour, long-term, ambulatory electrographic recordings.2 All patients had ventricular ectopic beats and atrial ectopic beats in each of the 24-hour periods. Forty-three patients had couplets, 37 had ventricular tachycardia (three or more consecutive beats) and 40 had ventricular bigeminy.

Thus, in absolute numbers our results are comparable to those of Michelson and Morganroth. However, the statistical assumption of normal distribution and homogeneous variance was quite closely satisfied for the logarithm of ventricular ectopic beats and atrial ectopic beats only. If one control 24-hour monitoring period is compared with one 24-hour treatment period, an 83% reduction in the mean hourly frequency of ventricular ectopic beats and an 85% reduction of atrial ectopic beats was required to demonstrate drug efficacy in an individual patient.

The hourly frequency of ventricular couplets, ventricular tachycardia and runs of ventricular bigeminy transformed to natural logarithm, however, showed a markedly skewed distribution with a heavy right tail in the individual patient as well as between patients. Further, the variances for the individual patients revealed large differences. Thus, according to Scheffe,3 an analysis of variance would be biased. We even doubt that the t test should be used to compute the necessary reduction of complex ventricular arrhythmias in a drug study.

From the data for complex ventricular arrhythmias given in tables 1 and 2 of the paper by Michelson and Morganroth, we suspect that there are skewed distribution and inhomogeneous variances, too.

Thus, it is our opinion that the statistical methods used by Michelson and Morganroth should not be employed. The use of these methods has led to the surprising result that complex ventricular arrhythmias, which occur more infrequently, required a lower reduction rate to demonstrate drug efficacy than simple ventricular ectopic complexes, which occur more frequently and with greater regularity. According to our data, and probably to those of Michelson and Morganroth as well, in most cases not even a total reduction of complex ventricular arrhythmias in one 24-hour period is an unequivocal proof of a drug effect in an individual patient.

Dietrich Andreason, M.D.
Ulrich Tietze
Enz-Rudiger von Leitner, M.D.
Karl Wegscheider
Rolf Schröder, M.D.
Klinikum Steglitz
Berlin, Germany

References


The authors reply:

To the Editor:

In 1978,1 we published, for the first time, an attempt to document the marked spontaneous variability in the frequency of ventricular premature depolarizations (VPDs) using sophisticated statistical methods. We chose a random effects model analysis of variance as the statistical basis from which we derived VPD percent reduction guidelines during an intervention that would overcome the marked changes from the control period in the frequency of VPDs due solely to biologic or spontaneous variability. These guidelines, as well as those for complex arrhythmias,4 were based on pooled patient data, even though we realized that there was a great deal of difference between individual patients in their degree of spontaneous variability. We now believe that the periodic (e.g., hourly) effects are serially correlated rather than completely random as initially assumed,5 particularly because these observations are obtained in a systematic, predetermined manner. Moreover, we subjected both our simple and complex VPD data to natural logarithmic transformation so that random errors would be more normally distributed with homogeneous variances. The guidelines for percent reductions were based on this transformed data and, thus, these reductions were calculated using geometric rather than arithmetic means. We agree with Andresen et al. that VPD data do not necessarily distribute normally, even with logarithmic transformation and, therefore, parametric methods such as analysis of variance have limitations. However, as pointed out by Scheffe,6 departures from normality will not lead to biased point estimates of the variance components in the model we chose to use. Because our methods used only the point estimates of the variance components (and made no other inferences about these components) to estimate the reduction in mean hourly VPD frequencies necessary to show therapeutic efficacy, the degree of normality of our data did not significantly affect our results.

Furthermore, we believe that the use of guidelines based on pooled patient data are too imprecise to be useful for antiarrhythmic drug research and should, therefore, be abandoned for research purposes. For example, some patients have VPD frequencies that are so variable that they would not be suitable subjects for testing new antiarrhythmic agents, while other patients have so little variability that they would require only a small percentage reduction to define drug efficacy. This is particularly relevant because new antiarrhythmic drug efficacy should be determined by the percentage of individual patients who respond rather than by use of pooled patient data.

We are now developing a time series analysis using a Poisson model to better define the extent of spontaneous VPD variability in individual patients and hope this will overcome many of the shortcomings of the previous methods. In the meantime, we believe that a fixed effects model analysis of variance using logarithmic transformation, though limited, is the best available approach for determining antiarrhythmic drug efficacy.

In addition, we must remember not to confuse "drug effect," i.e., whether the drug is effecting a statistically significant reduction (or complete abolition) of ventricular arrhythmias, with the issue of whether such a reduction or abolition will prevent sudden cardiac death. In these statistical exercises we are attempting to define more precisely how one can be confident that any observed reduction in VPD frequency can be attributed to "drug effect" rather than merely to spontaneous variability. We do not attempt to evaluate the question of whether complete abolition of one or all types of ventricular arrhythmias is necessary or, in fact, essential to prevent sudden arrhythmic death. This will require prospective controlled trials once new, effective and safe antiarrhythmic agents are available.

Joel Morganroth, M.D.
Eric L. Michelson, M.D.
Lankenau Hospital
Jefferson Medical School
Philadelphia, Pennsylvania
Complex ventricular arrhythmias.
D Andresen, U Tietze, E R von Leiter, K Wegscheider and R Schroder

doi: 10.1161/01.CIR.63.1.236

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on
the World Wide Web at:
http://circ.ahajournals.org/content/63/1/236.citation