Letter to the Editor

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Variability of Ventricular Premature Contractions

The study by M.I. Anastasiou-Nana et al. describes the same trend we reported in the same issue of *Circulation*—the increasing reduction rates needed for therapy to achieve significance with increasing length of control interval. The results differ somewhat from ours, which is due to a different selection of patients as well as a number of major weaknesses we perceive in the method they used.

One of the most serious defects, we believe, is the use of the constant +1 for calculating the spontaneous variability of repetitive ventricular arrhythmias without modifying the criteria for each individual patient. As we set forth in detail in our study, the assumption of a constant of +1 when calculating rare arrhythmia events such as couplets and salvos leads to a considerable underestimation of reduction rates required. We described at length the arithmetic error that arises due to a relatively high constant in the case of rather rare arrhythmias.

In accordance with our Equation 5, we will demonstrate the influence of the constant +1. Patient 3, for example, had 3.15 repetitive ventricular premature contractions (VPCs)/hr on day 1. According to the results of Anastasiou-Nana et al; a 95% reduction is required to assume drug efficacy if the control interval is between 4 and 10 days. This means that patient 3’s repetitive VPCs an hour on day 2 must be less than 0.158. However, the reduction rate must be applied to the repetitive VPCs an hour augmented by +1. Therefore, the following calculations must be performed: a 95% reduction of 4.15 (=3.15+1) leads to 0.21 repetitive VPCs/hr on day 2. Now the constant +1 must be subtracted, which yields −0.79 repetitive VPCs/hr on day 2. This means that a “true” reduction of more than −100% would be required. As we pointed out, the reduction criteria have to be altered by the ratio (VPCs/hr on day 1+1)/(VPCs/hr on day 1). This leads to a threshold at which a complete elimination of all events is required. In terms of the reduction rate of −95% and the constant (+1), this threshold is 19 repetitive arrhythmia events an hour, or 456 events a day! This frequency of repetitive events per day can be expected only in a minority of cases. In fact, only 21 of 47 patients (45%) studied by Anastasiou-Nana et al meet this condition. Figure 1 depicts the situation with a control interval between 4 and 10 days. The horizontal line in the upper panel indicates the reduction rate calculated by Anastasiou-Nana et al. The curved line represents the “true” reduction rates that increase with decreasing arrhythmia counts.

The authors were evidently unaware of the problem with this threshold and therefore took no notice of it. With the constant of 0.01 that we used, the threshold at which a reduction of more than 100% occurs arithmetically is much lower. At a reduction rate of −95%, this threshold would be 0.19 repetitive VPC/hr.

Nowhere do Anastasiou-Nana et al mention whether this transformation complied with the underlying assumptions (homogeneous variances and normal distribution).

Another problem is the insufficient number of patients in some of the “separation intervals,” particularly if the control interval is more than 1 year (n=6 patients).

The statements on the influence of the underlying cardiac disease or left ventricular ejection fraction on the spontaneous variability are also very problematic as to the extent of left ventricular impairment; we found similar results in an exploratory analysis of our data material. The same results have been known for some time. Therefore, we did not mention these data.

We analyzed the influence of the end-diastolic volumes and pressures in addition to the left ventricular ejection fraction. No influence of any of these variables could be detected.

As far as the impact of the kind of underlying heart disease on spontaneous variability is concerned, we observed no significant difference between patients with idiopathic dilated cardiomyopathy (IDC) (n=28) and those with coronary heart disease (CHD) (n=25) in Holter tapes recorded on two consecutive days. With respect to the number of patients, the power of detecting a significant difference is above 50% only if the true difference between the two means is greater than half the standard deviation. How low must the power of Anastasiou-Nana et al’s calculations be for smaller case rates (CHD, n=26; IDC, n=1; valvular heart disease, n=5; hypertension, n=1; idiopathic, n=14)?

Finally, we wonder why the authors present data collected in short control intervals of only 4 weeks, on the one hand, and control intervals of more than 1 year, on the other, whereas they say nothing about the period in between.

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References


Reply

Both our study1 and the study by Schmidt et al2 show that the range of spontaneous variability of ventricular ectopic activity in patients with chronic arrhythmia is substantial, widening progressively with time, such that at long-term intervals (months to years), the 95% confidence intervals of variability compared with baseline recordings are exceeded only by virtually complete (>95%) suppression of arrhythmias or huge (>10-fold) arrhythmia increases. The consistency of these findings is particularly striking, considering the independent study populations and methodologic approaches used. It is surprising that Schmidt et al, while raising several issues of secondary interest, failed to emphasize this message of primary importance. In so doing, they may misunderstand the major clinical implication of both studies—that further refinement of baseline measurements and comparisons, especially with a remote baseline, is an inadequate solution to the clinical dilemma of evaluating antiarrhythmic drug efficacy and toxicity. A different approach, interval comparisons of closely spaced drug-free versus drug-treatment recordings, is better supported by the data.

In response to the issues raised, we will address specific questions and then discuss the statistical model used for the selection of drug efficacy criteria proposed by Schmidt et al, because this specific model was used in the critique of our results.

Schmidt et al's first comment relates to the value of the constant added to arrhythmia rates. In determining variability for infrequent events, a constant must be added before taking the logarithm so that in the event of a "zero" rate, the log is defined. Addition of the constant +1 to frequency of total PVCs, the primary variable of interest, should not be problematic. Patients were required to have more than 30 PVCs/hr at baseline (mean, 533 PVCs/hr). Substitution of 0.01 (which Schmidt et al used) for +1 in calculations of variability of total PVCs an hour gives trivial (≤0.3%) differences in required percent suppression. Frequency of repetitive beats per hour was not a criterion for entry and was quite variable. Substitution of the smaller constant in calculations of variability of repetitive events does lead to widening of already broad limits of variability. However, this difference arises largely because of greater weight given to small absolute changes in patients with very low frequency events that we believe have little clinical meaning.

We do not propose the use of the constant for calculating individual rates of "required response" to therapy as they suggest in their example of patient 3. We believe that "splitting hairs" over fractions of events a day is an inappropriate clinical approach. In practice, recognizing the statistical problems of dealing with infrequent events, we disregard changes in low frequency events (e.g., couplets and salvos) in the determination of drug success if baseline event frequency is more than 10 a day. If analysis excludes patients with such low rates, then results with +1 or +0.01 as the constant approach each other (to within approximately 3%).

Next, they point to the small numbers of observations made at more than 1 year. This is recognized, but these observations are uninteresting because variability changes primarily between 1 day and 1 week and plateaus (at about 95%) at longer intervals. Unfortunately, Schmidt et al pool observations between 0 and 6 days, the time of greatest change in variability, and again between 7 and 89 days; therefore, they may miss the important incremental differences in short-term variability that we noted. Again, because variability changes primarily over days to weeks, we were less interested in looking at subdivisions of time between 1 month and 1 year, when effects have reached a plateau.

Schmidt et al's inclusion in their letter of a new subgroup of analyses on their data on variability by patient characteristics is welcome. Their new results concur with and strengthen the analyses previously published in our study. We disagree, however, with their description of the results of our analyses (performed at the suggestion of reviewers) as "problematic." Our conclusions are in striking concordance with theirs: Ejection fraction and type of underlying cardiac disease do not influence variability. Unfortunately, they have not provided an analysis of variability by baseline arrhythmia frequency, which we found to be the one factor to influence variability.

In discussing their ratio model, we wish to first acknowledge the contribution of Schmidt et al in the estimation procedure for the most appropriate value of the constant added to arrhythmia frequencies before mathematic manipulation (taking of ratios and logarithmic transformation). However, the mathematical derivation they present applies only to the ratio model they propose and not to the more traditional additive model of Morganroth et al3 that we1 and others4 have used. Furthermore, their caveats apply only to the ratio as used in the determination of the percent suppression comparing a baseline and a second (drug treatment) condition. We will show that the ratio model is not appropriately applied to the measure of variability during multiple baseline conditions.

First, the ratio model represents a between-patient measure of variability. The ratio of ectopic beats on day 1 to that on day 2 is obtained for each patient. These ratios are measures of within-patient variability. However, their next step is to find average variability between the ratios, distinctly a measure of between-patient variability. On the other hand, the more traditional additive model3,4 is a within-patient measure. Variability between days 1 and 2 and any number of additional days (the ratio model can use only two days) is obtained for each patient. These measures are then pooled to yield an average measure of within-patient variability. "Within-patient" is the measure of spontaneous variability that is appropriate and of interest because it represents the percent suppression required to establish drug efficacy when a comparison is made for a single patient between a baseline and a subsequent (e.g., drug treatment) recording. In these clinically relevant comparisons, the patient is always used as his own control.

Second, the ratio model of spontaneous variability is asymmetrical. The value of the ratio depends on which of the two days is used as the denominator. At first glance, the asymmetry may not appear problematic because when the logarithm of the ratio is obtained, it distributes symmetrically about 0. However, the variability induced by sampling order (whether the day used in the denominator happens to have the higher or lower rate of ectopic beats) adds to the ratio method, although it may have nothing to do with the patient's arrhythmia behavior. In contrast, the traditional additive model of spontaneous variability is unaffected by the ordering of days 1 and 2.

In conclusion, these several observations indicate that additional work needs to be done in the area of evaluating these two and other models of variability for clinical application. However, we believe that the largely concurrent results of Schmidt and our own group are an important step in that direction.

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