Spontaneous Variability of Simple and Complex Ventricular Premature Contractions During Long Time Intervals in Patients With Severe Organic Heart Disease

G. Schmidt, MD, K. Ulm, PhD, P. Barthel, L. Goedel-Meinen, MD, G. Jahns, and W. Baedeker, MD

Calculations of the spontaneous variability of ventricular arrhythmias are usually based upon the results of Holter electrocardiograms recorded either successively or separated by a short time interval. Only recently was it shown that the variability of ventricular premature contractions increases with longer intervals. This study was undertaken to investigate the variability of simple and complex ventricular arrhythmias over long periods to derive efficacy criteria for long-term antiarrhythmic therapy. In a prospective study, the influence of the length of the time interval on spontaneous variability was investigated in 100 patients with coronary artery disease or idiopathic dilated cardiomyopathy and untreated ventricular arrhythmia Lown grade IV. Patient follow-up was carried out for 260 ± 387 days. In each of the 498 ambulatory Holter tapes, the mean hourly arrhythmia count (AC) of ventricular premature contractions, couplets, and salvos was verified. The variability of arrhythmia counts between two Holter electrocardiograms was defined as the logarithm of the ratio of (AC day 1 + 0.01) to the 95% intervals for these ratios were calculated as ± 2 SD, considering the fact that all mean values did not differ significantly from zero. The lower limit of these intervals refers to the reduction that is required for assuming drug efficacy, whereas the upper limit refers to an aggravation. The 95% intervals were calculated for each of four ranges of control intervals (0–6, 7–89, 90–364, and ≥ 365 days). They increased significantly with longer control intervals. For ventricular premature contractions, reduction increased from 63% (0–6 days), 79% (7–89 days), and 92% (90–364 days) to 98% (≥ 365 days). The corresponding values of aggravation were 370%, 570%, 1,286%, and 5,495%, respectively. For couplets, reduction extended from 90%, 94%, and 98% to 99%; aggravation increased from 1,114%, 1,895%, and 6,153% to 14,032%. For salvos, reduction remained almost unchanged at a high level at 95%, 98%, 98%, and 99%. The figures for aggravation were 2,189%, 4,650%, 5,698%, and 9,650%, respectively. In individual patients, spontaneous variability at short control intervals was not found to predict long-term variability. We conclude that evaluation of antiarrhythmic drug efficacy by Holter monitoring is most easily distinguishable with short control intervals and is almost impossible after an antiarrhythmic therapy longer than 3 months. In many cases, long-term efficacy of an antiarrhythmic agent can only be proven after discontinuation of the drug and reassessment of spontaneous arrhythmia frequency. (Circulation 1988;78:296–301)

Adequate evaluation of antiarrhythmic drug therapy has been a problem ever since ventricular ectopy was established as being prone to marked spontaneous variability. In recent years, several attempts have been made to find criteria that differentiate between spontaneous and drug-induced variation at a sufficient probability level. But while spontaneous variability at short control intervals has repeatedly been the subject of intensive studies, it remains unclear whether criteria derived from short-term observations are good for long-term treatment as well.

These previous studies invariably have derived their calculations from the results of two to four ambulatory long-term (24-hour) electrocardio-
graphic recordings (Holter ECGs), recorded either successively or at intervals of several days. The length of longer control intervals between two recordings was only recently taken into consideration.6,7

This prospective study evaluates how the length of the control interval influences the spontaneous variability of ventricular premature contractions (VPCs), couplets, and salvos and thus the criteria of efficacy in patients with severe organic heart disease and frequent and complex ventricular arrhythmias, that is, the patients most likely to receive antiarrhythmic drug therapy.

Patients and Methods

Patients

This study included 100 patients (79 men, 21 women, aged 56 ± 12 years). All had at least 30 single VPCs each hour, as well as couplets, in the last Holter ECG before the study. They suffered from either coronary artery disease or dilated cardiomyopathy, proven by left heart catheterization or by radionuclide ventriculography (Table 1). Because a presentation of primary data of all patients in tabular form would be too unwieldy, these data are available upon request. All patients gave informed consent for participation in this study, including possible withdrawal of therapy.

There was a subgroup of 56 patients who were treated with antiarrhythmic drugs because of severe hemodynamic complications due to arrhythmia (such as syncope) because they had a history of cardiopulmonary resuscitation or because they participated in a clinical drug trial that included the administration of diprafenon, disopyramide, flecainide, prajmalium, propafenon, mexiletine, and toca

Calculation of Arrhythmia Variability

In each recording, the frequency and grade of arrhythmia were assessed by the mean hourly number of VPCs, couplets, and salvos. The spontaneous variability of arrhythmia counts (AC) between two Holter ECGs was defined as the ratio of AC_{day 2} to AC_{day 1}. If more than two Holter ECGs existed for a patient, all were compared with each other, for example, tape 1 with tape 2, tape 1 with tape 3, and tape 2 with tape 3.

To obtain normal distribution and homogeneous variances of the ratios, the variances were transformed into logarithm to base 10. To avoid the mathematically inadmissible transformation of log 0, a constant c was added to the arrhythmia counts on both days. Most investigators have used c = +1 arbitrarily.3–5 However, it should be mentioned that the variance of the ratios will be affected by the value of c to some degree. The larger the c is, the smaller the ratio will be, particularly with frequent arrhythmia counts.

To distinguish true antiarrhythmic effects from spontaneous variations, a confidence interval was calculated that covers 95% of all ratios observed. This was done separately for each of four ranges of control intervals (0–6, 7–89, 90–364, and ≥365 days). Using the fact that all mean values were close to zero, we defined the confidence interval as

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Data of the Patients</th>
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<tbody>
<tr>
<td>Symptoms (n)</td>
</tr>
<tr>
<td>Syncope</td>
</tr>
<tr>
<td>History of resuscitation</td>
</tr>
<tr>
<td>Underlying heart disease (n)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
</tr>
<tr>
<td>Bypass surgery</td>
</tr>
<tr>
<td>LV ejection fraction (%, mean ± SD)</td>
</tr>
<tr>
<td>β-Blocker therapy</td>
</tr>
<tr>
<td>Idiopathic dilated cardiomyopathy</td>
</tr>
<tr>
<td>LV ejection fraction (%, mean ± SD)</td>
</tr>
<tr>
<td>Arrhythmias (cph, mean ± SD)</td>
</tr>
<tr>
<td>VPCs</td>
</tr>
<tr>
<td>Couplets</td>
</tr>
<tr>
<td>Salvos</td>
</tr>
<tr>
<td>Treatment (n)</td>
</tr>
<tr>
<td>Class-I drugs</td>
</tr>
<tr>
<td>Diuretic</td>
</tr>
<tr>
<td>Digoxin</td>
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<tr>
<td>LV, left ventricular; VPCs, ventricular premature contractions.</td>
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<tr>
<td>n = 100 patients.</td>
</tr>
</tbody>
</table>

automatically analyzed by the ICR 6201-G-3 arrhythmia computer (Spacelabs, Redmond, Washington). In addition, all recordings were printed out in miniature and subjected to exact visual beat-to-beat analysis.
\[ [-2 \text{ SD} \leq \log \left( \frac{\text{AC}_{\text{day }2} + c}{\text{AC}_{\text{day }1} + c} \right) \leq +2 \text{ SD}] \]

The percent change (CH') in arrhythmia counts that is required to prove a drug effect is represented by the complementary areas:

\[(10^{-2\text{SD}} - 1) \cdot 100% > \text{CH}'(\%) > (10^{2\text{SD}} - 1) \cdot 100% \]

where CH' is computed according to the formula:

\[
\text{CH'} = \frac{(\text{AC}_{\text{day }2} + c)}{(\text{AC}_{\text{day }1} + c)} - 1 = \frac{(\text{AC}_{\text{day }2} + c) - (\text{AC}_{\text{day }1} + c)}{(\text{AC}_{\text{day }1} + c)} \quad (2)
\]

Thus, a modified change (Ch'), and not the "true" one (Ch), is calculated, which leads to an underestimation of the spontaneous variability (and the criteria derived) due to adding the value of the constant c.

However, this underestimation complicates the clinical use of the criteria derived. As a matter of fact, the true change (CH)

\[
\text{CH} = \frac{\text{AC}_{\text{day }2} - \text{AC}_{\text{day }1}}{\text{AC}_{\text{day }1}} \quad (4)
\]

is what the clinician is interested in. If CH were used to denote the change required for the change without any constant, the difference between the two values will be

\[
\text{CH} = \text{CH'} \cdot \frac{\text{AC}_{\text{day }1} + c}{\text{AC}_{\text{day }1}} \quad (5)
\]

Thus, only if the arrhythmia counts on day 1 (AC_{day 1}) are comparatively high or if the constant c is low, the difference between CH' and CH becomes negligibly small.

For different constants (c = 0.0001, 0.0005, 0.001, 0.005, 0.01, 0.05, 0.1, 0.5, 1.5, and 10), normal distribution of the variability ratios was checked by means of the Kolmogorov-Smirnov test separately for VPCs, couplets, and salvos within each of the four ranges of control intervals. Salvos were found to be normally distributed with constants ranging from 0.01 to 0.1 (Figure 1). Normal distribution of VPCs could be obtained over the whole range of constants. Couplets were found normally distributed with constants between 0.001 and 1. Because 0.01 was found to be the smallest constant consistent with normal distribution for all arrhythmia entities, this constant was selected for the calculations described below.

**Results**

Spontaneous variability of VPCs, couplets, and salvos was not influenced by digoxin, diuretics, and

\[
\beta\text{-blocker therapy. With regard to class I antiarrhythmic drugs, there was no difference between patients who were untreated throughout the observation period and those with intermittent therapy in drug-free control states.}
\]

Throughout the observation period of nearly 4 years, the sum of all variability quotients was almost 0 for VPCs, couplets, and salvos (Table 2), indicating that the overall arrhythmia incidence of the whole group remained unchanged.

For single VPCs, spontaneous variability was relatively small at short control intervals, but it increased continuously at longer control intervals, thus enlarging the area of confidence (Figure 2). This effect was already evident within the first weeks of follow-up.

During the 1st week of treatment, VPCs had to be reduced by at least 63% to establish antiarrhythmic efficacy. At intervals from 1 week to 3 months, 3 months to 1 year, and greater than 1 year, these figures increased to 79%, 92%, and 98%, respectively (Table 2). Along the same lines, the percentage of VPC-count increase considered to indicate a drug-induced aggravation of the arrhythmia had to be greater than 370 during the 1st week, and this margin increased continuously at longer control intervals to 570% from 1 week to 3 months, 1,286% from 3 months to 1 year, and 5,495% for more than 1 year (Table 2).

The variability of couplets was generally higher than that of VPCs, calling for a reduction of at least 90% at short control intervals (Figure 3). This rose to practically 100% after more than 3 months. Accordingly, the increase required to indicate an aggravation was in the order of 1,000–14,000% (Table 2).

The variability of salvos was very high even with extremely short control intervals and remained almost stable with reduction criteria near 100% and aggravation figures of 5,000–10,000% at intervals longer than 1 week (Table 2 and Figure 4).

In 38 patients, spontaneous variability could be investigated at control intervals shorter than 1 week
as well as at intervals in the range of 1 week to 3 months. According to the variability of VPCs at short intervals, the patients were divided into two equally sized subgroups: 19 patients with variability ratios less than or equal to ±0.13 versus 19 patients with ratios greater than ±0.13. Long-term variability did not differ in the two subgroups (Figure 5). Analogous results were obtained for couplets and salvos.

**Discussion**

Although several biostatistical models have been developed during the last decade, we decided to use one of our own in this study. Regarding the arithmetical procedure, the logarithms of the ratio arrhythmia count of day 2 divided by the arrhythmia count of day 1 were calculated, and (assuming the mean of these logarithms is zero) a 95% confidence interval was determined as ±2 SD. This approach is very similar to the model proposed by Pratt et al.\(^8\) who subtracted the logarithm of the arrhythmia count on day 1 from the logarithm of the arrhythmia count on day 2 and then computed the variance of the difference and determined a 95% confidence interval. Thus, the therapy criteria derived with either model are practically identical. However, we prefer the ratio model because it facilitates the analysis of any variable affecting spontaneous variability: the representation of the logarithm of the arrhythmia ratio on the y axis and the parameter of interest on the x axis allows for a vivid illustration of the results, thereby simplifying their interpretation.

When it is necessary to transform arrhythmia counts into logarithms, as is the case when calculating spontaneous variability with parametric models, one must add a constant to avoid the mathematically inadmissible form of log 0. The data will be modified not only by this transformation but also by the value of the constant added. Andresen and coworkers\(^2\) were the first to realize the importance of the constant and estimated its optimal value to obtain normally distributed data by means of the maximum likelihood method.\(^9\)

Moreover, according to Equation 3, the value of the constant added will lead to underestimation of variability with low arrhythmia counts (as is often the case for couplets and salvos). To minimize this effect, we chose the smallest constant (c = 0.01) consistent with a normal distribution of data. However, one should keep in mind that even then the variability is underestimated to a certain extent.

![Figure 2. Plot of spontaneous variability of ventricular premature contractions (VPC) in 100 patients during a period of nearly 4 years. Bars indicate the area of ±2 SD for four ranges of control intervals (≤1 week, 1 week–3 months; 3 months–1 year; and >1 year).](image1)

![Figure 3. Plot of spontaneous variability of couplets (Cpl).](image2)
The true reduction can be calculated by Equation 5. At arrhythmia counts equal to or greater than 0.33 each hour (or eight each day), the underestimation does not exceed 3% and can be disregarded.

Most workers chose a constant of +1 arbitrarily.\textsuperscript{3-5,8} As long as the variability of frequent events such as single VPCs is involved, this in fact will have only a negligible effect on the results. However, in the studies by Michelson and Morganroth\textsuperscript{3} and Toivonen,\textsuperscript{7} a constant of +1 was applied even for the calculation of infrequent events, that is, couplets and salvos. A significant underestimation of the therapy criteria was thus unavoidable: Michelson and Morganroth demanded a reduction of couplets by only 75% and of salvos by 65%; Toivonen required a reduction of repetitive VPCs of 77-78%. If a constant of 0.01 were used, these figures would far exceed 90%. Toivonen examined spontaneous variability of single and repetitive VPCs not only during short control intervals (2-14 days) but also over long time periods of up to 1 year. However, we see several shortcomings in this study. As set forth above, the arithmetic value of the constant was ignored. Moreover, the patient group was small (n=20) and included patients with miscellaneous heart conditions, with eight patients not showing any underlying heart disease.

In our study, we prospectively collected data of 100 patients with well-defined organic heart disease and frequent and complex ventricular arrhythmias. The maximum observation period was as long as almost 4 years. We found that within the 1st week of treatment reductions of at least 63% (VPCs), 90% (couplets), and 95% (salvos) were required to prove therapeutic effects. With control intervals longer than 6 days, reductions of 79%, 94%, and 98%, respectively, were required; control intervals longer than 90 days required reductions of 92%, 98%, and 98%, respectively, and control intervals longer than 1 year needed reductions of 98%, 99%, and 99%, respectively.

This statistical model is equally suitable for evaluating proarrhythmic drug effects. Within the 1st week of treatment, 3.7-fold rises (VPCs), 11-fold rises (couplets), and 22-fold rises (salvos) indicated aggravation; these figures grew to sixfold, 19-fold, and 47-fold rises, respectively, at control intervals of 1 week to 3 months, then to 13-fold, 62-fold, and 57-fold rises, respectively, between 3 months and 1 year, and 55-fold, 140-fold, and 97-fold increments, respectively, were required beyond 1 year.

A much-voiced desire is to develop valid therapy criteria for individuals rather than for groups. Our data enabled us to investigate the course of individual spontaneous variability over long time intervals. When long-term variability in single patients was compared with the baseline data of these patients, variability at short control intervals did not predict the further spontaneous course of the arrhythmia (Figure 5). Thus, to our present knowledge, it is not possible to derive individual criteria for a single patient, and this aim seems to be unachievable, irrespective of the number of baseline Holter ECGs available.

When interpreting the results of our study, one must keep in mind that drug effects can be insidious and complex, and even five half-lives free of a drug may not be sufficient for observing a greater than 95% dissipation of effects due to drug metabolites, irreversible membrane or cellular changes, or even a paradoxical provocation of arrhythmias at subtherapeutic drug levels during drug withdrawal. However, with a minimum interval of 5 days between final drug administration and the Holter ECG, five drug half-lives were exceeded by far in the majority of patients. Furthermore, spontaneous variability in patients with intermittent antiarrhythmic drug treatment did not differ from that in patients entirely free of antiarrhythmic drugs.

In terms of spontaneous variability of ventricular arrhythmia during long control intervals, a worsening or improvement in the patient’s condition might be the basis for altered arrhythmia counts. However, because a substantial increase of spontaneous variability was already observed within the first weeks of follow-up, a change in the patient’s heart condition is not likely to be the sole reason. With regard to clinically detectable changes, no interde-
pends was observed between an increase of the arrhythmia and cardiac events. Moreover, changes of the electrolyte plasma concentrations subsequent to long-term medication with diuretics were carefully ruled out as a possible cause of arrhythmia increase. Thus, in the presence of a stable cardiac disease, gradual alterations of autonomic tone over long time periods may cause changes in arrhythmia incidence and complexity.

The results reported here are of major clinical interest, for they demonstrate that it is extremely difficult to evaluate long-term drug effects in the majority of patients. These findings should be taken into consideration in clinical practice as well as in the design of future drug trials dealing with long-term antiarrhythmic drug efficacy. The results of previous studies investigating long-term antiarrhythmic efficacy should be called into question as should studies on proarhythmic drug effects. Our data support the need for regular reassessments of baseline arrhythmia to prove long-term efficacy. If evaluation of drug efficacy is mandatory (e.g., in drug trials dealing with long-term efficacy), regular withdrawal tests should be performed after every 3 months of therapy. In patients with a history of severe hemodynamic complications of arrhythmia (such as syncope or cardiopulmonary resuscitation), withdrawal tests must be performed under close clinical observation. With respect to the effects of drugs with long half-lives (e.g., amiodarone), accurate evaluation of long-term efficacy may be completely impossible.

Acknowledgment
We dedicate this study to Professor Dr. Hans Blömer on the occasion of his 65th birthday.

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Key Words • ventricular premature contraction • patients • heart disease • electrocardiogram
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