A Tale of the Spontaneous Variability of Premature Ventricular Contractions

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As data from mobile coronary units and coronary care units in the early 1970s accumulated, we saw a strong association between the incidence of premature ventricular contractions (PVCs) and sudden coronary death. The profession devised and delivered treatment in a climate charged with the fear that PVCs would inevitably trigger ventricular fibrillation. The picture was a familiar one in CCUs: physicians and nurses regarded every PVC on CCU monitors as life-threatening and aggressively treated these arrhythmias, especially in their complex forms, effectively they suppressed PVCs. We developed, tested, and prescribed many new compounds despite our lack of knowledge about whether they actually prevented sudden death: witness the proliferation of antiarrhythmic drug prescriptions between 1970 and 1986. It soon became apparent, however, that few antiarrhythmic agents abolished every PVC. Complete suppression of all PVCs by these drugs was, in fact, an unattainable goal. This realization led to other questions. How many PVCs should we suppress before feeling confident that we had significantly reduced the threat of sudden death? Had we identified the drug’s true antiarrhythmic activity, or were we looking at natural spontaneous variation?

This is when and why statistical criteria to determine Holter-guided antiarrhythmic drug efficacy came into play. Investigators who performed drug trials proposed different mathematically calculated definitions to compute the degree of PVC suppression and to circumvent spontaneous variability. It was believed that these formulas, by determining how much reduction was required to exceed the boundaries of the spontaneous variability of PVCs, would measure the true effects of antiarrhythmic drugs. As clinicians who treated individual patients, we had to rely on one baseline Holter monitoring to help us decide which drug to prescribe. Many in the profession, the FDA, and drug companies embraced these criteria; if an antiarrhythmic agent suppressed 70–85% of simple PVCs and 90% of complex ones, the drug was considered effective. New drugs and research protocols were approved according to these guidelines.

These criteria shaped clinical practice. Patients who had ventricular arrhythmias were treated by performing one baseline Holter, a second with the patient on the drug, and a third days or weeks after the drug had reached steady state. Then the readings were compared. If, by the above criteria, it was found that the drug suppressed PVCs, the drug was continued on a long-term basis. However, this approach had a major flaw. We assumed that the baseline PVC frequency and its short-term variability remained constant. But Pratt et al showed that baseline ventricular arrhythmias had marked variability over longer periods of follow-up. This meant that the
degree of suppression of PVCs required to demonstrate drug efficacy, inefficacy, or proarrhythmic effects fluctuated accordingly. Therefore, it was determined that baseline PVCs should be periodically assessed in order to judge a drug's long-term value. Subsequently, Schmidt et al12 and Anastasiou-Nana et al13 questioned the merit of short-term evaluation in assessing the drugs' efficacy in long-term use. Both groups confirmed the finding by Pratt et al that there is significant temporal variability; they independently demonstrated that PVCs eb and flow as a function of time over longer periods. They concluded that statistical criteria to determine drug efficacy were valid only for the short-term period, a finding supported by Schmidt et al who determined that it was almost impossible to evaluate antiarrhythmic therapy by Holter monitoring after three months.

In this issue of Circulation, Anderson et al14 show that even patients who had been treated with effective antiarrhythmic drugs—as determined by initial short-term assessment—eventually exhibited variability during follow-up. In a significant number of patients, one follow-up Holter showed that the drug fell below the threshold of positive antiarrhythmic drug effect. There was a spontaneous rise in PVCs over longer periods even though patients were still taking antiarrhythmic agents considered effective. So, if assessing a drug's short-term antieptopic effects does not predict its long-term antieptopic effect, why are we using this technique to treat patients?

First, it is still not known why there is marked long-term variation of PVCs over longer periods of time, from weeks to months to years. Many endogenous and exogenous factors can affect these arrhythmias: changes in the arrhythmia substrate, the autonomic nervous system, ischemia. But even though we do not fully understand how these factors influence PVCs, the observation by Anderson et al14 can easily be understood. Based on the data from Table 2 in Anderson et al, if 70% PVC-suppression is used as the threshold for a drug's true antiarrhythmic effects, when one follow-up Holter is recorded, the chance that it would show less than 70% PVC-suppression is about 17%. However, if five follow-up Holters are recorded, that likelihood increases to around 53%; if 10 Holters are recorded, that likelihood jumps to around 75%. The more tests one does, the more likely it is that one of them will be unusual. This is a predictable statistical phenomenon, a mathematical function that has nothing to do with the pharmacological properties of the drug or other biological phenomena. It is natural variability.

How do we deal with spontaneous variability in clinical practice? Anderson et al14 cautioned against concluding on the basis of one follow-up Holter that the number of PVCs rose because the drug had lost its efficacy. If a follow-up Holter showed that a drug was ineffective, they advise recording of more Holters to either confirm drug inefficacy or rule out spontaneous variability. But in so doing, we would disregard the temporal variance of the baseline PVC frequency. We might consequently misjudge the drug’s antieptopic effects. To avoid this, should we be diligent about periodically admitting patients to the hospital and taking them off the drug to determine new baseline PVC frequency? We must first know whether PVC suppression has predictive value for long-term clinical outcome.

In fact, cardiologists and arrhythmia researchers disagree about whether Holter-guided antiarrhythmic therapy does indeed correlate with a favorable outcome.15 The debate intensified after electrophysiological drug testing proved to be a viable diagnostic alternative,16,17 and multicenter trials are investigating the relative merits of electrophysiological drug testing and Holter-guided drug testing.17 Everyone agrees, however, that the Holter simplifies too much.18 For example, the Holter cannot distinguish between different underlying electrophysiological mechanisms of an arrhythmia. It cannot tell us which PVCs are caused by reflected reentry, which by circus movement reentry, or which by triggered activity.18 Also, different classes of antiarrhythmic drugs may affect different categories of PVCs at varying degrees of potency both in PVC suppression and prevention of ventricular fibrillation, and the two may have no correlation. Hypothetically, one antiarrhythmic agent may profoundly suppress one type of PVC while actually inducing another, or not affecting yet another. Even if the drug suppresses more than 80% of PVCs from baseline, the remaining 20%, irresistible PVCs, may have been caused by mechanisms other than those suppressed by the drug. If this type of PVC either triggered ventricular fibrillation or was caused by the same mechanism that led to ventricular fibrillation, the drug would be mistakenly considered effective, yet the patient would remain at risk. Are all of those factors that correlate with sudden death—ischemic substrate, arrhythmogenic drug effects—captured in this one measure: increased or decreased PVCs on Holter?

Finally, we must reconcile the report of Grabois et al,19 that PVC suppression on Holter predicts long-term outcome, with the CAST studies, which showed the opposite. The suppression of PVCs on Holter by Class IC agents, particularly encainide and flecainide, not only did not correlate with a good outcome but appeared to increase the risk of sudden cardiac death in survivors of myocardial infarction.20 Grabois' study had no placebo-control group to compare with either the responders or the nonresponders. Conceivably, had the responders been randomized into a placebo-treated group and an effective drug group, the placebo group might have done as well as the group treated with drugs. And indeed, this was one of the most intriguing findings from the CAST study. Its unique study design randomized only those patients whose PVCs were initially suppressed by antiarrhythmic agents during the open label phase, based on their Holter criteria, to placebo and effective drug groups. Furthermore, the CAST placebo group had the lowest sudden death rate
among survivors of myocardial infarction of any study. This emphasizes that the value of Holter monitoring is not in identifying the effective drug based on PVC suppression, but in identifying low- and high-risk patients based on their responses to antiarrhythmic therapy.

For these reasons, we should ask whether the use of long-term Holter monitoring to guide long-term antiarrhythmic therapy has merit. After all, Davis et al.11 and Tibbits et al.12 demonstrated that long-term monitoring is less specific than short-term monitoring. But even if we are willing to sacrifice some specificity and sensitivity, it appears that the criteria for effectiveness leave out so much that they are of little use; for however expertly the data are manipulated, it is possible to see clearly the flaw in this approach, i.e., that it predicts little about our true objective of deterring sudden death.

Nature has made PVC frequency on Holter monitoring quite unpredictable. We have the wisdom to acknowledge that PVCs on Holter could portend a poor prognosis in patients who have ischemic heart disease. But we have learned that their disappearance after antiarrhythmic therapy does not necessarily translate into a better prognosis. Although these observations have taken away our faith in these criteria, they have given us a motive to seek a better way.

References
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