Spontaneous Variability in Ventricular Ectopic Activity During Chronic Antiarrhythmic Therapy

Jeffrey L. Anderson, MD, Maria I. Anastasiou-Nana, MD, Ronald L. Menlove, PhD, Fidela Ll. Moreno, MD, John N. Nanas, MD, and Allan H. Barker, MD

Previous determinations of variability in frequency of ventricular arrhythmias have been based on repeated recordings obtained in the absence of therapy. We evaluate variability during “effective” treatment with antiarrhythmic drugs. Variability in the percent suppression of premature ventricular complexes (PVCs) was determined in 55 patients with chronic arrhythmias who underwent multiple ambulatory electrocardiographic recordings during evaluation of chronic therapy with antiarrhythmic drugs initially determined to be effective, which was defined as 70% or more reduction in total PVC frequency or 90% or more reduction in repetitive forms. During chronic therapy, total PVCs were suppressed by 92%, averaged after a logarithmic transformation step, and repetitive beats were suppressed by 88%. Variability in suppression was substantial. The one-sided 95% confidence intervals required a fall in suppression of total PVCs to 40% or less to exceed limits of spontaneous variability and of repetitive PVCs to 66% or less. Suppression declined at least once during therapy to less than 60% for total PVCs in 24 of 55 patients (44%) and to less than 80% for repetitive PVCs in 13 of 33 patients (39%); nine patients (16%) showed increases in PVC frequency at least once to levels above pretreatment baseline. Seven subgroups were analyzed for their effects on variability and loss of suppression: age, gender, disease etiology, cardiac function, baseline PVC frequency, use of β-blockers, and class of antiarrhythmic drug. Differences in confidence bounds and loss of suppression were found to be determined in a complex way by subgroup differences in variability and in initial levels of PVC suppression. Variability was greater for patient subgroups with greater PVC frequency, β-blocker therapy, and non–coronary artery disease. However, clinical loss of suppression was more common only in more elderly patients and those with worse cardiac function. In summary, substantial variability in arrhythmia frequency occurs during effective antiarrhythmic therapy, and the 95% confidence limits of spontaneous variability are broad and determined in a complex way. Careful consideration should be given before concluding on the basis of a single Holter test that changes (increases) in arrhythmia frequency, especially in certain subgroups, are caused by treatment failure. (Circulation 1990;82:830–840)

Ambulatory electrocardiographic monitoring has been widely used to identify and quantify complex ventricular arrhythmias in an effort to explain potentially related symptoms and to identify patients at increased risk of sudden cardiac death, including those surviving myocardial infarction.1–7 The prevention of sudden arrhythmic death by pharmacological intervention is based on the assumption, as yet unproved, that the abnormal impulse that initiates premature ventricular complexes (PVCs) may also trigger ventricular tachycardia or ventricular fibrillation and that antiarrhythmic drug therapy may inactivate this trigger.8–11 Alternatively, the risk of arrhythmias may be a marker but not a direct causative factor for sudden death. Support for a reduction in cardiac mortality by agents with antiarrhythmic effects is available only for the...
β-blockers\textsuperscript{12–14}; for the more commonly used class I drugs, evidence is sparse and controversial.\textsuperscript{15–20} The hypothesis that antiarrhythmic therapy may reduce arrhythmic death is currently being tested in a large mortality trial, the Cardiac Arrhythmia Suppression Trial (CAST).\textsuperscript{21} (Preliminary results of CAST suggest that some agents that reduce PVCs may increase risk.\textsuperscript{22})

The determination of the effects of pharmacological interventions on PVCs for both symptom relief and potential risk reduction is complicated by spontaneous variations in their frequency, which can mimic drug effect.\textsuperscript{23–32} Several guidelines for distinguishing therapeutic antiarrhythmic drug effects from spontaneous variability have been proposed as a result of these and other observations.\textsuperscript{25–32} These guidelines are based on variability data derived from recordings obtained while off antiarrhythmic therapy, both at baseline (often including consecutive recordings) and at follow-up, separated by varying time intervals.

However, little data are available on the variability of PVCs during continuous treatment with a constant regimen of antiarrhythmic drug. Because suppression of ventricular arrhythmias is used as an end point for drug efficacy, in both clinical trials and practice, spontaneous variability during treatment may be a source of confusion and, as such, important to recognize. Substantial increases in arrhythmia rates during treatment might be alarming to the clinician and lead to a change in drug dosage or to drug withdrawal. However, if an observed increase in ventricular arrhythmias is the result of transient, spontaneous variability, a more conservative approach to changes in treatment may be warranted for non-life-threatening arrhythmias. If due to spontaneous variability, the increased rate of arrhythmias would, by definition, subside spontaneously with time.

The purpose of the present study was to assess arrhythmia variability during chronic therapy for ventricular arrhythmias, to describe how often and in what type of patients clinically noteworthy variability and loss in suppression occur, and to provide guidelines to discriminate true loss of drug efficacy from spontaneous arrhythmia variability.

**Methods**

**Patient Selection Criteria**

Consecutive patients enrolled in PVC therapy studies\textsuperscript{20,33–37} in our clinic were included in the analysis if they had shown arrhythmia suppression on initial drug titration, had undergone serial ambulatory electrocardiographic monitor evaluations over time during chronic therapy, had been constantly maintained on the initially effective drug and drug dose, and had been clinically stable [e.g., no intercurrent myocardial infarction (MI) or cardiac surgery]. Patients were referred for antiarrhythmic drug therapy in each of five separate studies. The specific reasons for antiarrhythmic therapy were to conduct a feasibility study for mortality risk reduction in one study (35 patients)\textsuperscript{20} and to monitor symptom reduction in the remaining four studies (20 patients).\textsuperscript{33,34,36,37} Inclusion and exclusion criteria were the same in the symptom reduction studies but different in the pilot risk reduction study. In the risk reduction study,\textsuperscript{20} patient inclusion required a recent (<3 months) MI and more than 10 PVCs/hr on a baseline 24-hour ambulatory electrocardiogram recording. The symptom reduction studies\textsuperscript{33,34,36,37} excluded patients with a recent (<3 months) MI or cardiac surgery but required more than 30 PVCs/hr on a baseline 48-hour ambulatory electrocardiogram recording. The baseline recordings in all studies required that patients be off antiarrhythmic drug therapy for at least four half-lives. In all studies, qualifying arrhythmias could occur as isolated beats, couplets, and runs of unsustained ventricular tachycardia for as many as 10 beats. Patients with a history of sustained, symptomatic, or hemodynamically significant ventricular tachycardia or out-of-hospital cardiac arrest were excluded. Only one antiarrhythmic drug per patient was allowed during the study. Compliance was confirmed at each clinic visit by pill count. Concurrent β-blocker therapy was allowed at a constant dose for indications other than PVC suppression, such as hypertension (\(n=1\)) or post-MI prophylaxis (\(n=14\)). The criteria used to define drug efficacy were 70% or more suppression of total PVC frequency and/or 90% or more suppression of repetitive PVCs compared with a 24-\textsuperscript{20} or 48-hour\textsuperscript{33,36} baseline recording.

**Patient Entry Characteristics**

Fifty-five patients were included in the analysis. There were 42 men and 13 women [average age, 62.5±10.4 years (mean±SD), range, 35–81 years]. Underlying heart disease included coronary artery disease in 45 patients and valvular heart disease and cardiomyopathy in one patient each. Eight patients had no detectable organic heart disease. Antiarrhythmic agents and daily dosages used included encainide (class IC action)\textsuperscript{20} in 11 (mean, 117 mg/day; range, 105–150 mg/day), flecainide (class IC)\textsuperscript{20} in 11 (mean, 240 mg/day; range, 200–400 mg/day), arecamine (class I action)\textsuperscript{35–37} in six (mean, 1,250 mg/day; range, 900–1,500 mg/day), moricizine (a phenothiazine with class I action)\textsuperscript{20} in eight (mean, 638 mg/day; range, 600–900 mg/day), imipramine (tricyclic with class I action)\textsuperscript{20} in five (mean, 165 mg/day; range, 150–225 mg/day), and sotalol (class II/III action)\textsuperscript{33,34} in 14 (mean, 394 mg/day; range, 240–800 mg/day). Left ventricular ejection fraction averaged 0.49±0.12 (range, 0.22±0.83). Patients were followed during therapy for a median of 10.6 months (mean, 9.0±11.7; range, 1–39 months) and were evaluated for arrhythmia suppression on an average of 5.1±2.0 Holter recordings (range, two to 12 recordings). The demographic data for individual patients are summarized in Table 1.
TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Cardiac diagnosis</th>
<th>Baseline EF</th>
<th>Baseline arrhythmias</th>
<th>Drug studied</th>
<th>Initial suppression (%)</th>
<th>Qualifying recording</th>
<th>Time of f/u</th>
<th>No. of Holters in f/u</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TPVCs/hr</td>
<td></td>
<td></td>
<td>TPVCs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RPVCs/hr</td>
<td></td>
<td></td>
<td>RPVCs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients without recent myocardial infarction

1. 53 M Idio 0.61 1901.5 284.1 Sot 85.1 100.0 39 11
2. 44 F Idio 0.72 47.9 4.1 Sot 91.6 100.0 26 6
3. 59 F CAD 0.52 425.5 0.24 Sot 99.9 100.0 24 5
4. 81 F Idio 0.62 190.8 6.1 Sot 96.8 100.0 24 7
5. 77 M CAD 0.30 963.0 280.9 Sot 70.8 86.3 29 5
6. 78 M Idio 0.43 215.1 30.7 Sot 85.7 100.0 32 12
7. 57 M Idio 0.57 980.9 16.1 Sot 97.6 99.9 11 5
8. 35 F Idio 0.67 254.5 0.04 Sot 100 100.0 1 3
9. 72 M CAD 0.63 78.5 11.6 Sot 85.2 94.7 1 5
10. 73 M CAD 0.36 380.7 2.7 Sot 99.1 100.0 1 3
11. 77 M CAD 0.59 267.9 42.2 Sot 84.2 94.1 2 3
12. 44 M CAD 0.33 259.9 15.6 Sot 94.0 95.0 2 3
13. 74 M CAD 0.46 424.1 171.1 Sot 59.7 99.3 1 3
14. 79 M VHD 0.62 397.4 109.4 Sot 72.5 97.8 3 4
15. 60 M CAD 0.35 1095.5 162.5 Rec 85.2 100.0 2 6
16. 51 M Idio 0.59 575.3 96.4 Rec 83.2 98.6 9 7
17. 65 F Idio 0.61 36.6 12.0 Rec 67.3 100.0 18 11
18. 68 M CAD 0.49 1204.6 654.6 Rec 45.7 98.1 4 7
19. 39 M CM 0.47 58.0 3.9 Rec 93.3 100.0 13 9
20. 55 F Idio 0.57 219.6 9.6 Rec 95.6 100.0 2 2

Patients with recent (<90 days) myocardial infarction before entry

21. 67 M CAD 0.45 138.2 5.2 Fle 96.2 ... 12 5
22. 49 M CAD 0.43 81.9 15.4 Mor* 81.2 100.0 9 4
23. 71 M CAD 0.41 193.2 18.4 Mor 90.5 ... 10 5
24. 47 M Idio 0.51 34.8 0.69 Enc 98.0 ... 12 5
25. 71 M CAD 0.48 14.1 0.04 Fle 99.7 ... 12 5
26. 66 M CAD 0.38 216.3 24.3 Enc* 88.8 ... 11 5
27. 61 M CAD 0.65 161.3 11.6 Enc 92.8 ... 12 5
28. 67 F Idio 0.53 33.5 0.00 Mor* 98.0 ... 11 5
29. 68 M CAD 0.50 36.2 4.1 Mor 88.6 86.6 12 5
30. 70 M CAD 0.49 33.2 0.37 Fle 98.9 ... 12 5
31. 62 M CAD 0.32 651.5 92.3 Mor 85.8 ... 12 5
32. 74 M CAD 0.39 131.9 19.2 Mor* 85.4 90.2 11 5
33. 41 M CAD 0.34 891.1 12.2 Enc 98.6 ... 6 3
34. 66 M CAD 0.39 21.7 4.7 Fle* 78.1 ... 21 5
35. 52 F CAD 0.46 78.7 16.0 Fle 79.7 ... 11 5
36. 69 M CAD 0.44 67.7 12.5 Enc 81.6 100.0 11 5
37. 53 M CAD 0.22 10.9 1.1 Imi 89.4 ... 3 2
38. 50 F CAD 0.51 32.4 1.1 Enc 96.5 ... 12 5
39. 62 M CAD 0.39 17.4 1.5 Fle 91.4 ... 11 5
40. 60 M CAD 0.40 18.0 0.33 Fle 98.2 ... 11 5
41. 61 M CAD 0.32 35.3 6.1 Imi* 82.8 ... 2 2
42. 59 F CAD 0.39 11.9 0.65 Enc* 94.6 100.0 2 2
43. 46 M CAD 0.70 46.4 0.13 Mor* 99.7 ... 12 5
44. 69 M CAD 0.83 17.2 0.00 Enc 100 100.0 11 5
45. 69 M CAD 0.43 85.5 3.2 Imi* 96.3 90.5 11 5
46. 62 M CAD 0.51 59.4 11.6 Imi 80.5 ... 12 5
47. 69 F CAD 0.62 39.1 0.00 Fle 100 100.0 12 5
48. 67 F CAD 0.36 85.4 13.7 Enc* 84.0 ... 12 5
49. 60 M CAD 0.70 314.6 0.45 Fle 99.9 ... 12 5
50. 61 M CAD 0.40 145.9 17.7 Enc* 87.9 ... 12 5
51. 46 M CAD 0.52 39.7 3.4 Fle* 91.5 83.5 10 5
52. 66 M CAD 0.58 94.0 1.5 Imi 98.4 ... 12 5
53. 70 M CAD 0.43 780.6 111.9 Mor* 85.7 ... 11 5
54. 61 M CAD 0.51 95.2 20.1 Enc* 78.9 ... 11 5
55. 68 M CAD 0.36 14.2 0.34 Fle 97.6 81.5 9 4

Mean ± SD 62.4 ± 10.9 ... 0.49 ± 0.12 266 ± 378 28 ± 65 ... 89 ± 11 97 ± 6 9.0 ± 11.7 5.1 ± 2.0
Median ... ... 94 2.73 ... ... 10.6 ... 1-34 2-12
Range ... ... 0.22-0.83 11-1902 0-316 ... ... ... ... ... 0-316

EF, ejection fraction; TPVCs/hr, total premature ventricular complexes per hour; RPVCs/hr, repetitive premature ventricular complexes per hour; f/u, follow-up; Idio, idiopathic; CAD, coronary artery disease; VHD, valvular heart disease; CM, cardiomyopathy; Sot, sotalol; Rec, recainam; Fle, flecainide; Mor, moricizine; Enc, encainide; Imi, imipramine.

*Concurrent β-blocker therapy.

†Total numbers of males and females in study are 42 and 13, respectively. Totals for cardiac diagnosis are as follows: CAD, 45; Idio, 8; VHD, 1; and CM, 1.
### Table 2. Variability in Total Premature Ventricular Complexes During Therapy for Patient Subgroups With Differing Baseline Characteristics

<table>
<thead>
<tr>
<th>Category (n)</th>
<th>Patients with &lt;70% suppression any time during follow-up</th>
<th>Fisher’s Test</th>
<th>Mean Suppression (%)</th>
<th>ANOVA Test</th>
<th>One-sided 95% Bound Suppression (%)</th>
<th>Variance</th>
<th>F ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>p</td>
<td></td>
<td></td>
<td>(%)</td>
<td>p</td>
</tr>
<tr>
<td>All cases (55)</td>
<td>29</td>
<td>53</td>
<td>92.0</td>
<td>39.5</td>
<td>0.285</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>By age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤64 (27)</td>
<td>10</td>
<td>37</td>
<td>94.0</td>
<td>51.3</td>
<td>0.306</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;64 (28)</td>
<td>19</td>
<td>68</td>
<td>89.5</td>
<td>24.7</td>
<td>0.268</td>
<td>0.483</td>
<td></td>
</tr>
<tr>
<td>By gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (42)</td>
<td>25</td>
<td>60</td>
<td>91.5</td>
<td>29.2</td>
<td>0.312</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (13)</td>
<td>4</td>
<td>31</td>
<td>93.5</td>
<td>64.9</td>
<td>0.199</td>
<td>0.057</td>
<td></td>
</tr>
<tr>
<td>By disease category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic/non-CAD (10)</td>
<td>4</td>
<td>40</td>
<td>94.5</td>
<td>42.5</td>
<td>0.382</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD (45)</td>
<td>24</td>
<td>53</td>
<td>91.4</td>
<td>42.7</td>
<td>0.248</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>Recent MI (&lt;90 days) (35)</td>
<td>17</td>
<td>49</td>
<td>91.5</td>
<td>45.3</td>
<td>0.239</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No recent MI (20)</td>
<td>12</td>
<td>60</td>
<td>93.0</td>
<td>34.5</td>
<td>0.345</td>
<td>0.051</td>
<td></td>
</tr>
<tr>
<td>By left ventricular function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF ≥0.50 (25)</td>
<td>9</td>
<td>38</td>
<td>94.2</td>
<td>60.2</td>
<td>0.258</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF &lt;0.50 (30)</td>
<td>20</td>
<td>65</td>
<td>89.6</td>
<td>13.6</td>
<td>0.310</td>
<td>0.338</td>
<td></td>
</tr>
<tr>
<td>By total PVC frequency at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVCs &lt;95/hr (27)</td>
<td>16</td>
<td>59</td>
<td>86.5</td>
<td>23.9</td>
<td>0.207</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVCs ≥95/hr (28)</td>
<td>13</td>
<td>46</td>
<td>95.4</td>
<td>54.6</td>
<td>0.363</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>By β-blocker therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (29)</td>
<td>17</td>
<td>59</td>
<td>93.7</td>
<td>39.5</td>
<td>0.355</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (26)</td>
<td>12</td>
<td>46</td>
<td>89.6</td>
<td>40.7</td>
<td>0.211</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>By drug class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class IC (Enc/flec) (22)</td>
<td>8</td>
<td>36</td>
<td>91.8</td>
<td>54.8</td>
<td>0.202</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other class I (19)</td>
<td>13</td>
<td>68</td>
<td>89.3</td>
<td>14.9</td>
<td>0.297</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Class III (sotalol) (14)</td>
<td>6</td>
<td>43</td>
<td>94.9</td>
<td>47.2</td>
<td>0.380</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; MI, myocardial infarction; EF, ejection fraction; PVCs, premature ventricular complexes; Enc/flec, encainide/flecainide.

### Ambulatory Electrocardiographic Recording

Ambulatory electrocardiographic recordings were performed on simultaneous two-channel tape recorders (Spacelabs, Redmond, Wash.) and initially scanned locally (Marquette Systems) and then analyzed or validated centrally by experienced, computer-based, operator-interactive systems (Cardio-Data Systems, Haddonfield, N.J.33,36 or Clinical Data, Boston30). The technician analyzing the data was unaware of patient characteristics, treatment given, or study plan. Ventricular arrhythmias were quantified as hourly frequencies of total PVCs and repetitive beats.

The rate of PVCs per hour was measured during 24-hour ambulatory electrocardiogram recordings for each patient at baseline (off drug), at qualifying (first on-drug recording), and at other times during treatment with the same antiarrhythmic drug. Treated recordings were numbered consecutively beginning with 1 for the qualifying test. The number of days since qualifying ranged from 2 to 1,136. Initial efficacy was determined by a single- (six patients)36 or double-blind (35 patients), baseline-controlled dose-ranging phase20 or by a double-blind, placebo-controlled, crossover phase (14 patients).33 All recordings were analyzed double-blind.

### Statistical Analysis and Classification of Response

The primary data used in the analysis were the hourly rates of total PVCs and (when present) repetitive PVCs on 24-hour Holter recordings during a 1-day baseline (off drug) and subsequent intermittent days of monitoring during drug therapy. Notice that on-drug recordings are referenced to the one or two consecutive off-drug baseline recordings in all analyses and that off-drug recordings have been shown to show substantial variability over time.32

The pattern of variability during follow-up was used to classify long-term response of individual patients into six mutually exclusive categories, as defined in the legend to Figure 2. Both total and repetitive PVCs were used in this classification, and the κ statistic was used to test the association between the classes for total and repetitive PVCs.
Table 3. Variability in Repetitive Premature Ventricular Complexes During Therapy for Patient Subgroups With Differing Baseline Characteristics

<table>
<thead>
<tr>
<th>Category (n)*</th>
<th>Patients with &lt;70% suppression during follow-up</th>
<th>Fisher's p</th>
<th>Mean suppression (%)</th>
<th>ANOVA p</th>
<th>Suppression (%)</th>
<th>One-sided 95% bound variance</th>
<th>F ratio p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases (33, 24)*</td>
<td>18 55</td>
<td>88.0</td>
<td>65.8</td>
<td>0.0766</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤64 (14, 9)</td>
<td>6 43</td>
<td>91.5</td>
<td>75.9</td>
<td>0.0745</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;64 (19, 15)</td>
<td>12 63</td>
<td>85.3</td>
<td>57.8</td>
<td>0.0776</td>
<td>0.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (25, 18)</td>
<td>9 36</td>
<td>89.3</td>
<td>67.5</td>
<td>0.0859</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (8, 6)</td>
<td>4 50</td>
<td>83.1</td>
<td>58.9</td>
<td>0.0551</td>
<td>0.289</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By disease category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic/non-CAD (10, 6)</td>
<td>5 50</td>
<td>89.7</td>
<td>70.5</td>
<td>0.0776</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD (23, 18)</td>
<td>11 48</td>
<td>87.4</td>
<td>64.1</td>
<td>0.0761</td>
<td>0.923</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent MI (&lt;90 days) (13, 8)</td>
<td>6 46</td>
<td>73.2</td>
<td>65.0</td>
<td>0.005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No recent MI (20, 16)</td>
<td>12 60</td>
<td>92.0</td>
<td>74.2</td>
<td>0.117</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By left ventricular function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF ≥0.50 (17, 13)</td>
<td>9 53</td>
<td>85.7</td>
<td>65.9</td>
<td>0.0526</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF &lt;0.50 (16, 11)</td>
<td>9 56</td>
<td>90.3</td>
<td>65.4</td>
<td>0.113</td>
<td>0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By total PVC frequency at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVCs &lt;95/hr (12, 7)</td>
<td>7 58</td>
<td>70.0</td>
<td>32.0</td>
<td>0.0464</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVCs ≥95/hr (21, 17)</td>
<td>11 52</td>
<td>91.3</td>
<td>72.4</td>
<td>0.0935</td>
<td>0.035</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By β-blocker therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (22, 16)</td>
<td>12 53</td>
<td>89.9</td>
<td>66.9</td>
<td>0.0983</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (11, 8)</td>
<td>6 55</td>
<td>83.0</td>
<td>61.6</td>
<td>0.0461</td>
<td>0.017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By drug class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class IC (enc/flec) (9, 5)</td>
<td>3 33</td>
<td>77.3</td>
<td>68.9</td>
<td>0.006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other class I (10, 8)</td>
<td>7 70</td>
<td>85.4</td>
<td>54.3</td>
<td>0.0902</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class III (sotalol) (14, 11)</td>
<td>8 57</td>
<td>91.8</td>
<td>73.6</td>
<td>0.0937</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*First number is denominator (n) for column 1; second number is n for columns 2–4 (excludes patients with low frequency events for statistical reasons; see “Methods”).

Fisher’s exact test was used to analyze contingency tables with small ns (Tables 2 and 3).

The logarithm of the ratio of treatment to baseline PVC rates (log ratio) was computed as follows:

\[ \log\left(\frac{\text{PVCs/hr(on drug)}+c}{\text{PVCs/hr(baseline)}+c}\right) \]

The constant, c=1, needs to be added to the PVC rates to allow for computation even when there are no PVCs (complete suppression). The distribution of the log ratio was normal (Figure 1A), especially at the upper end of the distribution, which makes computation of upper confidence limits appropriate. The same procedure was followed for repetitive beats in patients with more than one repetitive beat per hour at baseline (24 patients), although the resulting distribution was not normalized as well (Figure 1B). Thus, conclusions regarding repetitive beats should be qualified by the reduced number of patients observed and by nonnormality in the log ratio of repetitive PVCs per hour.

The analysis of variance procedures of Pratt et al.\textsuperscript{28} were applied to the log ratios. These procedures provide estimates of central tendency and variability within individual patients that can be pooled over a group of patients. The pooled mean of the individual log ratios (m) is converted to percent change (m%) by

\[ m\% = 100\left(10^m - 1\right) \]

and m and the SDs (s) based on the pooled variance of the individual log ratios were used to define the upper bound (ub) of the one-tailed 95% confidence interval of the log ratio according to

\[ ub = m + 1.65s \]

The upper bound of the log ratio is converted to the upper bound of percent change (ub%) by

\[ ub\% = 100\left(10^{ub} - 1\right) \]

The m% and ub% were used descriptively, whereas m and s\textsuperscript{2} were used to identify differences among subgroups of patients. Specifically, the analysis of variance was used to test for differences in the
average log ratio among subgroups, whereas the \( F \) test for the ratio of variances was used to test for differences in the variability of log ratios between pairs of subgroups. The \( F_{\text{max}} \) test was used to test for equality of variances in the case (antiarrhythmic drug class) that compared three subgroups of patients. Each of the subgroups of patients was defined in terms of baseline characteristics, including age (greater versus less than median), sex, cardiac disease (coronary artery disease, yes/no; recent MI, yes/no), left ventricular function (ejection fraction <0.5, yes/no), arrhythmia frequency (less than the median of 95 PVC/hr, yes/no), treatment with beta-blockers (yes/no), and treatment with class IC agents (encainide/flecainide), other class I, and class II (sotalol) agents. The proportion of patients in each subgroup in which suppression fell below the “efficacy” criteria at least once was also noted and compared (Fisher’s exact test). A stepdown log linear model was used to show the degree of redundancy among the subgroupings.

The primary data set analyzed and presented consisted of all treatment recordings (“qualifying” drug treatment Holter test plus all follow-up recordings). Smaller data sets, consisting of only follow-up recordings and only patients suppressed more than 80% for total PVCs, were each analyzed, with similar results, but not fully presented.

Results

Arrhythmia Status on Pretreatment and Qualifying Treatment Recordings

Table 1 shows individual and arithmetic mean values for hourly total PVC and repetitive beat rates as well as the percent suppression in total PVCs (arithmetic mean, 89±11%; log mean, 92%) and repetitive PVCs [97±6%; log mean, 90% after excluding patients (n=31) with low frequency (less than one per hour) events] during the qualifying drug treatment recording.

Average Suppression and Variability in Suppression During Chronic Treatment

Substantial variability in response over successive recordings was noted, both as assessed by changes in categories defined by PVC suppression (Figure 2 and Tables 2 and 3) and by quantitative analyses of levels of and variability in suppression (Tables 2 and 3). In this study of treated arrhythmias, a statistically important relation was not found between time from baseline to chronic testing and variability in arrhythmia suppression (Figure 3).

Averaged over all patients, the log ratio during therapy was \(-1.097\), with variance of 0.285 for total
PVCs (Table 2), and -0.921, with variance of 0.766 for repetitive PVCs (Table 3). When the average log ratios are transformed to percent suppression, values of 92% for total and 88% for repetitive PVCs are obtained.

Large deviations from the suppression noted on the qualifying recording for total and repetitive PVCs were found to be necessary to confidently predict loss of suppression on a single test. The one-sided 95% confidence bound for spontaneous variability was exceeded by a fall in suppression to 40% or less for total PVC frequency and 66% or less for repetitive PVCs compared with baseline.

Analysis of overall response was also performed for patients (n=48) meeting the more stringent entry criterion of 80% or more suppression of total PVCs, with similar results: average suppression was 93%, variance in the log ratio was 0.308, and 95% confidence bound was 44%.

As defined by changes in categories of PVC suppression (Figure 2 and Table 2), 29 of the 55 patients (53%) showed a decline in suppression of total PVCs to less than 70% at least once during chronic therapy (categories II–VI). Five showed 70% or more suppression on all but one test and 60% or more suppression on that test (category II). Thus, suppression declined to less than 60% at least once in 44% of patients (24 of 55) (categories III–VI); in the other 56%, PVCs were virtually always effectively suppressed (categories I and II). Of the remainder, 14 (25%) had some recordings that showed 70% or more suppression of total PVCs, but these were interspersed with others showing between 0% and 60% suppression (categories III and IV). Nine (16%)

showed increases in PVC frequency at least once to levels above pretreatment (category V).

Change in category of PVC suppression was also determined for an analysis restricted to patients entering with 80% or more initial suppression in total PVCs: 22 of the 48 patients (46%) qualifying by this criterion showed tests with less than 70% suppression during follow-up and 18 (38%) showed tests with less than 60% suppression at least once.

The change in category defined by PVC suppression pattern for repetitive PVCs is also shown in Figure 2 and Table 3. In 18 of 33 patients (55%), suppression declined to less than 90% at least once during chronic therapy (categories II–VI). Five patients showed 90% or more suppression on all but one test and 80% or more suppression on that test (category II). Thus, suppression declined to less than 80% at least once in 33% of patients (13 of 33) (categories III–VI). Of the 13 others, nine (27%) showed 90% or more suppression of repetitive PVCs during many follow-up recordings. However, these recordings were interspersed with others showing between 0% and 80% suppression (categories III and IV). Three patients (9%) showed increases to levels above the pretreatment baseline at least once during follow-up (category V).

The association between parallel categories of PVC suppression for total and repetitive PVCs was evaluated with χ in the 33 patients with paired data and found to be significant (χ=0.413, p<0.01).

Treatment Response and Variability by Subgroup Characteristics

Response was determined for several patient subgroups based on specific baseline characteristics (Tables 2 and 3).

Age. Variability (variance) in suppression did not differ between younger (≤64 years) and older (>64 years) patients for total or repetitive PVCs. However, older patients tended to show lower average total PVC suppression. The 95% confidence limits, which are strongly influenced by differences in average suppression, also differed significantly, with older patients requiring a greater fall in suppression to exceed the one-sided bound of spontaneous variability. In parallel with this, a larger percentage of older patients showed loss of suppression during follow-up (p=0.03). However, differences for repetitive beats did not approach significance.

Sex. Men tended to show greater variability in suppression of total PVCs than women (p<0.06). Men had similar (to slightly lower) average suppression, but a greater fall in suppression was required for men to exceed the 95% confidence bound. In parallel with this greater variability, men tended to more frequently show a pattern of intermittent loss of suppression during follow-up (p=0.11). Gender differences for repetitive beats were not significant.

Disease etiology. Variance in suppression of total PVCs was significantly less for groups both with coronary artery disease (p<0.03) and with recent MI
limits were similar was also nonsignificant (p=0.05). However, patients with coronary artery disease also tended to show slightly lower average suppression. The net result was that the 95% confidence limits were similar for groups with and without coronary artery disease, and a similar proportion in each group lost suppression during serial observations.

For repetitive beats, less variance was noted for recent MI (but not for coronary artery disease in general), but average suppression of repetitive beats was also less. The net result was that the confidence limits and percent of patients losing suppression were similar in the groups with and without recent MI.

**Left ventricular function.** Poor left ventricular function (ejection fraction, <0.5) was associated with a trend toward greater variability in suppression that was nonsignificant for total PVCs (p=0.34) but significant for repetitive PVCs (p=0.012). Lower ejection fraction was also associated with a trend toward lower average percent suppression for total (but not repetitive) PVCs (p=0.10). The net result for total PVCs was that in patients with poor left ventricular function, substantially greater falls in suppression were required to exceed the 95% one-sided confidence bound for spontaneous variability of suppression. In parallel with this, almost twice as many patients with low ejection fraction showed “loss of suppression” sometime during follow-up (p≤0.03). In the smaller group of patients with repetitive PVCs, differences in confidence bounds and frequency of losing suppression did not emerge.

**Baseline arrhythmia frequency.** Variability in percent suppression was significantly greater in patients with more than the median arrhythmia frequency, for both total PVCs (p<0.003) and repetitive beats (p<0.04). However, average suppression was also significantly greater in the higher frequency subgroup for both total (p<0.002) and repetitive beats (p<0.02). The 95% confidence bounds, which are more strongly influenced by differences in suppression, were more removed (lower) from the target suppression of total and repetitive PVCs for those with lower frequency (less than the median) PVCs. (The chance of losing suppression was also slightly but not significantly greater in those with lower frequency PVCs at baseline.)

**β-Blocker therapy.** Variability in suppression was significantly greater for total (p=0.007) as well as repetitive PVCs (p<0.02) in patients given β-blocker therapy. However, mean suppression of both total and repetitive PVCs also tended to be greater in β-blocked patients. The net result was similar 95% confidence limits for spontaneous variability in each group and similar frequencies of patients losing suppression.

**Antiarrhythmic drug class.** Drugs were subgrouped into class IC (encainide and flecainide), other class I drugs (imipramine, moricizine, and recainain), and class II/III (sotalol) and compared (Tables 2 and 3). Significant differences in variance were observed among these drug groups (p<0.05). In this comparison, variances in PVC suppression were least during encainide/flecainide therapy. Encainide/flecainide also tended to be associated with less individual loss of suppression, but differences were not significant.

**Bivariate Relations Among Baseline Factors Associated With Variability**

The interrelatedness of several of the factors individually associated with PVC variance was explored by a step-down log linear analysis. Significant (p<0.05) two-way interactions included A) a diagnosis of recent MI with 1) a diagnosis of coronary artery disease, 2) a lower baseline frequency of PVCs, 3) use of class IC agents, and 4) use of β-blockers and B) gender with 1) a diagnosis of coronary artery disease and 2) frequency of PVCs at baseline.

**Discussion**

Our study evaluated variability in suppression of chronic ventricular arrhythmias both quantitatively and qualitatively during constant, initially “effective” antiarrhythmic drug therapy and found this variability to be complex and substantial. Variability was defined quantitatively by the variance in suppression, and the ratio of variances was used to test the significance of differences in variability between subgroups. The one-sided 95% confidence bound of suppression for spontaneous variability was also determined for the entire group and for subgroups and was found to be strongly influenced by differences in average levels of arrhythmia suppression as well as by variance. The frequency of loss of suppression during repeated testing, defined when clinically determined bounds (i.e., 70%, 90% suppression) were exceeded, generally varied in parallel with variations in the 95% confidence bounds.

Variability might also be influenced by changes in substrate (e.g., intervening MI), changes in compliance, or changes in drug metabolism. None of these within-patient independent variables was evaluated in the present study, except by the inclusion criteria, which specified that patients be clinically stable on entry. Differences in numbers of monitored tests and time intervals of observation are other factors that might influence variability results. However, the influence of these factors was minimized in our study by design. Despite this, loss of arrhythmia suppression occurred at least once during the median follow-up of 11 months in 40–50% of patients.

Greater variability (variance) in suppression was found to be associated with several baseline characteristics, including 1) greater than the median initial PVC frequency, 2) β-blocker therapy, 3) absence of coronary artery disease or recent MI, 4) male sex (trend), and for repetitive PVCs, 5) low ejection fraction. Other factors were associated with trends (p<0.1) toward lower average levels of arrhythmia suppression and included 1) older age, 2) lower ejection fraction, 3) lower frequency of pretreatment PVCs, and for repetitive PVCs, 4) recent MI. The net result in combining these effects was that “loss of
suppression” was found more often in older patients and those with worse cardiac function. These two groups and those with lower initial PVC frequency also had broader (lower) one-sided 95% confidence bounds for spontaneous variability in the percent of PVC suppression.

Goals for Arrhythmia Suppression

The optimal suppression goal for symptomatic or prognostically important, chronic ventricular arrhythmias is unknown. Possible goals might include 1) complete, continuous suppression of all ventricular ectopic activity (usually impossible or impractical), 2) suppression to less than an absolute PVC rate, or 3) suppression to more than a target percentage level. Most often, a percentage suppression (usually 70–80% for total PVCs and 80–100% for repetitive ectopy) has been used as the criterion for therapy to be “successful.” When applied to the long-term evaluation of therapy, such criteria assume that rates of spontaneous arrhythmic activity are constant over time. However, recent observations,36–31 including our own,32 indicate substantial variation over time in these spontaneous rates.

Treatment Problems Raised by Arrhythmia Variability

Our observations also point to variable arrhythmia behavior during therapy. Although closely paired studies would be needed to prove that this variability in suppression primarily reflects variation in underlying spontaneous arrhythmic activity and not variations in drug effect or pharmacology, the constant dosing regimens used and the clinically stable course of patients in our study suggest substantial “primary” arrhythmia variability during treatment.

Figure 4 shows a hypothetical rate of PVCs during baseline and a reduced but parallel rate of PVCs during treatment with an “effective” antiarrhythmic agent. Note that cycles of increasing (and decreasing) PVC frequency also occur during treatment, even though antiarrhythmic therapy maintains a constant percentage reduction in PVCs, because the spontaneous rate is changing cyclically over time. Not only does this suggest that chronic efficacy of therapy, based on a percentage arrhythmia reduction, cannot be decided by an absolute criterion, but it also illustrates the problem of using a temporally distant baseline for determining current and ongoing PVC suppression, as suggested by the examples shown in the figure and described in the figure legend.

Study Limitations

The present study shares the limitations of all retrospective studies. The number of monitored tests and time interval over which evaluations were made varied, although about 85% of patients clustered close to the median of five observations during 11 months. Greater weight should be placed on conclusions regarding total instead of repetitive PVCs because of the smaller number of patients with repetitive PVCs at baseline and because of departures from normality in the distribution of the log ratios of repetitive PVCs. Our findings for subgroups should also be tempered by the relatively limited number of patients in many of these groups. Also, subgroup hypotheses were not formulated prospectively, and analyses were derived from groups of variable size. However, several of the factors we found to affect variability during treatment have also been found to be important by others in other groups of untreated (and treated) patients.32,39 Patients with a history of sustained ventricular tachycardia or cardiac arrest were excluded. Treatment variability may possibly differ in these groups with more malignant arrhythmias. (However, electrophysiological testing is increasingly being viewed as a better evaluation method than Holter monitoring in these latter patients.)40–42 Drugs and drug subclasses were not all represented or were represented in relatively small numbers. However, our observations suggest that some variability will be seen with all antiarrhythmic therapy, although the degree of variability may be less with some drugs (i.e., class IC agents). Finally, the individual factors associated with greater PVC variability were often interrelated, in some cases by well-known clinical associations and in other cases by study design features. Thus, the independent contributions of these factors could not be definitively determined, although hypotheses may be generated for future studies.

Clinical Implications

What are the clinical implications of variations in arrhythmia rates during treatment? Because present
criteria for assessing treatment success are more arbitrary than scientifically based, only tentative answers can be given. Our observations suggest that the clinician should strongly consider intrinsic variation in arrhythmia frequency as well as true loss of pharmacological effect to explain variations in rates of arrhythmia and arrhythmia suppression during therapy. Rather than making a hurried decision to change drug or drug dose based on increased arrhythmia frequency in patients with symptomatic but non–life-threatening arrhythmias in a single recording, a physician may wish to first obtain a second (confirmatory) monitor at an acceptable follow-up interval (e.g., 1 month later). If arrhythmia suppression returns to the target range, therapy can be continued without change. If persistent loss of suppression is noted, drug dose may be adjusted or drug may be discontinued and Holter monitoring repeated after a four to five half-life drug washout period to reestablish a baseline rate and consider alternative therapy. Of course, some findings may be unacceptable even as single occurrences, such as sustained tachyarrhythmia or ominous runs of unsustained ventricular tachycardia [in the Cardiac Arrhythmia Pilot Study (CAPS)],\textsuperscript{11,20} 10 or more beats at a rate of more than 100 beats/min; in CAST,\textsuperscript{21,22} 15 or more beats at a rate of 120 beats/min].

Therapeutic implications of arrhythmia variability during treatment must also be put in perspective with recent findings in CAST,\textsuperscript{22} in which encainide and flecainide not only failed to reduce the risk of sudden death but also increased mortality. One possible explanation for a lack of efficacy of antiarrhythmic therapy to reduce sudden death may be that transient or periodic apparent loss of efficacy, as evidenced by transient increases in ectopy, might be a mechanism whereby fatal ventricular tachycardia or fibrillation could occur during apparently “effective” therapy with an antiarrhythmic drug. The implication in this case would be a more aggressive approach to monitoring arrhythmia suppression when antiarrhythmic therapy is given for risk reduction. However, suppression associated with encainide and flecainide was greater and variability was less than with the other antiarrhythmic agents; moreover, the problem in CAST was an increase in risk, not simply failure of risk reduction. Thus, other explanations should be considered for the CAST results. Certain antiarrhythmic drugs may possess excessive proarrhythmic potential (i.e., may predispose to sustained ventricular tachycardia or fibrillation, perhaps especially in the setting of ischemic disease), distinct from their antiectopic effects, that unfavorably tips the risk-to-benefit ratio for treatment in some patient groups. Another possibility is that asymptomatic PVCs in postinfarction patients may be “markers” of excessive risk but not causally related to the initiation of fatal ventricular arrhythmias. In this case, antiarrhythmic therapy may be generally ineffective for sudden death reduction. Treatment would then be useful only for symptomatic arrhythmia control and not for prophylactic risk reduction. Findings in the ongoing (moricezine) limb of the CAST study will be instructive in answering some of these questions, as will the results of other ongoing therapeutic trials for risk reduction in patients with prognostically important ventricular arrhythmias.

Conclusion

Our findings suggest that variability in percent suppression of ventricular arrhythmia is often observed in patients undergoing chronic treatment with antiarrhythmic drugs. This variability may be frequently seen as an increase in arrhythmia rates above the level targeted for drug efficacy (and occasionally, even to above baseline rates). However, these variations in rate often later return toward levels considered to be efficacious. Thus, careful consideration should be given before an adjustment in dose or change in antiarrhythmic agent is undertaken, particularly when rates during treatment are compared with a single initial baseline recording distant in time. Consistent trends on multiple recordings may be required to establish a true loss of drug efficacy or a progression of arrhythmie disease mandating a change in treatment approach.

Acknowledgments

We thank Keith D. Green and Shari Bailey for typing the manuscript. We thank Kaye Summers, RN, and Ellen Doran for assistance with nursing and data collection. We acknowledge the stimulation and support of the CAPS investigators and coordinating center.

References


**KEY WORDS** • ventricular arrhythmias • antiarrhythmics
Spontaneous variability in ventricular ectopic activity during chronic antiarrhythmic therapy.
J L Anderson, M I Anastasiou-Nana, R L Menlove, F L Moreno, J N Nanas and A H Barker

Circulation. 1990;82:830-840
doi: 10.1161/01.CIR.82.3.830
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 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/82/3/830