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## Utility of Ambulatory Electrocardiographic Monitoring for Predicting Recurrence of Sustained Ventricular Tachyarrhythmias in Patients Receiving Amiodarone

NEIL M. SOKOLOFF, MD, SCOTT R. SPIELMAN, MD, FACC,  
ALLAN M. GREENSPAN, MD, FACC, ALAN P. RAE, MD, PATRICIA M. BRADY, RN,  
HAROLD R. KAY, MD, LEONARD N. HOROWITZ, MD, FACC

*Philadelphia, Pennsylvania*

The prognostic implications of changes in ventricular ectopic activity on serial 24 hour ambulatory electrocardiographic (Holter) recordings were prospectively evaluated in 107 patients with a history of sustained ventricular tachyarrhythmias treated with amiodarone for at least 30 days. Twenty-seven patients (25%) had insufficient ventricular ectopic activity (<10 ventricular premature complexes/h and no repetitive forms) on baseline Holter recordings for serial statistical analysis. In 53 (66%) of the remaining 80 patients, serial 24 hour Holter monitor recordings showed efficacy of treatment, defined as a 75% decrease in ventricular premature complexes, a 95% decrease in ventricular couplets and absence of ventricular tachycardia. During a mean follow-up period of  $14.2 \pm 9.9$  months, 34 (32%) of the 107 patients had recurrence of a sustained ventricular tachyarrhythmia. Holter recording correctly predicted nine recurrences and correctly identified 37 patients who did not experience a recurrence. Holter efficacy failed to predict recurrence of a sustained ventricular tachyarrhythmia in 16 patients, and 18 patients remained free

of recurrence despite failure to achieve Holter efficacy. The positive predictive value of Holter monitoring efficacy was 33% and the negative predictive value was 70%; however, these differences were not statistically significant by chi-square analysis. Similar results were obtained using Holter recordings performed relatively early in therapy (6 weeks and 4 months).

Of the 27 patients without significant ventricular ectopic activity on the baseline Holter recording, 9 had an arrhythmia recurrence despite continued infrequent ventricular premature complexes and no repetitive forms on subsequent recordings. The recurrence rate in this group (33%) was similar to the overall recurrence rate.

Therefore, among patients taking amiodarone for sustained ventricular tachyarrhythmias: 1) 25% will have insufficient ventricular ectopic activity on 24 hour Holter recordings for serial statistical analysis; and 2) in the remaining 75%, data obtained from serial Holter recordings are not predictive of arrhythmia recurrence.

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Amiodarone, a benzofuran derivative with potent antiarrhythmic properties, has been reported in recent studies (1-7) to be effective in controlling recurrent sustained ventricular tachyarrhythmias in approximately 50 to 70% of patients in whom more conventional medical therapy was unsuccessful. It has been suggested (8-11) that in patients treated with amiodarone, in contrast to other antiarrhythmic

agents, continued inducibility of arrhythmia during serial electrophysiologic testing is not predictive of arrhythmia recurrence. Therefore, it has been proposed (6-9) that amiodarone therapy may be empiric or directed by data obtained from ambulatory electrocardiographic (Holter) monitoring. The purpose of the present study was to prospectively determine the value of suppression of spontaneous ventricular ectopic activity on serial Holter monitor recordings in predicting the recurrence of sustained ventricular tachycardia or fibrillation in patients treated with amiodarone.

From the Division of Clinical Cardiac Electrophysiology and the Computer Center of the Likoff Cardiovascular Institute, Hahnemann University Hospital, School of Medicine, Philadelphia, Pennsylvania.

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Address for reprints: Neil M. Sokoloff, MD, Clinical Cardiac Electrophysiology Laboratory, Likoff Cardiovascular Institute, Hahnemann University and Hospital, Room 6617 NCB, Broad and Vine Streets, Philadelphia, Pennsylvania 19102.

### Methods

**Patients.** The study group comprised 107 consecutive patients who had been taking amiodarone for at least 30

days and who had a history of either documented sustained ventricular tachycardia (n = 71) or cardiac arrest (n = 36) not associated with an acute myocardial infarction, metabolic abnormalities or proarrhythmic drug effects. The clinical characteristics of the patients are summarized in Table 1. After written informed consent was obtained (protocol approved by the Hahnemann Institutional Review Board on October 1, 1981), all antiarrhythmic medication was discontinued for at least five half-lives and a baseline 24 hour two channel Holter monitor recording was performed in all patients. Each patient then underwent a baseline electrophysiologic study using a previously described protocol (5). Amiodarone therapy was initiated after serial electrophysiologic testing failed to identify a single agent or combination regimen that was effective in preventing arrhythmia induction. Before amiodarone therapy a mean of 2.6 (range 0 to 7) drug studies were performed.

**Amiodarone administration.** Amiodarone was initially administered either orally (n = 81) or intravenously (n = 26). In the oral loading regimen patients received 1,000 mg/day for the first 7 days and 800 mg/day for the next 7 days and were then discharged receiving 600 mg/day. The intravenous loading regimen consisted of 10 mg/kg body weight per day intravenously plus 600 mg orally for the first 3 days and 800 mg orally for the next 6 days; the patients were then discharged receiving 600 mg/day orally. In all cases electrophysiologic testing was performed after the loading period, and if a ventricular tachyarrhythmia that the patient could not tolerate remained inducible, procainamide or quinidine was added to the regimen and the testing was repeated. If the combination regimen prevented arrhythmia induction or if a hemodynamically tolerable tachyarrhythmia was inducible the patient was discharged receiving the combination regimen.

**Protocol end points.** The protocol end points were: 1) Sudden cardiac death: unexpected, witnessed death occurring within 1 hour of the onset of symptoms. If the death was unwitnessed, the patient must have been seen within the previous 12 hours in his usual state of health. Patients resuscitated from a sustained ventricular tachyarrhythmia were defined as having had sudden cardiac death. Sudden

cardiac death was considered an arrhythmia occurrence. 2) Documented sustained ventricular tachycardia: electrocardiographically documented ventricular tachycardia lasting more than 30 seconds. 3) Nonsudden death from cardiovascular causes. 4) Drug discontinuation due to toxicity. 5) March 1, 1985.

**Follow-up.** All patients were discharged taking amiodarone, 600 mg/day, either alone or in combination with other agents. The patients were then seen in the arrhythmia clinic 1 month after discharge (6 weeks after initiation of amiodarone therapy), then at 4 month intervals during the first year and subsequently at 6 month intervals. The amiodarone dose was decreased to 400 mg/day in those patients remaining in the evaluation at the 4 month follow-up clinic visit (13 patients had a sustained ventricular tachyarrhythmia recurrence between the 1 and 4 month evaluations). In 10 patients the dose was subsequently decreased because of toxicity, but administration of the drug was not discontinued. The clinical management of the patients was not altered by the results of Holter monitoring and the protocol remained unaltered throughout the study.

*All patients had 24 hour Holter monitor recordings obtained at baseline and at each clinic visit.* In all cases a Holter recording was obtained within 2 months before the time when a protocol end point was reached. This final recording was used for the overall statistical analysis. In addition, data from Holter recordings obtained at the 1 and 4 month clinic visits were analyzed separately to assess the utility of recordings obtained relatively early in the course of therapy. A Holter monitor recording was defined as being predictive of successful therapy if it showed a 75% decrease in ventricular premature complexes and a 95% decrease in ventricular couplets compared with the baseline recording and no episodes of ventricular tachycardia (three or more consecutive ventricular complexes). If these criteria were not met, the Holter recording was judged predictive of failure of therapy. A baseline Holter recording was considered to have insufficient ventricular ectopic activity for statistical comparison if there were fewer than 10 ventricular premature complexes/h and no repetitive forms were present.

**Statistical analysis.** Statistical evaluation was performed using chi-square analysis. A probability (p) value of 0.05 or less was considered significant. Data are expressed as the mean ± SD or the mean and the range.

## Results

**Clinical course.** All 107 patients had a sustained ventricular tachyarrhythmia inducible at the baseline electrophysiologic study. In 98 patients sustained monomorphic ventricular tachycardia was inducible, and ventricular fibrillation was inducible in the remaining 9. Thirteen patients were discharged taking a second drug in addition to amiodarone (procainamide in nine and quinidine in four). Thirty-four (32%) of the 107 patients had an arrhythmia recurrence

**Table 1.** Characteristics of Study Group (n = 107)

Age (yr)	
Mean ± SD	60.4 ± 8.8
Male/female ratio	84/23
Left ventricular ejection fraction (%)	
Mean (range)	26.3 (8 to 61)
Underlying disease	
Coronary artery disease	83
Cardiomyopathy	22
Valvular heart disease	1
No organic heart disease	1
Follow-up (mo)	
Mean (range)	14.2 (2 to 37)

during a mean follow-up period of  $14.2 \pm 9.9$  months. The mean time to recurrence was 9.6 months (range 2 to 37). Of the 34 recurrences, 11 (32%) were fatal. Nine patients had nonsudden cardiac death and in nine patients amiodarone was discontinued because of toxicity. The remaining 55 patients continued taking amiodarone until the protocol end point. The proportion of patients on a combination regimen who had an arrhythmia recurrence (31%) was similar to that of the overall study group.

Eighty patients (75%) had sufficient ventricular ectopic activity to be analyzed by serial 24 hour Holter recordings. On the basis of final Holter monitor data, 56 patients (66%) were predicted not to have a recurrence and 27 patients (34%) were predicted to have a recurrence.

**Holter monitoring results.** Correlation of Holter monitor prediction of success or failure of amiodarone therapy with clinical outcome is shown in Table 2. Holter analysis correctly predicted successful therapy in 37 patients and correctly predicted failure of therapy in 9. It incorrectly predicted successful therapy in 16 patients and incorrectly predicted failure of therapy in 18. The positive predictive value (that is, predicting recurrence) was 33% and the negative predictive value (that is, predicting no recurrence) was 70%. However, these differences are not statistically significant by chi-square analysis.

*Analysis of data from the 1 and 4 month Holter recordings produced similar results.* The 1 month recordings correctly predicted arrhythmia recurrence in 11 of the 25 patients with a recurrence (in 9 of the total group of 34 patients with a recurrence, there was insufficient baseline ventricular ectopic activity for serial evaluation); it also correctly predicted nonrecurrence in 33 of the 55 patients who did not have a recurrence. The positive and negative predictive values were 33 and 70%, respectively ( $p = \text{NS}$ ). The 4 month recordings correctly identified a subsequent recurrence in 6 of the 17 patients with a later recurrence of arrhythmia (5 of the patients with a recurrence between the 1 and 4 month evaluations had insufficient baseline ventricular ectopic activity for serial evaluation), and correctly predicted absence of recurrence in 38 of the 49 patients who had no recurrence.

**Table 2.** Correlation of Clinical Outcome With Overall Result Predicted by Holter Monitoring

	Recurrence of Arrhythmia	
	Yes	No
<b>A. Patients Receiving Amiodarone Therapy Alone</b>		
Holter monitoring predicted success of therapy	16	37
Holter monitoring predicted failure of therapy	9	18
<b>B. Patients Receiving Combination Therapy</b>		
Holter monitoring predicted success of therapy	2	3
Holter monitoring predicted failure of therapy	2	4

$p = \text{NS}$ .

The positive and negative predictive values were 30 and 78%, respectively ( $p = \text{NS}$ ).

*A total of 27 patients (25%) had insufficient ventricular ectopic activity on the baseline Holter recording for serial analysis.* The arrhythmia recurrence rate in this group was 33%, similar to that of the overall study group and of the 80 patients with frequent baseline ventricular ectopic activity. Of these 27 patients, 2 had nonsustained ventricular tachycardia (<30 seconds) on subsequent Holter recordings; neither of these patients has had a sustained arrhythmia recurrence. The remaining 25 patients continued to manifest infrequent ventricular ectopic activity (<10 ventricular premature complexes/h and no repetitive forms) on serial Holter recordings despite a sustained ventricular tachyarrhythmia recurrence in 9.

## Discussion

We have demonstrated that in patients taking amiodarone for otherwise medically refractory sustained ventricular tachyarrhythmias, ventricular ectopic activity on serial 24 hour Holter monitor recordings cannot identify patients who will experience an arrhythmia recurrence. Furthermore, 25% of patients do not have sufficient ventricular ectopic activity on a baseline Holter monitor recording to permit follow-up analysis.

**Value of Holter monitoring.** Other groups have also investigated the utility of ambulatory electrocardiographic monitoring to assess efficacy of amiodarone therapy. In a similar patient population, Marchlinski et al. (6) obtained a Holter recording a mean of 11 days after initiation of amiodarone therapy. They found that a recording that demonstrated, relative to baseline, an 85% decrease in ventricular premature complex frequency and abolition of repetitive forms was highly predictive of successful treatment and that failure to meet these criteria was predictive of arrhythmia recurrence. This group also reported that 26% of patients had insufficient ventricular ectopic activity on baseline recording for serial analysis. They found, as we did, that in patients with infrequent baseline ventricular ectopic activity the clinical outcome did not differ from that of patients with frequent ventricular ectopic activity, and that in this group an increase in the frequency and complexity of ventricular ectopic activity assessed by Holter recording was not predictive of arrhythmia recurrence. In a study of 42 patients with apparently less impairment of left ventricular function (mean ejection fraction of 36%) relative to our study group, Veltri et al. (7) found that the presence of ventricular tachycardia on a 24 hour Holter recording obtained during the second week of amiodarone loading correlated with sustained arrhythmia recurrence. In addition, however, they noted that the occurrence of nonsustained ventricular tachycardia on serial 24 hour recordings during long-term follow-up did not correlate with clinical outcome. Baseline drug-free recordings were not used for comparison and the

protocol for determination of amiodarone maintenance dosage was not clearly delineated in this particular investigation.

Morady et al. (4) also evaluated the prognostic utility of a 24 hour Holter recording performed shortly after amiodarone loading. In contrast to the studies by Marchlinski (6) and Veltri (7) and coworkers, they found that results of recordings obtained 1 week after initiation of amiodarone therapy were not predictive of the outcome. This group also did not use baseline drug-free recordings for comparison. In a retrospective study of a larger heterogeneous population, Nademanee et al. (9) reported that adjustment of chronic amiodarone dosage on the basis of ventricular ectopic activity suppression on serial Holter monitor recordings resulted in an "excellent" clinical response (<10% recurrence). They suggested that if baseline Holter recordings are not available or if ventricular ectopic activity is infrequent, amiodarone therapy can be administered empirically. Their results are difficult to interpret because the study protocol appears to have varied throughout the evaluation.

Our study differs from these others in that 24 hour Holter monitor recordings were performed at baseline and serially throughout amiodarone treatment and the protocol was not changed during the study. In addition, patient management was not altered by the results of the evaluation. We believe that this provides a more thorough assessment of the correlation of ventricular ectopic activity on Holter recordings with clinical outcome.

**Implications.** The mechanisms of the clinical antiarrhythmic effect of amiodarone are not known. It has been demonstrated that with more conventional antiarrhythmic agents the occurrence of ventricular ectopic activity on ambulatory electrocardiographic recording does not correlate with spontaneously occurring sustained ventricular tachycardia or fibrillation (12-14). The same appears to apply to amiodarone therapy. The concept that amiodarone prevents recurrence of sustained tachyarrhythmias by suppressing "triggering" ventricular ectopic activity is not supported by our data, but our study was not specifically designed to evaluate underlying mechanisms and, therefore, a conclusion cannot be drawn. Marchlinski et al. (6) suggested that suppression of frequent ventricular ectopic activity may merely be a "marker" for antiarrhythmic efficacy. However, in our study 18 patients who had frequent ventricular ectopic activity including repetitive forms throughout amiodarone therapy did not have an arrhythmia recurrence. Conversely, 16 patients whose ventricular ectopic activity was suppressed did experience a recurrence. Therefore, on the basis of our results in patients treated with amiodarone for sustained ventricular tachycardia or fibrillation, we conclude that neither suppression nor lack of suppression of ventricular ectopic activity on serial 24 hour Holter recordings can be used to predict arrhythmia recurrence.

Because patients with recurrent sustained ventricular

tachyarrhythmias treated with amiodarone have a 30 to 50% rate of recurrence (1-7), it would be desirable to identify those at high risk of drug failure so that adjunctive or alternative therapy may be instituted. Recent evidence (15) suggests that results of programmed electrical stimulation may assist in identifying such patients; however, the present study indicates that data obtained from ambulatory electrocardiographic monitoring do not.

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