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Predictive Value of Electrophysiologic Studies During Treatment of Ventricular Tachycardia With the Beta-Blocking Agent Nadolol

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Sixty patients with recurrent inducible sustained ventricular tachycardia were prospectively treated with nadolol (40 or 80 mg/day). Old myocardial infarction was present in 43 patients and dilated cardiomyopathy in 12. In group I (n = 36), nadolol was given alone, whereas in group II (n = 24), previously ineffective treatment with amiodarone was continued in combination with nadolol. Left ventricular ejection fraction was higher in patients in group I (0.40 ± 0.12) than in group II (0.30 ± 0.10, $p < 0.01$) patients. Electrophysiologic study was repeated after short-term treatment with nadolol, which was continued regardless of the results of this test, according to the scheme of the parallel approach.

Recurrence of spontaneous tachycardia or sudden death occurred in 21 patients after 10 ± 9.2 months; sustained tachycardia was inducible in 19 on nadolol therapy. The remaining 39 patients (of whom 21 had inducible tachycardia while taking the drug) have had no recurrence of tachycardia after 27.8 ± 9.3 months of follow-up study. Sensitivity, specificity and predictive value of a positive and negative test were 90.5%, 46%, 47.5% and 90%, respectively. The results differ between group I and group II patients, the latter having a high percent of false positive responses. This difference is even more obvious with respect to left ventricular ejection fraction: the predictive value of a positive test was 86% when ejection fraction was >0.40 and 39% when it was <0.40. A long (>400 ms) cycle length of the induced ventricular tachycardia seems more predictive of recurrence or sudden death (11 of 14 compared with 9 of 26 faster tachycardias, $p < 0.01$).

Electrophysiologic studies are suitable for evaluation of the antiarrhythmic effect of a beta-blocker on the ventricular tachycardia substrate, with the same restrictions as for other drugs in patients with low left ventricular ejection fraction. A beta-blocker should be included in serial drug testing in patients with sustained ventricular tachycardia.

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Serial drug testing with electrophysiologic studies is often proposed to assess the efficacy of antiarrhythmic therapy in patients with serious ventricular arrhythmias. Controversy concerning the value of these tests has been recently reported; Brugada and Wellens (1) proposed using a parallel approach to assess the validity of a test before considering the classic serial approach.

In almost all studies, the tested drugs were class I antiarrhythmic drugs and, more recently, amiodarone (2–8). No consistent data on the value of these tests in the patient on beta-adrenergic blocking therapy are yet available. We have prospectively used beta-blocking agents alone or with other antiarrhythmic agents to control sustained ventricular arrhythmias for several years. This report presents our experience with electrophysiologic studies using a parallel approach in these patients.

Methods

Study patients. A cooperative prospective study involving four centers included 60 patients with sustained recurrent monomorphic ventricular tachycardia who consented to the study protocol, which was approved by the regional Ethics Committee. All patients had an electrophysiologic study before the onset of beta-blocking therapy, and sustained

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Table 1. Predictive Value of Electrophysiologic Study in 60 Patients

Group	No.	Positive Test	Negative Test	True Positive	False Positive	True Negative	False Negative
I	36	20	16	12	8	14	2
II	24	20	4	7	13	4	—

Group I: sensitivity = 86%; specificity = 64%; predictive value of a positive test = 60%; predictive value of a negative test = 87.5%. Group II: sensitivity = 100%; specificity = 24%; predictive value of a positive test = 35%; predictive value of a negative test = 100%.

monomorphic ventricular tachycardia was inducible with the study protocol. There were 55 men and 5 women, 51 ± 11 years of age (mean ± SD) with coronary artery disease in 43, dilated cardiomyopathy in 12, primary right ventricular disease in 3, aortic valve disease in 1 and an apparently normal heart in 1. The pattern of the clinical ventricular tachycardia was right bundle branch block in 47 patients, left bundle branch block in 12 and undetermined in 1; the tachycardia cycle length was 286 ± 17 ms. Spontaneous tachycardia occurred during exercise in only 6 patients; its clinical tolerance was acceptable in 51 patients, whereas 5 experienced syncope and 4 had cardiac arrest. Cardioversion terminated the tachycardia in 53 of the 60 patients.

Patients were divided in two groups. In the 36 group I patients, beta-blocking therapy (nadolol) was given alone and all other previously used antiarrhythmic drugs were stopped. In the 24 group II patients, nadolol was combined with amiodarone, which had been used for >6 months and was continued at the same dosage during the study. In this latter group, the initial electrophysiologic study with the patient on amiodarone therapy induced sustained ventricular tachycardia. Patients in groups I and II did not differ in age, gender ratio or underlying heart disease, but group II patients had had more attacks of ventricular tachycardia (6.4 ± 5.1 versus 3.4 ± 3.2, $p < 0.05$) and had a lower isotopic left ventricular ejection fraction (0.301 ± 0.096 versus 0.401 ± 0.125, $p < 0.01$).

Electrophysiologic study. In the following order, our protocol included 1) twice threshold ventricular pacing with progressive reduction in the cycle length to 260 ms; 2) single extrastimulation up to the refractory period then double extrastimulation up to the refractory period on a basic ventricular paced cycle length of 600 ms; and 3) single then double extrastimulation on a paced cycle length of 400 ms. The right ventricular apex was used as a first site, and in the case of a negative response, the right ventricular outflow tract as a second site. No catecholamine infusion was used. Induction of sustained (>30 s) monomorphic ventricular tachycardia was called a positive electrophysiologic study result, whereas induction of nonsustained monomorphic or polymorphic ventricular tachycardia as well as noninducibility of any arrhythmia were called a negative response.

Treatment. Beta-blocking therapy consisted of nadolol, 80 mg/day in patients with >70 kg body weight and left ventricular ejection fraction >0.30, or 40 mg/day in patients <70 kg or with an ejection fraction <0.30. The dose of nadolol was not statistically different between groups I and II (67 ± 19 versus 60 ± 22 mg/day, respectively, p = NS). In patients with an ejection fraction <0.40, beta-blocking therapy started with acebutolol or celiprolol, drugs having an intrinsic sympathomimetic activity; nadolol was substituted for acebutolol or celiprolol after 3 to 5 days. Electrophysiologic study was performed after 5 to 7 days of nadolol therapy, and the patients were discharged on this drug regardless of the results of the electrophysiologic study, according to the plan of the parallel approach. Clinical response was judged as 1) spontaneous recurrence of sustained ventricular tachycardia necessitating a therapeutic intervention, or 2) death. End points of the study were both sudden death (<1 h after initial symptom) and spontaneous sustained ventricular tachycardia.

Statistical analysis. The chi-square test or Student's *t* test was used to compare the two groups of patients. Actuarial incidence of tachycardia recurrence was evaluated by Kaplan-Meier curves and compared by the log-rank test. Probability (p) values <0.05 were considered significant.

Results

Results of the electrophysiologic study. In group I, electrophysiologic study results were negative in 16 patients (44%) and remained positive in 20 (56%), whereas in group II patients, they were negative in only 4 (17%) and positive in 20 (83%). This difference between the two groups is significant ($p < 0.02$), which may mainly be due to the difference in left ventricular ejection fraction because a retrospective subgroup analysis of the results shows an even more significant difference according to this variable; the electrophysiologic study results were negative in 13 (65%) of 20 patients with an ejection fraction >0.40 compared with 7 (17.5%) of 40 patients with an ejection fraction of <0.40 ($p < 0.001$).

Predictive value of the electrophysiologic study. Table 1 indicates the long-term outcome on nadolol therapy assessed by the electrophysiologic study in the two groups. The follow-up period in the 39 patients free of recurrence of sustained ventricular tachycardia or sudden death is 27.8 ± 9.3 months, longer than the delay of recurrence of ventricular tachycardia or sudden death in the remaining 21 patients (10 ± 9.2 months, $p < 0.001$).

For the entire series, the sensitivity of the electrophysi-

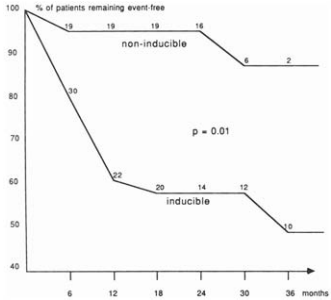

Figure 1. Kaplan-Meier survival curves for patients free of tachycardia recurrence and sudden death, according to the results of the electrophysiologic study in 60 patients on nadolol therapy. Numbers represent patients available for comparison at each time interval. The difference between patients with inducible and noninducible tachyarrhythmia is significant ($p < 0.01$).

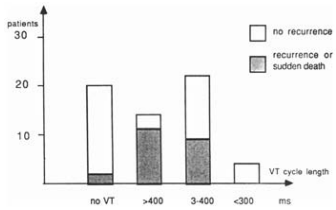

Figure 2. Incidence of ventricular tachycardia (VT) recurrence or sudden death (**dashed area**), according to the cycle length of the induced ventricular tachycardia.

ologic study was 90.5%, its specificity was 46%, the positive predictive value of a positive test was 47.5% and that of a negative test was 90%. However, these values differed between the two groups (Table 1), with a higher number of false positive results in group II patients (13 of 24 patients compared with 8 of 36 in group I, $p < 0.01$). Again, this difference between groups may mainly be due to differences in left ventricular function rather than to the treatment because all except one false positive result appeared in patients with a left ventricular ejection fraction <0.40 (Table 2).

The actuarial incidence of recurrence of ventricular tachycardia (Fig. 1) was statistically higher in patients with inducible tachycardia ($p < 0.01$).

Role of the ventricular tachycardia rate. The value of the induced ventricular rate seems to be related to the clinical outcome (Fig. 2). Among 14 patients with an induced tachycardia cycle length >400 ms during nadolol therapy, 9 had a recurrence of tachycardia and 2 died suddenly, whereas only 9 recurrences and no sudden deaths occurred in the 26 patients with an induced tachycardia cycle length <400 ms at electrophysiologic study ($p < 0.01$). Conversely, a slower induced tachycardia was not related to the clinical outcome. Among 14 patients with an increase in tachycardia cycle length of >50 ms, 7 had a tachycardia recurrence, and among 26 patients with unchanged tachycardia cycle length, 12 had a tachycardia recurrence (p = NS).

Tolerance to nadolol. Side effects were relatively rare in this prospective study. Aggravation of heart failure occurred in six patients, leading to discontinuation of nadolol in four, which was also necessary in one patient with intolerable fatigue. An atrial demand (AAI) or dual chamber (DDD) pacemaker had to be implanted in nine patients (three in group I, six in group II) because of severe sinus bradycardia. Nine patients died during the follow-up: four of heart failure (in two after nadolol treatment was discontinued) and five suddenly (two within 2 months after stopping nadolol therapy and one 4 months after stopping amiodarone because of hyperthyroidism).

Discussion

Beta-blockers and ventricular tachycardia. Very few reports on electrophysiologic studies of patients with ventricular tachycardia include patients treated with a beta-blocking agent (9,10) and these reports described only small series. More recently, some larger series (11,12) included patients treated with sotalol, a beta-blocker that also has a

Table 2. Role of Left Ventricular Ejection Fraction in 60 Patients

LVEF	No.	Positive Test	Negative Test	True Positive	False Positive	True Negative	False Negative
>0.40	20	7	13	6	1	11	2
<0.40	40	33	7	13	20	7	—

Left ventricular ejection fraction (LVEF) >0.40: sensitivity = 75%; specificity = 92%; predictive value of a positive test = 86%; predictive value of a negative test = 85%. Left ventricular ejection fraction <0.40: sensitivity = 100%; specificity = 26%; predictive value of a positive test = 39%; predictive value of a negative test = 100%.

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direct class III antiarrhythmic effect, but their favorable results cannot be extrapolated to the usual beta-blocking agents. This fact contrasts with the well recognized importance of an increased sympathetic tone in the genesis of sudden death from ventricular tachyarrhythmias (13,14) and with the preventive effect of beta-blocking agents on sudden death after myocardial infarction (15,16). This effect is correlated with the obtained sinus bradycardia (17). The mechanisms of sudden death from ventricular tachyarrhythmias, especially in chronic coronary artery disease, include an electrophysiologic substrate of ventricular tachycardia or fibrillation and triggering factors, namely, ventricular premature beats and increased sympathetic tone (18). If such is the case, it could be hypothesized that beta-blocking agents may have a favorable effect on the ventricular tachycardia substrate in addition to their effects on triggering factors.

Effects of nadolol on the electrophysiologic substrate. Our study seems to confirm this hypothesis because 46% of patients treated with nadolol alone had a negative electrophysiologic study result, which was a possibility mentioned in the initial studies (2,3). However, in group II patients previously treated with amiodarone, only a small proportion (17%) responded to nadolol on the basis of the electrophysiologic study. It is important to discriminate between a true antiarrhythmic effect on the electrophysiologic properties of the ventricular tachycardia substrate and an artifact due to an inadequate protocol or lack of reproducibility of the electrophysiologic study. It has been demonstrated that induction of polymorphic ventricular tachycardia (19) or ventricular fibrillation (20) has a low clinical relevance compared with induction of sustained monomorphic ventricular tachycardia (21). Similarly, using three extrastimuli (22) or multiple sites of stimulation (23) increases the sensitivity of the study, but decreases its specificity dramatically, and the majority of the admitted "standardized" protocols of electrophysiologic study (24) include only two extrastimuli and a maximum of two sites. Our protocol was in accordance with these recommendations.

Recently, some investigators (25,26) reported results suggesting that modifications of the ventricular tachycardia substrate are sufficient to obtain a significant degree of clinical efficacy in the prevention of spontaneous ventricular tachycardia or sudden death; obtaining a slowed induced ventricular tachycardia may be sufficient in some cases. However, other studies (27,28) showed that slowing intraventricular conduction (assessed by paced QRS duration) is more marked in nonresponders than in responders. In our study, considering a slowed ventricular tachycardia as a negative response to electrophysiologic study does not change the number of false positive responses.

Determinants of the response to a beta-blocker. If the electrophysiologic study protocol is not a source of error, it could be concluded that the percent of responders is lower in the patients receiving combined amiodarone and nadolol therapy and even more different between patients with conserved versus severely impaired left ventricular function. In our study, these findings were established by retrospective analysis and are thus subject to criticism; however, similar data have been reported (29–31) with other antiarrhythmic drugs and the data appear nonspecific for beta-blocking therapy. The reasons for this higher rate of responders among patients with good left ventricular function are unknown. The degree of left ventricular dysfunction seems to be a determinant not only of the percent of responders to electrophysiologic study, but also of clinical outcome. Discrepancies between electrophysiologic study results and outcome were mainly due to a high rate of false positive results, which were observed almost exclusively in patients with depressed left ventricular function. In this case, false positive responses could be due to a predominant effect of antiarrhythmic drugs on the other factors leading to spontaneous ventricular tachycardia (that is, triggering factors or sympathetic tone, or both).

Beta-blocking therapy is the only effective treatment for reducing sympathetic drive and it is not surprising to observe a high percent of false positive responses at electrophysiologic study (ventricular tachycardia substrate is still present, but no clinical ventricular tachycardia will occur because of the effect of the drug on the main predisposing factor). This difference between effects of beta-blocking agents on ventricular tachycardia substrate and triggering factors has been observed experimentally (32).

Clinical implications. Beta-blocking agents may have a direct effect on the ventricular tachycardia substrate in addition to an effect on the factors predisposing to clinical ventricular tachycardia. Results of electrophysiologic testing are not different from those obtained with other drugs, like amiodarone; there is a good clinical correlation in patients with preserved left ventricular function and a higher proportion of false positive results in patients with left ventricular dysfunction. There is no reason to consider beta-blocking agents differently from other antiarrhythmic drugs or to minimize their usefulness in the treatment of ventricular tachyarrhythmias.

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