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Programmed Electrical Stimulation Studies for Ventricular Tachycardia Induction in Humans. II. Comparison of Indwelling Electrode Catheter and Daily Catheter Replacement

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Suppression of the ability to induce ventricular tachycardia by programmed electrical stimulation during serial drug testing has been used as a therapeutic end point to identify long-term prophylactic antiarrhythmic therapy. However, ventricular tachycardia induction, particularly with an indwelling electrode catheter, has not been systematically assessed over the time period required for serial drug testing. In this study, the results of programmed electrical stimulation were evaluated daily during serial drug-free conditions before testing various antiarrhythmic drugs. Twenty-four patients were randomly allocated to be studied with the electrode catheter left in place or replaced daily.

All patients had inducible sustained ventricular tachycardia during the first study. Loss of the ability to induce ventricular tachycardia occurred in 8 of 13 patients whose catheter was left in place whereas this did not occur in patients whose catheter was replaced daily ($p < 0.01$). In addition, use of an in situ catheter was accompanied by significant ($p < 0.05$) changes in other electrophysiologic measurements, including number of extrastimuli required to induce ventricular tachycardia and length of ventricular functional and effective refractory periods. The serial changes seen with indwelling catheters in the drug-free state may mimic effective antiarrhythmic drug action.

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The use of serial electrophysiologic studies with programmed electrical stimulation has been demonstrated to be a valuable approach to the identification of antiarrhythmic therapy for patients with ventricular tachycardia (1–4). Suppression of the ability to induce ventricular tachycardia by programmed stimulation has been taken to predict an effective antiarrhythmic response. This association presupposes the absence of other time-dependent changes that affect inducibility of ventricular tachycardia. Because an electrode catheter can produce electrophysiologic changes in adjacent myocardium (5,6), the use of a recently placed indwelling catheter for serial studies introduces the possibility of time-dependent changes in ventricular tachycardia inducibility unrelated to antiarrhythmic drug use. The purpose of this study was to determine whether the use of a recently placed indwelling electrode catheter for serial electrophysiologic studies could mimic effective antiarrhythmic drug activity more frequently than would daily replacement of the electrode catheter.

Methods

Study patients. Twenty-four consecutive patients with sustained ventricular tachycardia induced by programmed electrical stimulation participated in this study. The patients were referred for treatment of symptomatic ventricular tachycardia or had syncope of obscure etiology, and sustained unimorphic ventricular tachycardia was induced in all.

Protocol. After withdrawal of all antiarrhythmic agents for at least four half-lives and determination of left ventricular ejection fraction by radionuclide angiography, programmed electrical stimulation studies were performed with the electrode catheter at the right ventricular apex. Sustained ventricular tachycardia was elicited by programmed electrical stimulation at baseline and was reproduced at least once. Sustained ventricular tachycardia was defined as that

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Table 1. Clinical Characteristics of Group I and Group II Patients

	Group I	Group II
Sex	11 male, 2 female	9 male, 2 female
Age (yr ± SD)	59 ± 11	51 ± 17
Range	(41 to 77)	(28 to 74)
Cardiac diagnosis		
Ischemic heart disease	13	9
Right ventricular dysplasia	0	2
Clinical presentation		
Ventricular fibrillation	0	1
Sustained ventricular tachycardia	5	7
Nonsustained ventricular tachycardia + syncope	4	3
LV ejection fraction (percent ± SD)	40 ± 17	45 ± 19

LV = left ventricular.

lasting for 30 seconds or requiring premature termination because of serious hemodynamic compromise.

Patients were then randomized into two groups: in Group I the electrode catheter was left in the same position at the right ventricular apex for subsequent study whereas in Group II the electrode catheter was replaced daily before programmed electrical stimulation studies. The end point of this study was loss of the ability to induce ventricular tachycardia (five or more depolarizations) at a subsequent drug-free study. When this end point occurred, a second electrode catheter was positioned as close as possible to the original catheter. The results of electrophysiologic study from the "new" catheter were compared with those from the indwelling catheter.

Serial drug-free programmed electrical stimulation studies were performed daily before acute antiarrhythmic drug testing. Drug infusions were designed to produce constant therapeutic blood levels that would rapidly decrease because of both distribution and elimination when the infusions were stopped. These infusions were based on population estimates of A, B, α, β and clearance (7–9). A subsequent drug-free state was considered to be present under either of two circumstances: 1) when the serum level of the medication tested 24 hours before was below the detectable limits

Figure 1. Ventricular tachycardia induction with daily replacement of electrode catheter compared with that with an in situ catheter in 24 patients. + = ventricular tachycardia induced; − = ventricular tachycardia not induced; * = results with a new second electrode catheter in patients whose ventricular tachycardia became noninducible with an in situ catheter. S = development of staphylococcal bacteremia.

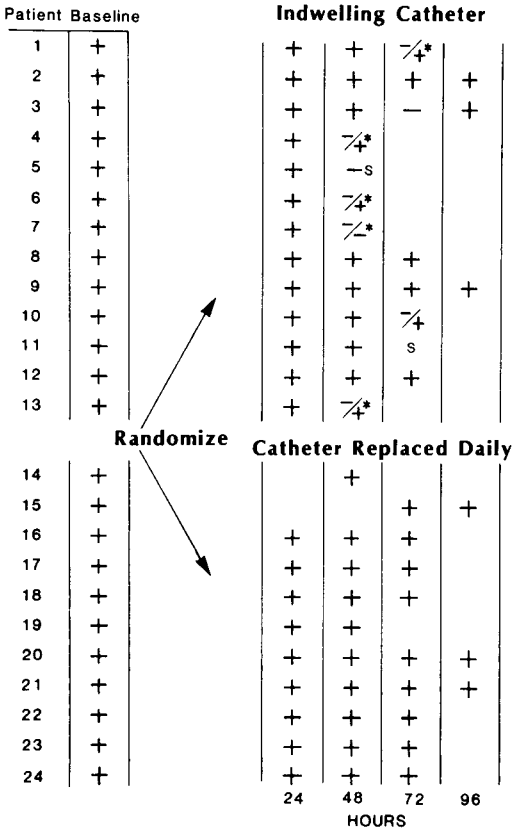
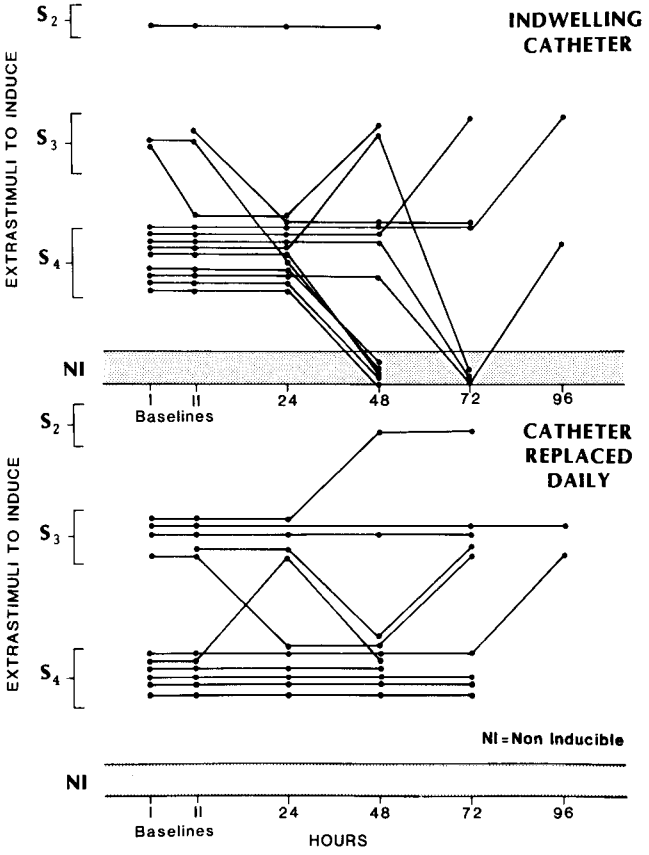


Figure 2. Time-dependent change in the number of extrastimuli required to induce ventricular tachycardia. The **upper panel** shows changes occurring with an in situ catheter and the **lower panel** shows changes occurring when the catheter is replaced daily. NI = noninducible with three extrastimuli and burst pacing; S_2 = one extrastimulus; S_3 = two extrastimuli; S_4 = three extrastimuli.



of the assay, or 2) when serum levels were below the lower limits of the therapeutic range in those patients who did not respond to that medication. To minimize the possibility of residual drug effects, medications with the longest biologic half-lives were given last. The usual sequence of drug infusions was 1) procainamide, 2) disopyramide, 3) propranolol, and 4) quinidine.

Electrophysiologic studies. Programmed electrical stimulation techniques used during baseline and all subsequent studies included the introduction of up to three extrastimuli (pulse width 2 ms; intensity 3 mA or twice diastolic threshold, whichever was greater, and 2 ms pulse width) during ventricular pacing at cycle lengths of 600, 500 and 400 ms. This protocol is based on results of our previous study (10). If ventricular tachycardia was not induced at the completion of the protocol then ventricular burst pacing at cycle lengths decreasing from 300 to 240 ms in steps of 10 ms was also used. The possibility that a time-dependent change could mimic a beneficial drug effect was considered when no ventricular tachycardia (five or more depolarizations) could be induced in a subsequent drug-free state. In this study, S_1S_2 represents the stimulus artifact of the last beat of the ventricular drive train and the first extrastimulus, respectively. Corresponding ventricular electrograms were designated as V_1V_2. The ventricular effective refractory period of S_2 was the longest S_1S_2 interval at which S_2 failed to capture (11). The ventricular functional refractory period of S_2 was the minimal V_1V_2 coupling interval during determination of the ventricular refractory curve.

Analytic drug assays. Serum samples were obtained at each drug-free study. Samples were assayed for procainamide, disopyramide, lidocaine, quinidine and propranolol by enzymatic immunoassays (EMIT). The therapeutic range for each of these medications in this laboratory was: pro-

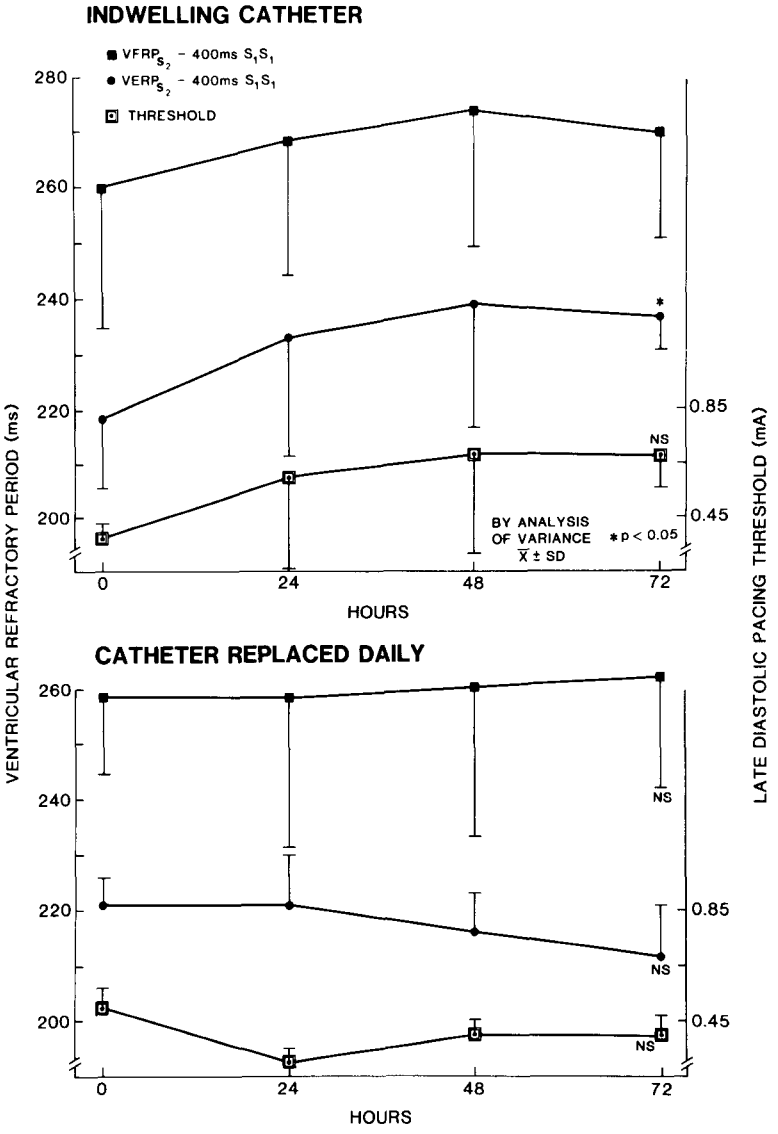


Figure 3. Time-dependent changes in ventricular functional refractory period (VFRP) of S_2, ventricular effective refractory period (VERP) of S_2 and late diastolic pacing threshold. The **upper panel** shows changes with an in situ catheter, the **lower panel** shows those occurring when the catheter was replaced daily. NS = not significant.

cainamide, 17 to 34 μmol/liter; disopyramide, 3 to 5 μg/ml lidocaine, 1.5 to 5 μg/ml; quinidine, 7 to 14 μmol/liter; propranolol, 20 to 1,000 ng/ml. The lower limits of the detectable range of the assay for each of these medications were 4.3 μmol/liter, 0.5 μg/ml, 1.0 μg/ml, 1.5 μmol/liter and 10 ng/ml, respectively.

Statistics. Chi-square analysis was used to assess significance of change in the proportion of individuals in whom ventricular tachycardia could still be elicited over time. Time-dependent changes in ventricular effective and functional refractory periods and late diastolic threshold were evaluated using analysis of variance. The null hypothesis was rejected at $p < 0.05$.

Results

Table 1 lists the clinical characteristics of Group I (electrode catheter left in situ) and Group II (catheter replaced daily). There were no significant differences between Groups I and II with respect to cardiac diagnosis, clinical presentation or left ventricular ejection fraction.

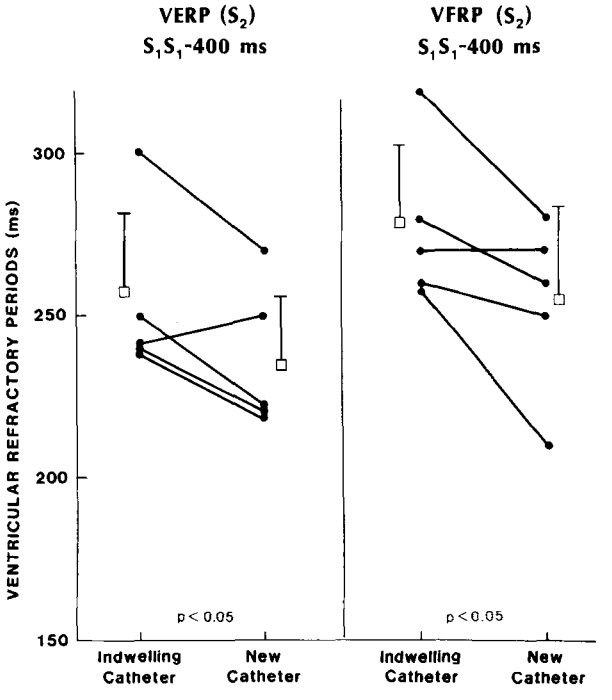
Time-dependent changes in electrophysiologic measurements. Figure 1 shows the time dependence of ventricular tachycardia induction in the two patient groups. Although ventricular tachycardia could not be induced on at least one occasion in 8 of 13 patients when the catheter had been left in place for 72 hours, it was consistently induced when the catheter was replaced daily ($p < 0.01$). Even when the catheter had been left in place for only 48 hours, inability to induce ventricular tachycardia occurred in 5 of 13 patients ($p < 0.05$). Other time-dependent changes in electrophysiologic measurements in patients with an indwelling catheter included an increased number of extrastimuli ($p < 0.05$) to induce ventricular tachycardia (Fig. 2) and increased ventricular effective and functional refractory periods ($p < 0.05$) (Fig. 3). These time-dependent changes were not seen when the catheter was replaced daily. No significant time-dependent increase in late diastolic threshold was seen.

A second electrode catheter was introduced as near as possible to the original catheter site in five of eight patients whose ventricular tachycardia was not induced from the indwelling catheter. Three did not have a new electrode catheter inserted as a replacement: one because of technical problems, one because of the development of fever and suspected *Staphylococcus aureus* bacteremia and one because of withdrawal of patient consent. Ventricular tachycardia was then inducible from the new catheter in four of the five patients (Fig. 1). The electrophysiologic measurements obtained from the second catheter were compared with those from the indwelling catheter (Fig. 4). Programmed electrical stimulation from the indwelling catheter not only failed to induce ventricular tachycardia, but ventricular functional and effective refractory periods (254 ± 26 ms and 278 ± 28 ms, respectively) were prolonged relative to those measured with the new electrode catheter (234 ± 22 and 254 ± 27 ms, respectively). There was no significant difference in late diastolic threshold comparing the measurement from the indwelling catheter at the time of loss of inducibility with the new replacement catheter or with the measurement when the indwelling electrode catheter had been first inserted (threshold of the indwelling catheter at time zero was 0.4 ± 0.2 mA; that of the indwelling catheter at time of loss of inducibility was 0.8 ± 0.5 mA and that of the new replacement catheter was 0.4 ± 0.1). Similarly there was no significant change in the ratio of stimulus intensity to threshold.

Serial drug-free states. Serum drug levels were below the detectable limits of the appropriate assays on 11 of 25 occasions and below the lower limit of the therapeutic range on all but 2 occasions. In these two patients, one in each group, ventricular tachycardia remained inducible. When ventricular tachycardia could no longer be induced in the eight patients with an indwelling catheter, serum levels of the medication given 24 hours before were nondetectable in six and below the lower limit of the therapeutic range in one; in one the sample was not available. Serum levels of the local anesthetic lidocaine were consistently below the lower limit of the therapeutic range.

Adverse effects. *Staphylococcus aureus* bacteremia occurred in two patients and blood culture-negative fever oc-

Figure 4. Ventricular effective refractory period (VERP) of S_2 and ventricular functional refractory period (VFRP) of S_2 using the indwelling catheter at the time when ventricular tachycardia was not inducible, as opposed to daily catheter replacement.



curred in one additional patient whose catheter was left in place. In contrast, no bacteremia or fever occurred in patients whose catheter was replaced daily.

Discussion

Several investigators (12–14) have emphasized the importance of differentiating a true drug effect from spontaneous variability in arrhythmia occurrence during antiarrhythmic drug evaluations. The separation of true drug effect from spontaneous variability generally involves the use of a control group examined repeatedly during placebo treatment. It is difficult to apply this method of investigation to patients with life-threatening ventricular arrhythmias. Nevertheless, the effects of antiarrhythmic therapy must be separated from the effects of time if the ability of a medication to suppress ventricular tachycardia induction during serial electrophysiologic studies is to be used as a criterion to select prophylactic therapy.

Can time-dependent changes associated with an indwelling electrode catheter mimic a true antiarrhythmic drug response? Because this study was not intended to assess the reproducibility of sustained ventricular tachycardia induction, this end point was not pursued. We wished to determine whether time-dependent changes associated with an indwelling electrode catheter could mimic a true antiarrhythmic drug response. To minimize the chances of detecting an unimportant time-dependent change because our definition of response was insufficiently rigorous, we chose to use the similarly demanding end point for response previously reported by Mason et al. (15), that is, inability to induce five or more repetitive ventricular depolarizations. Had a less demanding end point been used, time-dependent changes would only have been observed more frequently than we report here. Using this definition of response we found that over a 72 hour period, a drug response was falsely suggested in 8 (62%) of 13 patients with an indwelling electrode catheter in an antiarrhythmic drug-free state. No such response was observed in 11 patients undergoing daily catheter replacement. Furthermore, in the five patients whose arrhythmia became noninducible with an in situ catheter, immediate placement of a second right ventricular apical electrode catheter restored inducibility in four. Our data are relevant to the interpretation of studies that assess reproducibility of the induction of ventricular tachycardia over time. Unless catheters are replaced daily, the reproducibility of ventricular tachycardia induction cannot be adequately assessed. A recent study by Lombardi et al. (16) suggested that ventricular tachycardia induction by daily programmed electrical stimulation was not reproducible. However, such data cannot be interpreted without an indication of the proportion of patients whose second and subsequent assessments were performed with an indwelling electrode catheter.

In the companion report (10) we show that increasing stimulus intensity above twice diastolic threshold decreases ventricular effective refractory period but does not change either ventricular functional refractory period or ventricular tachycardia inducibility. Therefore, the change in ventricular effective refractory period in patients with an in situ catheter (illustrated in Fig. 3) might be explained by the trend toward a decrease in the ratio of stimulus intensity to threshold over time. However, because the stimulus intensity used was at least twice threshold in every instance, this explanation does not account for the time-dependent increase in ventricular functional refractory period or for the loss of ventricular tachycardia inducibility.

Mechanisms of time-dependent changes. The present study does not directly address the mechanisms underlying the time-dependent changes seen with an indwelling catheter. Potential explanations include local tissue reaction at the electrode catheter/endomyocardial interface (17,18), or systemic effects such as change in autonomic tone relating to the instrumentation procedure. Deleze (19) showed, in Purkinje fibers, that local injury causes alteration in the membrane potential and in the local cable properties. However, we have no evidence that the presence of a foreign object on the endomyocardial surface similarly alters these electrophysiologic properties in vivo.

Conclusions. If the electrode catheter is left in situ during serial electrophysiologic studies, time-dependent changes in electrophysiologic measurements occur. These changes can include loss of the ability to induce ventricular tachycardia by programmed electrical stimulation, which may be mistaken for effective antiarrhythmic drug therapy. Serial electrophysiologic studies therefore require daily catheter replacement.

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