Electrophysiologic studies have gained wide acceptance in clinical cardiology, particularly for the diagnosis and management of patients with symptomatic ventricular tachycardia and survivors of sudden cardiac arrest. Clinical studies have shown that the suppression of induced ventricular arrhythmias during serial electrophysiologic-pharmacologic testing is predictive of a favorable long-term outcome (1-3).

In contrast, a high recurrence of arrhythmic events and poor long-term survival are noted in patients in whom antiarrhythmic agents do not prevent the induction of the tachyarrhythmia (4). Of equal importance, electrophysiologic studies, in addition to having considerably enhanced our knowledge of impulse formation and transmission, have been partly responsible for ushering in new therapeutic modalities that have already demonstrated a positive impact on the survival of high risk patients exposed to the specter of sudden arrhythmic death (5-7).

**Issues raised by evolutionary aspects of programmed electrical stimulation.** Simultaneously, we have witnessed a mushrooming of new and so-called aggressive stimulation protocols for the induction of ventricular arrhythmias in the laboratory. Stimulation techniques have evolved from relatively simple protocols using rapid pacing (8,9), to the introduction of up to two premature stimuli during one or two ventricular pacing drives, to aggressive protocols utilizing up to four premature stimuli at two or more ventricular pacing drives at a current of 5 mA or more at two or more right ventricular sites, and occasionally in the left ventricle as well. These evolutionary aspects of programmed electrical stimulation have been a source of confusion and criticism. Although it is just to seek information in the name of knowledge and to counter with the words of John Milton, "Where there is much desire to learn, there of necessity will be much arguing, much writing, many opinions, for opinions in good men is knowledge in the making," it is likewise important to acknowledge several issues that the evolutionary aspects of programmed electrical stimulation have raised. Some of these issues are: 1) What is an acceptable stimulation protocol? 2) What is the day to day reproducibility of the rate and configuration of induced ventricular tachycardia using different protocols? 3) Should stimulation protocols be tailored to the specific patient group being studied? and 4) What is the significance of polymorphic forms of ventricular tachycardia and ventricular fibrillation induced with conventional versus aggressive stimulation protocols?

The answers to some of these questions are not readily available and are difficult to obtain for several reasons: 1) Animal models of ventricular tachycardia vary substantially from clinical ventricular tachycardia, such that information obtained in the animal laboratory is not readily applicable to humans. 2) The mechanism (reentry versus triggered automaticity) and site of origin (endocardial versus intramural or epicardial) of ventricular tachycardia may be different in patients with different disease entities. 3) In a given patient, there may be more than one site of origin of ventricular tachycardia. Thus, both the clinical and the induced tachycardia may have different rates and configurational characteristics. 4) Different stimulation protocols may result in substantial alteration of conduction and refractory characteristics of the arrhythmogenic substrate and the normal myocardium, resulting in changes in rate and configuration of ventricular tachycardia, which may in part be dependent on the exit site of the tachycardia. In addition, different stimulation protocols (for example, burst pacing versus premature stimulation) may result in hemodynamic and ischemic consequences that may also influence the electrophysiologic characteristics of the arrhythmogenic substrate. 5) There may be inherent differences in the electrophysiologic characteristics of the arrhythmogenic substrate in patients with monomorphic ventricular tachycardia compared with those whose tachycardia readily degenerates into ventricular fibrillation. 6) Programmed electrical stimulation may be the best test currently available to alter the "dormant" arrhythmogenic substrate, as the induction of ventricular tachycardia is dependent on the creation of functional delays in conduction, block and differential refractoriness, but these requisite conditions for the induction, maintenance and termination of a reentrant arrhythmia may only rarely occur spontaneously in an as yet poorly defined clinical milieu.

**Inducibility and reproducibility of ventricular arrhythmias by programmed electrical stimulation.** The inducibility of ventricular arrhythmias in the clinical electrophysiology laboratory is dependent on several factors, of
which the stimulation protocol, the presenting arrhythmia and the underlying heart disease are of paramount importance. The chances of inducing ventricular tachycardia are very high in patients with recurrent monomorphic ventricular tachycardia. With the use of two premature stimuli at two ventricular basic drives introduced in the right ventricular apex, the incidence of ventricular tachycardia induction ranges from 88 to 91% (10,11). The addition of a third extrastimulus to the pacing protocol can increase the rate by 12 to 24% (11-13). Stimulation in the right ventricular outflow tract and in the left ventricle has been shown to result in a further increase in the induction of ventricular tachycardia. Of patients presenting with sustained ventricular tachycardia, approximately 89 to 97% (12,14) have inducible arrhythmias, compared with 61 to 81% of patients who present with cardiac arrest (12,14). The induction of polymorphic forms of ventricular tachycardia and ventricular fibrillation with aggressive modes of stimulation (third and fourth extrastimuli) may be a nonclinical response, as these forms of arrhythmia have been induced in some patients who do not have a history of clinical sustained ventricular tachycardia or aborted sudden death (11). The clinical significance of induction of polymorphic ventricular tachycardia and ventricular fibrillation with conventional pacing protocols is unclear at this time; however, it is probably an important finding in patients with documented sustained ventricular tachycardia or out-of-hospital aborted sudden death. The induction of a monomorphic ventricular tachycardia is a highly specific finding.

In this issue of the Journal, Kudenchuk et al. (15) report on their study of the inducibility and reproducibility of ventricular arrhythmias in 114 patients. They found a stepwise, significant increase in inducibility of ventricular arrhythmias as the stimulation protocol was carried to more aggressive modes of stimulation, particularly with the use of three and four extrastimuli. They noted an induction rate of 10% for rapid ventricular pacing, 10% for a single premature stimulus, 28% for two extrastimuli, 48% for three extrastimuli and 64% for four extrastimuli. These induction rates are substantially lower in comparison with those in previously reported series of patients with sustained ventricular tachycardia and survivors of sudden death. The low sensitivity of programmed ventricular stimulation in the study of Kudenchuk et al. may have occurred for the following reasons: 1) there was marked heterogeneity in the patient group with respect to disease entity, drug history, incidence of ventricular fibrillation versus ventricular tachycardia and isolated versus recurrent episodes of ventricular tachycardia; and 2) an extremely high proportion of their patients (74 [65%] of 114) had been receiving class I agents for Lown class 1 to 4a arrhythmia at the time of the out-of-hospital arrhythmic event. It is likely that in most of these patients this event was causally related to the type I agents, which underscores the potential pro-arrhythmic effects of the antiarrhythmic agents for treatment of ventricular premature beats. A high proportion of these patients had no inducible arrhythmia by single and double extrastimuli when they were not receiving type I agents and this group probably contributed to the low inducibility rate with conventional stimulation protocols. Although the difference in inducibility decreased when three and four extrastimuli were used, no data are provided regarding polymorphism and ventricular fibrillation in these patients. It is likely that the induced arrhythmia in some of these patients in response to an aggressive stimulation protocol may have been a nonspecific response. In our laboratory (16), we induced ventricular arrhythmias in only 23% of patients with Lown class 4a arrhythmia with the use of up to two extrastimuli and burst pacing. Although our patients with class 4a arrhythmia are not comparable with those studied by Kudenchuk et al. (15), our observation of a good survival rate in the patients with noninducible arrhythmia suggests that noninducibility with conventional protocols may be of greater clinical relevance than inducibility with aggressive stimulation protocols.

Utilizing a point score change of 3 or more, Kudenchuk et al. (15) noted that induced arrhythmias were more frequently nonreproducible (7 to 27%) in rate or duration, or both, as the number of extrastimuli increased from one to four; however, the rate of nonreproducibility when three and four extrastimuli were used did not differ significantly from that when two extrastimuli were used. The authors are to be lauded for using the duration as well as the rate of induced ventricular arrhythmias in their reproducibility scoring system, unlike the systems used in previous studies. The limitations of their study, however, include the following: 1) If a patient’s score increased from 5 (rate of 100 to 160/min) to a score of 7 (rate of 201 to 300/min) the arrhythmia was considered reproducible; however, if the same patient’s score increased to 8 (rate > 300/min or ventricular fibrillation) the arrhythmia was considered nonreproducible. In such a patient it is likely that a score of either 7 or 8 would result in a hemodynamically unstable arrhythmia. 2) In 14% of the patients the arrhythmia was induced with stimulation in the outflow tract, whereas reproducibility studies in these patients were performed in the cardiac apex. These differences in methodology could have partly accounted for nonreproducibility. 3) Serum levels of lidocaine were monitored in 22 patients during the first study and achieved therapeutic concentration in a high proportion (32%). Because lidocaine was not used during the second study, this could have partly influenced reproducibility. 4) The configuration of the induced arrhythmia was not clarified to determine whether the nonreproducible arrhythmias fell in the category of polymorphic ventricular tachycardia and fibrillation. This may have been the case, as nonreproducibility was highest with the use of four extrastimuli.
Implications. Kudenchuk et al. (15) have reservations about drug studies based on a nonreproducibility rate of 17 to 27% and therefore recommend two baseline studies. This recommendation is not currently acceptable, because the inducibility and reproducibility data provided by the authors apply only to the patient group they studied and to the protocol used in their laboratory. There is evidence to suggest that replacement of the stimulation catheter improves reproducibility of arrhythmia induction (17). Furthermore, before their recommendation is accepted, it would perhaps be better to tailor the stimulation protocol to the patient group being studied and, in addition, to assess the configurational characteristics of the induced arrhythmia. Patients with documented sustained ventricular tachycardia and survivors of out-of-hospital aborted sudden death may be subjected to a stepwise increase in stimulation protocol, as suggested by Kudenchuk et al. (15). However, this leaves the option of the introduction of “n number” of premature stimuli, which is to be discouraged at this time.

An appropriate protocol in such patients seems to be the introduction of up to three premature stimuli at two paced cycle lengths at twice diastolic threshold at two right ventricular sites (apex and outflow tract) and burst pacing. Utilizing this protocol in our laboratory, ventricular tachycardia can be initiated in more than 90% of patients with documented recurrent sustained ventricular tachycardia and in 70% of patients with aborted sudden death. The induction of monomorphic ventricular tachycardia does not need confirmation of reproducibility in two separate studies. The induction of a polymorphic ventricular tachycardia, particularly with a third extrastimulus, may need reproducibility studies. It is noteworthy that the number of electrocardiographic leads recorded during electrophysiologic studies and during out-of-hospital events limits the assessment of configuration in both spontaneously occurring and induced arrhythmias. Ventricular fibrillation that results from a run of monomorphic ventricular tachycardia may be of clinical relevance in contrast to that resulting from a run of polymorphic tachycardia. Prospective studies are needed in a large number of patients to clarify this issue. In patients with noninducible arrhythmia with aborted sudden death, other causes such as ischemia, use of antiarrhythmic therapy and electrolyte imbalance should be carefully assessed and corrected. Whereas it is crucial to continue to seek knowledge in this important area, it is time to critically review past experience regarding the role of electrophysiologic-pharmacologic testing to establish the most appropriate protocols with the best sensitivity, specificity and reproducibility.

References