FEATURES

Programmed electrical stimulation of the heart in patients with life-threatening ventricular arrhythmias: What is the significance of induced arrhythmias and what is the correct stimulation protocol?

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Following its introduction into the practice of cardiology in 1972, programmed electrical stimulation (PES) of the heart has developed from a technique used for diagnostic purposes into one used for clinical management of patients with life-threatening ventricular arrhythmias.

During the same years we have seen a gradual change from relatively simple pacing protocols using one or two premature stimuli during ventricular stimulation to “aggressive” protocols using up to four premature stimuli, many basic pacing rates, and different sites of ventricular stimulation.

During PES some factors can, but many cannot, be controlled by the investigator. Among those that are controllable are (1) stimulus strength, duration, type of current, number and rate of basic stimuli, number and interval of premature stimuli, (2) stimulation site, (3) mode of stimulation (unipolar or bipolar), and (4) interelectrode distance. Some factors that are not controllable are (1) type of spontaneous tachycardia, (2) etiology of spontaneous tachycardia, (3) resting heart rate, (4) autonomic state, (5) electrophysiologic properties of the arrhythmia substrate, (6) autonomic response to pacing or the administration of drugs, and (7) hemodynamic and ischemic consequences of pacing and drug administration. In our opinion a discussion on the value of PES in the study and treatment of life-threatening ventricular arrhythmias and the importance of the stimulation protocol should include three aspects: (1) What is the significance of different ventricular arrhythmias induced during PES and how do these arrhythmias relate to the “aggressiveness” of the protocol? (2) What then is the most effective, safest, and least time-consuming protocol in relation to the clinical problem? (3) What implications do these considerations have for the use of PES in selecting antiarrhythmic treatment?

The significance of different ventricular arrhythmias induced during PES and their relationship to the aggressiveness of the PES protocol

Our definitions of the different ventricular arrhythmias that can be induced during PES are as follows: Sustained arrhythmias are those greater than 30 sec in duration or requiring an intervention for termination. Spontaneously occurring arrhythmias must require an intervention for termination to be considered sustained. Nonsustained arrhythmias are those 6 beats to 29 sec in duration. Spontaneous nonsustained ventricular tachycardia is considered to be that of 3 or more beats in duration. Monomorphic ventricular tachycardia is a ventricular rhythm faster than 100 beats/min with a regular rate and consistent beat-to-beat morphology. Polymorphic ventricular tachycardia is a ventricular tachycardia characterized by frequent changes in QRS morphology and/or axis, which must occur at least every 1 to 2 sec or every 6 beats. Ventricular fibrillation is a ventricular rhythm characterized by totally disorganized activity and no discernible QRS complexes on the surface electrocardiogram. It is important to realize that these definitions vary in the
different institutions performing PES. An induced arrhythmia is considered to be clinical when it is similar to the one occurring spontaneously.

**Sustained monomorphic ventricular tachycardia.** The observation that sustained monomorphic ventricular tachycardia could almost never be induced during PES in patients without a cardiac abnormality and could be induced in up to 95% of patients with spontaneous episodes of sustained monomorphic ventricular tachycardia led to the belief that the initiation of sustained monomorphic ventricular tachycardia during PES was a highly significant finding.

In patients with recurrent sustained monomorphic ventricular tachycardia the chance of reproducing the same arrhythmia in the catheterization laboratory is very high. With the use of one right ventricular stimulation site (the right ventricular apex) and two premature stimuli and at least two basic pacing rates, the incidence varies from 70% to 90% in patients with ventricular tachycardia occurring late (more than 5 weeks) after myocardial infarction.

Adding a third extrastimulus to the pacing protocol increases the rate of induction of the clinically documented arrhythmia by 12% to 24%. Stimulation in the right ventricular outflow tract in addition to that from the usual site (the apex of the right ventricle) and pacing in the left ventricle have been described to lead to a further increase in rate of induction of ventricular tachycardia. The use of isoproterenol will facilitate the induction of ventricular tachycardia in those patients in whom the arrhythmia is related to exercise or emotions.

Recently we reported that a stimulation protocol using a single right ventricular stimulation site (the apex), three basic pacing rates, and a maximum of three extrastimuli induced the clinically documented arrhythmia in 93% of patients with recurrent sustained monomorphic ventricular tachycardia after myocardial infarction. Such a protocol can be performed in less than 1 hr. Increasing the stimulus strength of the premature beat to 20 mA or changing the stimulation site from the right ventricular apex to the outflow tract did not result in a higher incidence of induction of tachycardia than did the previously described protocol.

The ability to induce the clinically occurring sustained monomorphic ventricular tachycardia depends on the cause of the arrhythmia. The arrhythmia can be initiated in close to 100% of patients with an old myocardial infarction, 75% to 90% of patients with idiopathic ventricular tachycardia, and 50% to 60% of patients with cardiomyopathy or prolapse of the mitral valve.

Induction of sustained monomorphic ventricular tachycardia has been accepted as indicative of the presence of an arrhythmia substrate or pathway. The demonstration of such a situation in the survivor of myocardial infarction has been suggested as an independent marker of increased risk of sudden (arrhythmic) cardiac death.

The problem is, however, that in our experience, using the protocol mentioned, the initiation of sustained monomorphic ventricular tachycardia is nearly as common in patients resuscitated from sudden death as in patients after myocardial infarction who never suffered from life-threatening ventricular arrhythmias (60% vs 45%). When only two ventricular premature depolarizations were used the rates of induction of sustained monomorphic ventricular tachycardia were 45% and 22%, respectively. Typically, and in contrast to the patient with clinically documented sustained monomorphic ventricular tachycardia, in these two groups of patients the monomorphic ventricular tachycardia is usually fast, poorly tolerated, and frequently deteriorates into ventricular fibrillation. While the work of the group of Richards et al. indicates that induction of this arrhythmia carries a poor prognosis in the infarct survivor, this could not be confirmed by other groups, including our own. This suggests to us that the induction of monomorphic sustained ventricular tachycardia in the arrhythmia-free survivor of infarct could be a nonspecific finding. Therefore, although initiation of such an arrhythmia in patients who have survived an episode of sudden death might reflect what happened clinically, since most survivors of sudden death have extensive coronary artery disease and 40% have had a previous myocardial infarction, one has to consider the possibility of a nonspecific event. The question of whether an event is specific or not cannot usually be answered because multiple-lead documentation of the arrhythmic event at the time of an episode of sudden death is usually not available and therefore comparison with the arrhythmia induced by PES is impossible.

**Monomorphic nonsustained ventricular tachycardia.** It is extremely uncommon to induce nonsustained monomorphic ventricular tachycardia in patients without structural heart disease and who have had no documented ventricular arrhythmias. Ten years ago we found that the clinical arrhythmia could be induced by pacing in only 8% of patients with documented nonsustained monomorphic ventricular tachycardia but no heart disease. Recently Buxton et al. found a higher induction rate in patients with documented monomorphic nonsustained ventricular tachycardia and corro-
nary artery disease than in patients with idiopathic ventricular tachycardia (83% vs 30%). Use of isoproterenol increased the rate of induction in the group with idiopathic ventricular tachycardia.

Our group found that shortly after myocardial infarction nonsustained monomorphic ventricular tachycardia could be initiated in 20% of patients,\textsuperscript{11} regardless of the clinical occurrence of this arrhythmia. The arrhythmia could be induced in 14% of patients with one or two extrastimuli. These observations suggest that one should question the use of induction of a nonsustained ventricular tachycardia (from 3 beats to more than 10 sec) as an end point for assessing antiarhythmic therapy or identification of risk for subsequent development of ventricular arrhythmias.\textsuperscript{13} We conclude that the significance of induction of nonsustained monomorphic ventricular tachycardia is presently unknown.

**Polymorphic ventricular tachycardia.** Polymorphic ventricular tachycardia is the most frequent ventricular arrhythmia initiated by PES in patients without spontaneous sustained arrhythmias or structural heart disease and the incidence of this arrhythmia increases with the number of extrastimuli used in the stimulation protocol.\textsuperscript{3,14} This suggests that polymorphic ventricular tachycardia is a "non-specific response to aggressive stimulation protocols."\textsuperscript{14}

Sustained polymorphic ventricular tachycardia is induced more frequently in patients resuscitated from sudden death than in those presenting with sustained ventricular tachycardia without cardiac arrest, suggesting that it may be a precursor of ventricular fibrillation. The initiation of nonsustained polymorphic ventricular tachycardia has also been interpreted to be indicative of a greater risk of ventricular fibrillation and sudden death.

We recently compared the incidence of inducible polymorphic ventricular tachycardia in 32 patients without structural heart disease who were evaluated for suspected supraventricular arrhythmias with that in 36 patients who had spontaneous sustained ventricular tachycardia or ventricular fibrillation more than 10 days after myocardial infarction.\textsuperscript{15} We found no difference between the normal subjects and the patients with previous myocardial infarction with respect to the incidence of greater than 5 beats of polymorphic ventricular tachycardia when ventricular pacing protocols up to the step including three extrastimuli delivered at a cycle length of 600 msec were used. The cumulative risk of inducing this arrhythmia with up to two extrastimuli during sinus rhythm and ventricular pacing at cycle lengths of 600, 500, and 430 msec was 38% in the normal subjects and 51% in the myocardial infarction group (p = NS).

We therefore conclude that the initiation of polymorphic ventricular tachycardia per se during PES is a nonspecific finding. Its incidence increases with the use of more aggressive stimulation protocols. Polymorphic ventricular tachycardia can, however, initiate a sustained monomorphic ventricular tachycardia and therefore be the initiating mechanism of a clinically significant arrhythmia. In a consecutive series of 26 patients with clinically documented sustained monomorphic ventricular tachycardia we found that during PES polymorphic ventricular tachycardia preceded the monomorphic type in 19%.\textsuperscript{15}

**Ventricular fibrillation.** Ventricular fibrillation can be induced during PES in patients with normal hearts, those with abnormal hearts without documentation of ventricular arrhythmias, those with abnormal hearts and documented ventricular arrhythmias, and in patients resuscitated from sudden death.\textsuperscript{5,13} The number of premature ventricular stimuli required to induce ventricular fibrillation in the normal heart is usually higher than that required in the abnormal heart.\textsuperscript{5} In view of the overlap between the two groups, however, induction of ventricular fibrillation should in our opinion be considered an aspecific finding. The incidence of ventricular fibrillation induction increases with use of more aggressive stimulation protocols.

In patients with coronary heart disease we found no differences in the incidence of induction of ventricular fibrillation in patients with 3-week-old myocardial infarctions without spontaneous ventricular arrhythmias, patients with 3-week-old myocardial infarctions and documented nonsustained monomorphic ventricular tachycardia, patients suffering from clinically documented sustained monomorphic ventricular tachycardia after myocardial infarction, and patients with coronary heart disease resuscitated from sudden death.\textsuperscript{11} These findings stress again the nonspecificity of induction of ventricular fibrillation.

**What is the proper stimulation protocol?**

PES is used in different categories of patients with proven or suspected ventricular arrhythmias. Since different protocols are used in different institutions and no unanimity of opinion exists as to the correct one to use to facilitate comparison, we favor presentation of the results of PES in the way shown in figure 1, which is similar to a survival analysis curve. A display of results in the way shown in this figure can be used to (1) analyze the sensitivity of different programmed stimulation protocols, (2) compare modes of induction.
in different patient populations when the same protocol is used (as illustrated in figure 1), (3) refine programmed stimulation protocols in relation to type and cause of ventricular tachycardia, (4) assess significance of induced arrhythmias in relation to mode of induction, and (5) assess changes in inducibility pattern before and after drug treatment.

The patient with a documented sustained monomorphic ventricular tachycardia. In accordance with the findings with regard to monomorphic ventricular tachycardia that we discussed above, we believe that to reproduce the arrhythmia in patients with documented sustained monomorphic ventricular tachycardia, right ventricular apical stimulation using one site, three basic pacing rates, and a maximum of three extrastimuli is usually sufficient. Stimulation from another right ventricular site or the left ventricle is indicated only in the rare patient in whom this stimulation protocol does not result in initiation of the clinical arrhythmia and in whom endocavitary mapping is essential for subsequent surgical treatment.

The patient resuscitated from sudden death. Holter recordings have shown that most episodes of sudden death are the result of ventricular fibrillation. In patients in whom no acute ischemia is the underlying mechanism ventricular tachycardia frequently precedes fibrillation. Unfortunately, in these patients multiple-lead electrocardiographic documentation of QRS configuration of this ventricular tachycardia is not available. Therefore, determination of the end point of the stimulation study becomes difficult. Initiation of a monomorphic sustained ventricular tachycardia, which is frequently observed during PES in the patient resuscitated outside hospital, indicates that the substrate for sustained ventricular reentry is present.

In a recent study we found that in 60% of patients resuscitated from sudden death more than 3 weeks after a myocardial infarction a monomorphic ventricular tachycardia could be initiated. Typically, and in contrast to the patient coming to the hospital with sustained monomorphic ventricular tachycardia, the arrhythmia in the patients we studied was fast and frequently required cardioversion because of hemodynamic compromise or deterioration into ventricular fibrillation. As already discussed, with the use of the same PES protocol the same arrhythmia can be induced in 45% of patients who have survived acute myocardial infarction but have never had an episode of a life-threatening ventricular arrhythmia.

In 20% to 40% of patients resuscitated outside the hospital no life-threatening ventricular arrhythmias can be induced by PES. In these patients other causes for their fatal arrhythmias, such as ischemia, electrolyte abnormalities, the administration of antiarrhythmic drugs, have to be identified and, when possible, corrected. This allows effective long-term management.

We conclude that in patients resuscitated from sudden death a rapid ventricular tachycardia resulting in severe hemodynamic changes or deteriorating into ventricular fibrillation can frequently be initiated with the pacing protocol described above for patients with documented sustained monomorphic ventricular tachycardia. The hemodynamic consequences of the arrhythmia initiated by this method usually do not allow endocardial mapping, so that PES is not helpful in
localizing the site of origin of the arrhythmia under these conditions. Initiation of ventricular fibrillation by PES is in itself a nonspecific finding.

The patient with short-lasting ventricular tachycardia. The purpose of PES is to induce the clinically occurring arrhythmia. This requires electrocardiographic registration of the arrhythmia in several simultaneously recorded leads both before and during PES to document their similarity. Proving similarity of polymorphic ventricular tachycardias presents a formidable problem. Also, as discussed above, initiation of a non-sustained polymorphic ventricular tachycardia during PES is common, even in normal hearts. We do not believe, therefore, that PES is useful in patients with polymorphic ventricular tachycardia.

Initiation of clinically documented nonsustained monomorphic ventricular tachycardia seems to be more common in patients with coronary heart disease than in those without structural cardiac abnormalities. Therefore, PES is of dubious or no value in patients with nonstained polymorphic ventricular tachycardia and of questionable (cause-related) value in those with the nonstained monomorphic type.

The patient with syncope. Syncope of cardiovascular origin can be related to bradycardia or tachycardia. In view of the previously discussed observations during PES in patients without documented ventricular arrhythmias, we believe that initiation of nonstained polymorphic ventricular tachycardia or ventricular fibrillation is of no diagnostic value. Only when sustained ventricular tachycardia is induced can a causal relation to syncope be surmized and antiarrhythmic therapy instituted. The PES protocol should, in patients being evaluated because of syncope, not only consist of the steps mentioned above for patients with monomorphic ventricular tachycardia, but should also include steps to exclude the possibility of disease of the sinus node and the atioventricular conduction system.

Identification of the patient at high risk of sudden death after myocardial infarction

It has been suggested that results of PES studies are independent markers in the recognition of infarct survivors at risk of dying suddenly. The induction of ventricular tachycardia of 10 sec or more was found to be related to an important increase in arrhythmic death in the first year after myocardial infarction. However, there is no unanimous opinion about the value of PES in identifying those at high risk of sudden death after myocardial infarction.

Marchlinski et al., using up to two extrastimuli, induced sustained monomorphic ventricular tachycardia 2 to 8 weeks after myocardial infarction in 13% of 40 patients, none of whom subsequently died suddenly or developed sustained ventricular tachycardia over a mean follow-up of 18 months. Using up to three extrastimuli, we have found that a sustained monomorphic ventricular tachycardia could be induced in 45% of patients with previous myocardial infarction who had had no spontaneous episodes of sustained ventricular tachycardia. None of these patients died during a mean follow-up of 6 months.

Since the risk of sudden death after hospital discharge in the first year after myocardial infarction was found to be less than 10% in two recent multicenter studies, the initiation of a sustained monomorphic ventricular tachycardia must be of limited prognostic significance in many patients who are not suffering from spontaneous occurrences of this arrhythmia before undergoing PES.

The value of PES in the selection of antiarrhythmic therapy. The possibility of reproducible initiation and termination of clinical arrhythmias in patients with recurrent sustained ventricular tachycardia by PES led to the use of this technique for rational selection of antiarrhythmic drug therapy. If one drug does not prevent initiation of ventricular tachycardia during PES, the effect of the next drug is studied. The protocol followed during serial drug testing in these patients is shown in figure 2. When such an approach is used patients with true- and false-negative test results after taking the drug are not identified. The value of this method, however, is supported by reports indicating that identification and use of a drug that prevents induction of ventricular tachycardia results in a much better prognosis than if no such drug can be found. Unfortunately, a drug that prevents induction of ventricular tachycardia can be identified in only 25% of patients with documented life-threatening ventricular arrhythmias, and this percentage will be even lower when aggressive stimulation protocols or left ventricular stimulation is used. Also, with newer antiarrhythmic agents like amiodarone and propafenone the drug may be clinically effective, but fail to prevent induction of ventricular tachycardia during PES. This finding led to the acceptance of other indicators during PES pointing to a beneficial effect of a drug such as slowing in rate of the induced tachycardia, change from sustained to nonsustained tachycardia, or the need for a more aggressive PES protocol to initiate the arrhythmia.

We believe that the predictive value of PES in the patient with documented sustained monomorphic ventricular tachycardia can be summed up as follows:
Excellent: prevention of induction of tachycardia during PES
Satisfactory: induced tachycardia has slower rate or is self-terminating
Questionable: more "aggressive" PES protocol required to initiate tachycardia
Unknown: no changes in induction of tachycardia

Taking into consideration our discussion of the significance of ventricular arrhythmias induced by PES, it seems clear that it is not acceptable to base therapeutic decisions on the effect of antiarrhythmic drugs on an induced arrhythmic response such as polymorphic ventricular tachycardia or ventricular fibrillation.

To find answers to the questions raised, especially in regard to the newer antiarrhythmic drugs, we favor the approach shown in figure 3. This will not only allow us to obtain information on the effectiveness of a drug for the prevention of the tachycardia initiating premature depolarization, but also will give us an idea about the true value of PES in the selection of antiarrhythmic therapy.

**Conclusions**

PES is being used increasingly in the management of patients with proven or suspected ventricular arrhythmias. In our opinion, however, only the induction of clinically documented sustained monomorphic ventricular tachycardia has convincingly been demonstrated to be a significant finding during PES, so that only in patients with this disorder can the value of PES for selecting antiarrhythmic therapy be tested.

Although one is tempted to accept the induction of sustained monomorphic ventricular tachycardia as an important finding in the patient with syncope, cardiac arrest, or myocardial infarction, our observations indicate that in diseased hearts such an arrhythmia may be induced but may never become clinically manifest. Further study is required to inform us about the significance of induction of sustained monomorphic ventricular tachycardia in the patient without documented arrhythmias of this type. As pointed out, no convincing evidence has been presented that the induction of nonsustained ventricular tachycardia, polymorphic ventricular tachycardia, or ventricular fibrillation is a reliable indicator of risk of arrhythmic death or a dependable method for evaluating efficacy of therapy with antiarrhythmic agents. We cannot exclude the possibility that refinements in characterization of the ventricular arrhythmias induced may lead to different conclusions.

The stimulation protocol used should be able to demonstrate the presence or absence of the substrate for sustained monomorphic ventricular tachycardia. A single right ventricular stimulation site, three basic pacing rates, and up to three extrastimuli can generally
be considered adequate. More study is needed, however, to reduce the steps necessary for the stimulation procedure. A reduction in time period of the investigation will have obvious financial benefits and will make PES more comfortable and possibly safer for patient and investigator.

Prevention of induction of ventricular tachycardia after drug administration is a useful therapeutic finding. Persistence of the arrhythmia after antiarrhythmic therapy, however, does not rule out clinical effectiveness of the drug.

References

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