NASPE HISTORY SERIES

Electrophysiology of Ventricular Tachycardia: A Historical Perspective
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Introduction
The purpose of this article was to review the history of the use of programed electrical stimulation (PES) and endocardial catheter mapping to evaluate the mechanisms of ventricular tachycardias (VTs) and develop therapy to treat them. While most of the information initially regarding tachycardia mechanism came from studies of VT in the setting of coronary artery disease, subsequent studies of VT in a variety of other conditions revealed mechanisms other than reentry were operative. The methods used to define mechanisms were then used to develop therapy for these arrhythmias. As such, this article is divided into two parts, Mechanisms and Therapy (Tables I and II)

Mechanisms (Table III)

Mode of Initiation
The electrophysiological evaluation of VT began in 1972 when Wellens et al.1 described five patients in whom VT could be initiated and terminated by properly timed extrastimuli (Fig. 1) suggesting a reentrant mechanism. This study led to the recognition that PES could be used to study VT safely. Shortly thereafter, these investigators studied patients with VT in acute myocardial infarction (24 hours) and demonstrated that such VTs could not be reproducibly initiated.2 This led them to suggest that the VT mechanism in acute infarction was different from that in chronic infarction. These investigators went further by suggesting that during induction an inverse relationship of the coupling of the extrastimulus used to initiate the VT and the first beat of the VT meant that slow conduction was necessary to generate the tachycardia, supporting reentry as the underlying mechanism. The site of reentry was uncertain, but the specialized conducting system was suggested as a possible site.3 These investigators also noted that occasionally different sites of stimulation were required for initiation and termination. The field rapidly advanced in the late 70s when Josephson and his colleagues at the University of Pennsylvania helped further characterize VT by introducing a more aggressive, stimulation protocol that included up to three extrastimuli on a routine basis, multiple drive cycle lengths (including sinus rhythm, and paced cycle lengths at 600 and 400, and others if needed), and multiple sites of stimulation from the right (RV) and left ventricles.4-11 These investigators demonstrated that induction of monomorphic VT was a reproducible and a specific response to PES, while the initiation of ventricular fibrillation and polymorphic VT was nonspecific. These conclusions were supported by subsequent studies.12-21 All these studies suggested that the optimal method to achieve maximum sensitivity and specificity for VT induction using PES was a protocol incorporating three extrastimuli from the RV apex and outflow tract, during at least 2 drive cycle lengths (600 and 400 ms).

The presenting arrhythmia and underlying pathological state also markedly influenced the arrhythmia induced by PES. In the setting of prior infarction, nearly 95% of patients who presented with monomorphic sustained VT could have their tachycardia reproduced by PES. In patients with coronary artery disease presenting with cardiac arrest, only 55% had a monomorphic VT induced. In patients with prior infarction, a low ejection fraction, but only nonsustained VT, only 35% had monomorphic VT induced. This latter observation22-24 was the basis for the Multicenter Unsustained Tachycardia Trial (MUSTT) study for management of nonsustained VT. The induction of ventricular fibrillation or polymorphic VT was considered nonspecific since they could be induced in patients without heart disease. Poll et al.25,26 also demonstrated that if monomorphic VT was the presenting arrhythmia, it was reproducibly initiated, regardless of the underlying pathology.

In patients with coronary artery disease the presenting arrhythmia influenced the number of extrastimuli required to initiate the arrhythmia. Two thirds of the patients with tolerated monomorphic VT could have their VT replicated by one or two extrastimuli, whereas those that presented with cardiac arrest required two or three extrastimuli in 66% of the cases.11 It was rare to have a cardiac arrest patient have their arrhythmia replicated by a single extrastimulus, while it was not unusual in those presenting with a slow tolerated rhythm.

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### Table I.

**History of Electrophysiology: Mechanisms of Ventricular Tachyarrhythmias**

- 1972—first demonstration of reproducible initiation and termination of VT
- 1974–78—further characterization of VT, by use of aggressive RV and LV stimulation
- 1978–85—sensitivity, specificity, and reproducibility of PES
- 1978–86—development of endocardial mapping to define origin, ECG correlates of sites of origin, and role of fragmented electrograms to define electrophysiological substrate of VT, NSVT, and cardiac arrest in CAD.
- 1983–88—description of pathologic correlates of fractionated electrograms; i.e., separation of viable myocytes by scar
- 1980–88—use of PES and pharmacologic perturbations to understand the mechanisms of cardiac arrest and NSVT
- 1981–93—entrainment and resetting of VT, implications for mechanism and therapy (ATP and ablation)

**ATP** = adenosine triphosphate; **CAD** = coronary artery disease; **ECG** = electrocardiographic; **LV** = left ventricular; **RV** = right ventricular; **NSVT** = nonsustained ventricular tachycardia; **PES** = programmed electrical stimulation; **VT** = ventricular tachycardia.

### Table II.

**History of Electrophysiology: Therapy of Ventricular Tachyarrhythmias**

- 1977–1986—use of PES to guide antiarrhythmic therapy for VT, cardiac arrest, and NSVT in CAD; concern in CM
- 1977–85—antitachycardia pacing for VT
- 1978–85—development of surgery for VT
- 1980—development of the implantable defibrillator
- 1984–93—development of catheter ablation for VT; fulguration to RF
- 1985–91—mechanism of antiarrhythmic drug action on VT

**CAD** = coronary artery disease; **CM** = cardiomyopathy; **NSVT** = nonsustained ventricular tachycardia; **PES** = programmed electrical stimulation; **RF** = radiofrequency; **VT** = ventricular tachycardia.

An additional RV or LV stimulation site was required more often in patients presenting with cardiac arrest. Moreover, VTs induced by comparable extrastimuli were faster in patients presenting with cardiac arrest than in those with tolerated VT. By the early to mid-1980s, a stimulation protocol including triple extrastimuli from two sites in the RV at two different cycle lengths became the minimum standard in the study of ventricular tachyarrhythmias.

The role of conduction delay in the genesis of arrhythmias was further characterized by the Philadelphia group after Wellens’ initial suggestion of reentry by noting an inverse relationship of coupling interval of the initiating extrastimulus and the onset of the tachycardia. They found an inverse relationship between the coupling interval of the initiating impulse and the time to the onset of the tachycardia in a larger number of patients. These investigators also suggested that site specificity for induction also supported reentry, since induced rhythms due to triggered activity would not depend on the direction of the stimulated wavefront. They further suggested that the PES should be done with a single extrastimulus at each drive cycle length, from each site, before more aggressive therapy was used. Only in this manner could one assess the relative ease of induction from any given site. They noted that when PES was used in this manner, 25% of patients could demonstrate a differential ease of initiation among different sites in the ventricle.

An example of VT that was inducible with a single extrastimulus from the RV outflow tract, but not inducible with three extrastimuli at the RV apex is shown in Figure 2.

A quantum leap in the understanding of the mechanisms of VT came with the development of catheter endocardial mapping of the human left ventricle by Josephson et al. in the mid-1970s. These investigators demonstrated that one could safely and reproducibly map the endocardium of the LV and RV. They subsequently defined normal, abnormal, fractionated, and late electrograms using amplitude, duration, and the ratio of amplitude and duration measurements (Fig. 3). They related the electrogram characteristics to the
presence of arrhythmias and the underlying pathology in patients with coronary artery disease and cardiomyopathy. Patients with inducible sustained monomorphic VT had more abnormalities of conduction in terms of number and percentage of the endocardium with abnormal, late, and fractionated electrograms than patients with coronary disease and no inducible arrhythmia or those without coronary disease. The abnormal electrograms were correlated with the underlying pathology in an elegant study by Fenoglio et al. who identified the underlying pathology of arrhythmogenic tissue from pieces of endocardium removed at the time of arrhythmia surgery (Fig. 3). This was the first time that abnormal and fractioned electrograms, a hallmark of arrhythmogenic tissue, was defined pathologically by islands of viable myocardial fibers inbedded in scar tissue following infarction. Later studies confirmed the relationship of this pathologic substrate with abnormal electrograms and potential pathways of reentry. Early studies suggested that the epicardium was often the site of fractionated and late potentials in patients with cardiomyopathy; however, Cassidy et al. demonstrated that patients with idiopathic dilated cardiomyopathies (IDCMs) presenting with sustained monomorphic VT had as many abnormal electrograms as patients with coronary disease, but fewer fractionated and late signals. Recent studies using three-dimensional electroanatomic mapping showed almost as many endocardial as epicardial abnormal electrograms in patients with IDCM presenting with monomorphic VT. Thus, patients with IDCM can have endocardial epicardial or transmural reentrant circuits.

The Penn group was able to map VTs in patients with and without coronary disease. They demonstrated that in coronary disease, 85% of VTs had their “site of origin” (the earliest diastolic activity) located in sites with abnormal, fractionated, or late electrograms. They observed that while this arrhythmogenic substrate could be identified, one could not predict the site of origin from the substrate. They did note that late electrical activity during sinus rhythm was often associated with presystolic, diastolic activity during VT. They demonstrated that VT in the setting of a prior myocardial infarction almost uniformly (≈96%) arose from the endocardial surfaces of the LV, while in patients with IDCM, VT could arise from either chamber of the heart. Idiopathic tachycardias could arise from either chamber as well. In addition, mapping helped characterize certain QRS morphologic patterns with “sites of origin.” These investigators demonstrated for the first time that VT originating in the LV could have a left bundle branch block (LBBB) morphology. They demonstrated that the global activation of the RV and LV determined the morphology, not the specific site of origin. The activation sequence of the ventricles could be markedly influenced by prior scar. The mapping techniques developed during this period have been refined and form the basis for all ablative therapy currently being used to manage tolerated and nontolerated VTs (see subsequent paragraphs on ablation).

Response to Stimulation During VT

While analyzing the modes of initiation of VT yielded useful indirect evidence for arrhythmia
mechanism (reentry, triggered activity, automaticity), the response to PES during the tachycardia provided more diagnostic information. Waldo et al.\textsuperscript{45,46} were the first to demonstrate the phenomenon of entrainment of VT by overdrive pacing from the RV apex. These investigators described entrainment as the demonstration of fixed fusion of the paced QRS and the tachycardia at any paced cycle length, and progressive fusion at decreasing paced cycle lengths (QRS becomes more like a pure paced QRS), and at each paced cycle length the tachycardia resuming upon cessation of pacing. The demonstration of fusion during pacing was diagnostic of reentrant mechanism because it implied that two wavefronts could exist at the same time on the heart with an interaction between the paced impulse and the VT. This implies an entrance and an exit to a reentrant VT circuit. These and other investigators also demonstrated that VT could be entrained by atrial pacing.\textsuperscript{46,47} The appearance of electrocardiographic (ECG) fusion was dependent upon the site of pacing.\textsuperscript{48} The closer the site of pacing to the “exit” site of the circuit, the less likely fusion would be seen since the paced QRS would look similar to the QRS of the VT, or the paced QRS would capture the exit site not allowing any expression of the VT to be manifest on the surface QRS.

Almendral and colleagues,\textsuperscript{49–53} in a series of elegant studies, analyzed the response of a VT to a single extrastimulus. The interaction of a single extrastimulus with a tachycardia was termed resetting, and its presence implied the presence of an excitable gap in the tachycardia circuit. These investigators demonstrated that resetting could qualitatively and quantitatively characterize the extent of the temporal excitable gap of a VT circuit. Resetting responses demonstrating identical return

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**Table III.**

Mechanisms of Ventricular Tachycardia

- Reproducible initiation
  - Relationship of initiation to conduction abnormalities and/or heterogeneity of recovery
  - Relationship of VES coupling interval or PCL on interval to onset of VT
  - Site specificity for induction
  - Effect of antiarrhythmic agents or isoproterenol on induction of VT
- Effects of stimulation during VT
  - Resetting, entrainment, or termination with fusion
  - Effects of overdrive pacing or VES on return cycle
  - Site specificity for termination
- Effects of antiarrhythmic agents
- Mapping techniques for successful ablation

PCL = paced cycle length; VES = ventricular extrastimuli; VT = ventricular tachycardia.
cycles over a range of coupling intervals (>30 ms) defined a fully excitable gap. Increasing return cycles mixed (flat plus increasing) responses were also observed (Fig. 4). The excitable gap was 15–35% of the VT cycle length. Entrainment, unlike resetting, does not characterize the tachycardia circuit per se, but evaluates the effects of resetting a reset circuit. As a result, entrainment was often associated with what appeared to be decremental conduction in the VT circuit. Callans et al. 54 clarified the differences between resetting and entrainment. With resetting only a single extrastimulus interacts with the VT circuit. If stimulation at the exact same coupling interval that resets the VT is continued, subsequent extrastimuli interact with the previously reset circuit and conduction delay could occur until a longer, fixed, stable conduction time was established. The extent of the excitable gap, established by resetting, determined if entrainment, at any particular cycle length, would produce decremental conduction. Nevertheless, resetting with fusion or entrainment with fusion on the surface ECG or an intracardiac (LV) electrogram was diagnostic of a reentrant mechanism. Overdrive pacing of tachycardias due to triggered activity never demonstrates fixed fusion; the response to overdrive pacing usually is one of acceleration of the tachycardia, at least for the initial beats, and a shortening of the return cycle.

Another feature suggestive of reentry is site specificity for termination. Since triggered activity is a focal event, depolarization of the cell responsible for this mechanism is all that is required for termination, independent of the direction stimulated impulse. However, the wavefront of activation may be important if there is an anatomic circuit with separate entrance and exit sites.

Figure 4. Characterization of the excitable gap in the ventricular tachycardia (VT) circuit by resetting. Schema of mechanism of resetting and types of responses (left). Analogue recordings of resetting of VT with a fully excitable gap of at least 100 ms. See text for explanation. (Adapted from reference 12.)
Response to Antiarrhythmic Agents

The effects of antiarrhythmic agents were also used to sort out the underlying mechanisms. Most importantly was the recognition that triggered activity due to delayed afterdepolarizations most often occurred in response to catecholamines. This was due to enhanced adenylcyclase activity, which subsequently led to increased intracellular calcium, which then triggered a nonspecific transient inward current carried by sodium. This phenomenon would result in afterdepolarizations leading to tachycardia. Lerman et al. were the first to demonstrate that adenosine was able to terminate such delayed afterdepolarizations. Vagal maneuvers were also effective. The rhythm that most commonly produced by this mechanism was RV outflow tract VT, which is frequently induced by exercise. β-Blockers and verapamil could also be used to terminate such afterdepolarizations, but this response is not specific for triggered activity.

A diagnostically and clinically useful response to antiarrhythmic drugs is the conversion of polymorphic VT to monomorphic VT. This was first noted by Horowitz et al. who demonstrated that nonsustained polymorphic VT in patients with coronary artery disease could be changed to a uniform VT with morphology similar to one of the complexes seen in the polymorphic run by a class I antiarrhythmic. This was sequentially confirmed and evaluated in more detail by Buxton et al. who demonstrated that this phenomenon was specific for polymorphic VT associated with infarction. These investigators suggested that this finding reflected an insufficient substrate of slow conduction that was increased by the drug, resulting in stabilized reentry. The change from polymorphic VT to monomorphic VT was not seen in cardiomyopathies or in normal patients in whom polymorphic VTs are considered to be a nonspecific response to PES. Confirmation of the clinical relevance of this observation was the demonstration that map-guided operation of drug induced uniform VTs in patients who presented with syncope or cardiac arrest prevented recurrent syncope or cardiac arrest (unpublished observations).

Mapping of VTs

As noted above, endocardial catheter mapping not only provided information allowing for the understanding of the underlying pathophysiological substrate of VT in coronary artery disease, but it also enabled investigators to localize specific arrhythmogenic areas that could be ablated by surgical or catheter-based techniques. Activation mapping, while critically important for localizing a focal mechanism of VT by nothing the earliest site of impulse formation using bipolar and/or unipolar recordings, was just as valuable in localizing critical components of a reentrant circuit. In fact, despite the fact that during reentrant excitation activation is continuous, the earliest recorded sites of electrical activity in inducible VT due to coronary artery disease (reentrant VT) were recorded earlier in diastole than sites of origin of “focal” (triggered or automatic) VT. Sites at which mid-diastolic potentials or continuous activity were recorded were considered sites potentially related to the reentrant circuit. Proof that these diastolic sites were within the reentrant circuit and not dead-end pathways was required. The demonstration of a fixed relationship of the diastolic electrogram to subsequent QRS complexes in response to spontaneous or pacing induced changes in the VT cycle length suggested that these diastolic potentials were in or attached to a diastolic pathway that is orthodromically activated during VT. Occasionally, mid-diastolic potentials disappear, proving their lack of importance to the VT mechanism. Occasionally, complete reentrant circuits could be demonstrated in the operating room or using electroanatomic mapping, but this was uncommon.

In the absence of demonstrating reentrant excitation, another method was needed to identify critical areas of reentrant circuit that could ultimately be targeted for ablative procedure (i.e., the critical central common pathway). The concept of entrainment mapping was developed initially in the mid-1980s by Almendral et al. who demonstrated that diastolic potentials that could be orthodromically activated were in or attached to the central pathway in the circuit, and that entrainment from the exit site or within the circuit could lead to an identical QRS as a VT itself. Return cycles could only equal the VT cycle length if pacing was produced from the circuit itself. While use of the above principals of mapping was suggested to the investigators of the Catheter Ablation Registry, they were rarely applied (unpublished observations). It was not until several years later that the careful studies of Stevenson et al. presented the concept in a more understandable way. The reentrant circuit was described as being anatomically created and composed of a critical protected area through which the impulse conducted in diastole. This had been referred to as the central common pathway in experimental models. Entrainment of VT from this critical central common pathway was associated with an identical QRS as the tachycardia, a stimulus to QRS approximating that of the electrogram to QRS, a return cycle equal to the tachycardia cycle length. Entrainment from the reentrant circuit outside the

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isthmus (outer loop) would produce a different QRS than the tachycardia QRS, but an identical return cycle as a tachycardia cycle length. While pacing outside the circuit (either far from the circuit or from a dead-end pathway attached to the circuit) would produce return cycle greater than that of the tachycardia cycle length. Other investigators 75–77 used slightly different methodologies with different tolerances and definitions of “identical QRS,” equivalent return cycles and stimulus at QRS intervals. Nevertheless, the use of concealed entrainment to identify critical sites in macroreentrant VT circuits became accepted.

Pacemapping was developed to localize the site of origin of a focal tachycardia. This technique was based on the hypothesis that an identical QRS induced by pacing would identify a site from which a spontaneous arrhythmia arose. Unfortunately, the area over which some of the morphologies could be reproduced was 1–4 cm². Thus, this technique has more often been used as a confirmation of activation mapping. Pacemapping was noted to be less valuable for macroreentrant VT related to infarction, since similar morphologies could be produced by pacing over a larger area, including sites that were outside the reentrant pathway. Pacing from the center of a diastolic isthmus during sinus rhythm generally produces a totally different morphology than during VT, since during sinus rhythm activation from the pacing site would be centrifugal resulting in orthodromic and antidromic activation through the isthmus, while during entrainment of VT activation would only be orthodromic.

Application of the different mapping techniques for different tachycardia mechanisms is described below under Ablative Procedures. Epicardial mapping has been introduced using similar methodologies to endocardial mapping described above.80–83 Epicardial origins of VT may be seen in 15% of cases of coronary disease (usually inferior infarction and in cardiomyopathies. Entrainment mapping may be useful in either condition). Epicardial mapping may also be useful for arrhythmias that are focal in origin, arising on the epicardium, particularly near or at the aortic and mitral annuli. An additional site of impulse formation may be in the aortic coronary sinuses or the pulmonary artery, both of which have muscle fibers extending onto them, which may be sources of focal arrhythmic activity.83–87

Application of Electrophysiological Studies and Developed Therapy for VT

Pharmacological Therapy

With the recognition that most VT, due to coronary artery disease could be reproducibly initiated and terminated, the concept of the use of PES to guide antiarrhythmic therapy evolved. Although the vast majority of the arrhythmias for which pharmacologic testing was used were related to prior infarction, patients with cardiomyopathies, particularly right ventricular dysplasia, and other disorders in which VT could be reproducibly initiated were also treated in this manner. The basic concept of this methodology was that the ability to initiate a tachycardia suggested that an arrhythmogenic substrate was present that enabled spontaneous or induced triggers to initiate sustained arrhythmias. The ability of a drug to prevent initiation of a tachycardia by PES was assumed to be an effect of that drug on the substrate that prevented it from enabling the occurrence of a sustained arrhythmia. Initial studies by Fisher et al.,88 Horowitz et al.,89–91 and Mason and Winkle92 demonstrated the feasibility of such drug testing with oral and/or intravenous (IV) agents in patients with monomorphic sustained VT. A variety of antiarrhythmic drugs were tried for several days to determine a drug that prevented initiation of VT. Ultimately, if a drug was successful in preventing VT acutely, following achievement of steady-state levels shown to be acutely effective, a repeat test was done. If the VT was shown to be noninducible, the patient was sent home on that day. This form of testing was also subsequently applied to patients presenting with cardiac arrest93 and nonsustained VT.22,94–99 While these studies suggested benefit to patients whose tachycardias were rendered noninducible, none of the trials were randomized and many were, in fact, a combination of prospective and retrospective data. Drug follow-up was short (12–20 months). However, in all studies there was a higher reoccurrence rate and/or mortality in those patients with persistently inducible ventricular tachyarrhythmias. In the absence of other options for therapy, such testing was accepted. With the advent of additional therapies like implantable cardioverter defibrillators (ICDs) and ablation (see below), the use of antiarrhythmic drugs and drug testing diminished despite the fact that the drugs were still administered and this was probably the best method to evaluate efficacy.

The usefulness of the electrophysiological studies was evaluated by the Electrophysiologic Stimulation versus Electrocardiographic Monitoring (ESVEM) study.100 This study tested the ability of PES or Holter monitoring to judge efficacy of class I antiarrhythmic agents or sotalol in preventing spontaneous occurrences of VT. This was a highly selected patient population in whom VT could be reproducibly initiated and in whom spontaneous ventricular ectopy was frequent enough to be evaluable by Holter monitor.
This population represents ~15% of patients with sustained VT. The results of ESVEM suggested that neither method was good, both having a 40% recurrence rate of VT in a year. This was nearly double the recurrence rate suggested by PES in nonrandomized trials.88–92,101–104 The study also suggested that sotalol was better than class I agents. Several criticisms arose with the analysis of this data. Two thirds of the patients had already failed class I agents and prior studies by Waxman et al.,105 suggested that if procainamide failed to prevent initiation of VT, other class I agents would also fail. This resulted in a significant bias toward benefit for sotalol. Moreover, patients who had been successfully treated with class I agents, however, were not included. In addition, a major limitation was an inadequate stimulation protocol used to test drug efficacy. Stimulation was never more aggressive than baseline, in terms of number of extrastimuli, and completion of a protocol of three ventricular extrastimuli was not even achieved at baseline if VT was induced with a lesser number of extrastimuli. The author has observed that a number of drugs increase the number of extrastimuli required for initiation of VT, but that this “increase in difficulty” is not associated with freedom from recurrence (104). Therefore, failing to test more aggressive stimulation protocols may have eliminated patients who normally would have been classified a failure, thereby implying PES was not an accurate method of assessing drug effectiveness. Despite these limitations, the use of PES to guide drug therapy was reduced to a minimum and other treatment modalities were used.

Antitachycardia Pacing (ATP) and ICDs

From 1977 through 1985 an active interest in ATP as a mode to treat VT was noted. This was natural consequence of the electrophysiological studies, which showed that most of these arrhythmias could be reproducibly terminated by PES. While increasing the number of stimuli from a single extrastimulus to bursts of rapid ventricular pacing increased the ability to terminate tachycardias from approximately 25% to 75%, an increasing incidence of acceleration of the tachycardia to a faster VT or ventricular fibrillation was noted (35%).106–108 Even VTs with rates >200 beats/min could be terminated by pacing 50% of the time; but the remainder required cardioversion. Thus, while a number of ATP modalities were developed for implantable devices, stand-alone ATP devices were never developed because acceleration of VT and/or degeneration of VT to ventricular fibrillation by antitachycardia pacing was too unsafe. It was obvious that defibrillation backup was needed. Fortunately, by 1980 Mirowski et al.109 developed and implanted an automatic ICD in humans. By the late 1980s, ICDs incorporated ATP and low energy cardioversion therapies and a variety of diagnostic features. The diminution in size of the device and incorporation of dual chamber capabilities in a pectoral implantable system has revolutionized the treatment of lethal ventricular arrhythmias. The ease and low morbidity of implantation, and nearly uniform success in terminating VT and ventricular fibrillation has made the ICD the most popular method of treating VT or ventricular fibrillation.

Ablative Procedures

In the hierarchy of therapy of ventricular tachyarrhythmias, prevention of the arrhythmia by preventing substrate formation (i.e., infarction) of destruction of the substrate by surgical or catheter ablation should be the highest goal. Termination of VTs by drugs or ATP or slowing of the arrhythmia to hemodynamic tolerance would be a second option, and rescue by cardioversion or defibrillation with an ICD should be the last goal. Despite the recognition that the goal should be to prevent the arrhythmia, ICDs have become the major form of therapy used. Nevertheless, the concept of ablative therapy of ventricular tachyarrhythmias to cure the arrhythmia evolved from early mapping studies in the mid-70s. A variety of surgical procedures were developed in the late 1970s that could be described as map-guided or visual or electrically determined substrate-guided.111–119 Guiraudon et al.111 developed the first technique, the encircling ventriculotomy for patients with VT due to coronary disease, but his procedure was rapidly discontinued due to the high mortality associated with interruption of blood supply to viable tissue. Shortly thereafter, Josephson et al.112 developed the technique of map-guide subendocardial resection which was based on their mapping techniques demonstrating that most ventricular tachyarrhythmias arose on the endocardial surface of the heart. These investigators ultimately operated on more than 300 patients with a high clinical success rate (92%) and an operative mortality of 15%.120 Mortality was due to pump failure, which was not surprising since these patients had severe LV dysfunction, and usually underwent simultaneous aneurysmectomy and coronary artery bypass grafting. In the Penn series the mean ejection fraction was 0.28, with 50% of patients having ejection fractions of <0.25, and 25% having ejection fractions <0.20. Nevertheless, their clinical success rate was remarkable. Nonmap-guided surgery involved modifications of Guiraudon’s encircling ventriculotomy. Removal or isolation of the entire scarred endocardium, diagnosed visually or the endocardium in which fragmented electrograms and late potentials were recorded,
by cryoablative therapy or subendocardial lesions were used by a number of individuals with a success rate in the 80% range. With the advent of the ICD, surgical therapy, a curative procedure that ameliorated ventricular dysfunction, coronary obstruction and the arrhythmia, became nearly extinct.121

**Catheter Ablation of VT in Coronary Disease**

In the mid-1980s catheter ablation for VT was developed using direct current (DC) energy.122,123 This subsequently has envolved over the past decade and a half, as we have seen the energy source changed from DC energy to radiofrequency energy. Newer energies are being evaluated at this time. Hemodynamically tolerated monomorphic VT associated with coronary artery disease can be successfully ablated using entrainment mapping techniques to define a critical isthmus through which the impulse must pass.69–72,74–76,124–127 The technique involves locating a mid-diastolic site and demonstrating that pacing at that site at a slightly faster rate than the VT produces: (1) an identical QRS as the VT (in all 12 ECG leads); (2) a stimulus-QRS approximately equal to the electrogram QRS (±10 ms); and (3) a return cycle equal to the VT cycle length ±10 ms.75 Other authors allow a tolerance of up to 30 ms69,74; this may be less specific. Entrainment from a site in the central common pathway of the reentrant circuit produces and exact 12-lead match. Pacing from outside the common pathway but still within the circuit (outer loop) would produce a fused QRS but a return cycle equal to the VT cycle length and a stimulus QRS equal to the electrogram QRS. If the pacing site is distant from the VT circuit, the paced QRS will differ from that of the VT, and the return site will exceed the VT cycle length. Pacing from a bystander site attached to the central pathway will produce a QRS identical to that of the VT but a longer stimulus QRS than the electrogram QRS and a longer return cycle than the VT cycle length. In the current experience, the vast majority of tolerated VTs can be terminated with a lesion at a single site using this technique, usually (75%) in less than 10 seconds (Fig. 5).73 Others have observed termination of VT by RF delivered at sites not meeting the criteria described above. This demonstrates some of the limitations of the techniques. Stimulation and recording may be from different electrodes than that delivering RF energy (distal electrode), and high current used for pacing may depolarize sites distant from the recording site. Other reasons for failure of ablation include an isthmus that is broader than the lesion made by the RF energy, intramural or epicardial locations, or the presence of a mural thrombus. Epicardial locations are suggested by more slurred and wider QRS. Epicardial mapping through a direct intrapericardial approach was pioneered by Sosa et al.80 and has been used to ablate such tachycardias.

It is unclear whether it is necessary to ablate all inducible (tolerated or nontolerated) VTs in such patients since the mortality from sudden cardiac death in patients presenting with tolerated VT is low (2–3%/year).125 In most series of VT ablation there is a ~70% success rate acutely with a recurrent rate of 10–40%, 69,73–76,126–128 These results depend on the accuracy of mapping, the number of tolerated VTs induced, and, perhaps, the extent of ablation. The shorter the time to VT termination, the higher the success rate for ablation of that VT. The efficacy of catheter ablation is unclear since results are rarely reported on an intention to treat basis. In a small series Callans et al.127 reported a 60% success rate on an intention to treat basis primarily due to access problems or failure to induce or adequately map tolerated VT.

The patient with untolerated VT and coronary artery disease is a particularly vexing problem. While mapping is possible using inotropic agents and/or an intraaortic balloon pump for support, there is now an active interest in using substrate mapping to guide ablation. This procedure is based on the ability of catheter mapping to identify and localize arrhythmogenic sites, which are characterized by abnormal, fractionated, and/or delayed potentials. It is now possible to accurately localize and quantify the extent of abnormal electrograms and scar tissue. Using the Carto electroanatomic mapping system ( Biosense Cordis),129,130 the voltage of electrograms from normal tissue exceeds 1.5 mV and that from scar tissue is defined in the author’s laboratory by ≤0.1 mV. The value for scar tissue is based on prior data from his laboratory (unpublished observations) that demonstrated amplitudes of <0.1 mV were associated with dense scar tissues seen at surgery and pathologically. Soejima et al.131 have used electrical inexcitability as a means to identify dense scar tissue. This correlates with electrogram amplitude and duration as demonstrated by Kienzle et al.132 He and his colleagues demonstrated a direct relationship of excitability and electrogram duration and an inverse relationship to electrogram amplitude. Using the electroanatomic mapping system one can identify dense scar. Of note, that when tolerated VTs are mapped and the central common pathways are identified, these sites correlate with scar tissue and late potentials. Pacemapping to identify a QRS comparable to the induced rapid tachycardia allows one to identify an exit point from the circuit. Linear lesions can be made from the border zone of infarction at the
Figure 5. Entrainment mapping to guide ablation of infarction related VT. Perfect entrainment map (upper right), return cycle and stimulus to QRS equal to spontaneous VT cycle length and electrogram (EGM) to QRS, respectively (lower left). Termination of VT with application of radiofrequency energy at this site (lower right). VT = ventricular tachycardia.

site of the best pacemap to the dense scar. The author and others have also targeted late potentials to guide ablation. Another approach is to eliminate all viable channels between dense scars that could potentially develop into isthmuses of reentrant circuits. Scars can be connected by radiofrequency lesions eliminating these channels. The pathophysiological basis of substrate-guided RF ablation comes 25 years following its use during nonmap-guided surgery for VT. The success rate of substrate-guided catheter ablation remains unknown and awaits prospective studies.

Arrhythmogenic RV Dysplasia (ARVD)

A ARVD is a disorder primarily, but not exclusively, of the RV in which there is fibrofatty replacement of the free wall of the RV. Involvement of the LV, although less common pathologically, is even rarer clinically. VT in ARVD ranges from asymptomatic nonsustained episodes to sudden cardiac death. Besides the fibrofatty infiltration, the hallmarks of this disorder include: inversion of T waves in the precordial leads (V1–V3), epsilon waves (which represent late potentials) in these leads, ventricular premature contractions or VT with varying axes and LBBB patterns, and a family history of this disorder. Perhaps 30% of the patients will have a hereditary basis for the disease.

It is the author’s impression that in different stages of the disease the arrhythmia mechanisms may vary. Early in the disease exercise induced arrhythmias are common and these appear to be caused by triggered activity due to delayed afterdepolarizations. Three general areas are arrhythmogenic tissue have been noted to include the RV outflow tract, the RV inflow tract and the free wall near the apex right of the ventricle. With the
development of marked fibrofatty infiltration, the electrograms of the RV become fractionated and extremely long in duration. These long electrograms are associated with the epsilon waves seen on the ECG. These electrograms are similar to those seen in myocardial infarction, and most likely represent the same phenomenon of viable myocytes imbedded fibrofatty tissue with poor intercellular communications. As such, therapy of ARVD was addressed in a similar manner as that for VT due to coronary artery disease. At this stage of the disease, reentrant VTs are common, most of which are stable, but in some instances can be hemodynamically untolerated. Antiarrhythmic agents have been used in ARVD, but the efficacy of pharmacologic therapy has not been determined in any prospective study. Early attempts to operate on such patients using ventriculotomies or even disarticulation of the right ventricle have largely been abandoned. ICDs have been used in many patients since they have the advantage of pacing for reentrant VT and can rescue patients that have hemodynamically untolerated VT; however, the role of ICDs in ARVD has not been established. Ablation in the author’s opinion offers an excellent opportunity to treat such patients. Entrainment mapping been successfully used to ablate VTs in ARVD, although additional lesions are often necessary because the central pathways (isthmuses) appear to be wide. VTs in which the tricuspid valve forms one barrier of a central pathway are ablatable by identifying and destroying the isthmus. Other ablation techniques to treat such VT include encircling areas of late potentials or connecting scars to prevent the formation of isthmuses (see ablation of VT in coronary artery disease). Although some investigators have found ablation to be useful in the management of such patients, in most laboratories ICDs are additionally used. In the current patient population of VT in ARVD, ICDs have only been implanted in patients with untolerated tachycardia. The author has been able to successfully ablate VT in seven patients with no recurrence with a follow-up averaging 3 years.

Idiopathic VT

Idiopathic VT falls into two major categories. The most common variety are due to focal mechanisms, primarily catecholamine induced delayed afterdepolarizations, which are dependent upon enhanced adenyl cyclase activity.

While these arrhythmias were able to be initiated by programmed stimulation (rapid pacing easier than timed extrasimuli), induction often required the addition of isoproterenol. Arrhythmias may also be initiated by phosphodiesterase inhibitors and modulated by other agents that influence adenyl cyclase activity (e.g., muscarinic, purinergic, and alpha 1 receptors). Clinically, a common stimulant of these arrhythmias is milrinone, particularly when it is used in a setting of an intensive care unit in combination of catecholamine stimulation (endogenous/exogenous). This combination of adenyl cyclase stimulation (catecholamines) and diminished breakdown (phosphodiesterase inhibitors) is a potent stimulant of triggered activity by increasing intracellular calcium loading that induces a transient inward current carried by sodium to produce afterdepolarizations. Termination of these arrhythmias may be seen with such vagal maneuvers, administration of adenosine, calcium blockers, β-blockers, and sodium blockers. Since these arrhythmias most commonly occur in patients without heart diseases, curative procedures like ablation are the therapy of choice.

The most common triggered VT occurring in the general population is that arising from the RV outflow tract. These tachycardias, which were described more than 80 years ago, present with the LBBB, right inferior, or left inferior axis depending on their site of origin in the RV outflow tract. The closer to the pulmonary valve and more septally located the VT, the more right and inferior the axis. Wellens et al. (personal communication, September 7, 2002) have recently found VTs arising above the pulmonary value in the pulmonary artery where muscle fibers extend. Less commonly (~10%), VTs arise from the LV outflow tract, the LV epicardium, particularly around the superior mitral annulus near the area of aortomitral continuity, or in the sinuses of valsalva, where extensions of myocardium are often found. VTs arising from the epicardium or at the mitral-aortic annulus have a right bundle branch block (RBBB), inferior axis with concordant precordial R waves. LV outflow tract VTs and those from the sinus of valsalva can have RBBB or LBBB morphology. When LBBB morphology is present there is frequently an R wave in lead 1 and V1 and an early transition in V2 or V3. Characteristics of the LV outflow tract, LV epicardial, and coronary cusp VT QRS morphologies have been recently described by several investigators. Occasionally, these tachycardias behave more like automatic tachycardias, which are also susceptible to induction by catecholamines, but are neither inducible nor terminatable by PES.

The methods by which these focal VTs are ablated include a combination of activation mapping and pacermapping. The author always uses both bipolar and unipolar recordings in these patients. It is critical to demonstrate the distal unipolar recording has earlier activation that the proximal pole and correlates with the earliest onset of electrical activity on the bipolar recording, since the
radiofrequency energy is delivered thru the distal pole. The unipolar recording should also have a QS morphology at the earliest site, with a rapid intrinsicoid deflection. Pacemapping can also be used, but as mentioned earlier in this article, similar pacemaps can occur over 1- or 2-cm area.

The more normal the heart, the smaller the area over which identical pacemaps can be generated. The success rates of ablation of these tachycardias are extremely high, usually exceeding 90%. In the author’s opinion, ablation should be considered as a primary form of therapy in such patients.

Uncommonly, other triggered rhythms may appear from the fascicles. These rhythms are usually transient and treatment usually involves removing the offending trigger (e.g., digitalis, milrinone). Occasionally they require specific therapy. β-Blockers are usually quite effective, but if symptomatic VT persists, ablation may be undertaken using activation mapping to localize the earliest Purkinje potential.

The second type of idiopathic VT is one from the LV septum adjacent to the posterior papillary muscle. This VT is known as “verapamil-sensative VT” because of its unique responsiveness to this agent.147–159 These VTs typically have a RBBB/left anterior descending morphology, but may have a right superior axis when located more apically. Initially many investigators believed this rhythm was due to triggered activity, but it is now commonly accepted that it is due to reentry. This reentrant arrhythmia can be initiated and terminated by atrial or ventricular pacing and/or extrasimuli. The interval to the onset of the VT usually demonstrates an inverse relationship to the coupling interval of the initiating extrastimulus or paced cycle length. It is also entrainable with fusion from the atrium or ventricle. Of note is the fact that Purkinje spikes typically precede the onset of the QRS and local ventricular activation during VT. This led some investigators to call this fascicular VT the author believes this term is inapppropriate since the exact role of the Purkinje system in this VT is unclear. For example, atrial pacing can entrain the VT with total antegrade capture (normal QRS and HV interval) suggesting that the Purkinje system is used antegradey. Whether or not it is used retrogradely is unproven.

Recently, several investigators have described mild-diastolic potentials that define a protected zone of slow conduction that can be traced over several centimeters on the septum to approach the exit site at the inferior septum at which site a Purkinje spike is typically observed.150 Of note, the Purkinje spike at the “exit” of the diasolic pathway may not be the earliest Purkinje potential recorded. During pacing or in response to verapamil or lidocaine,153–159 there is progressive delay the block between the diastolic potential and the Purkinje spike. The frequency with which the diastolic potentials are observed is variable. Multiple mapping techniques have been used to guide ablation of this arrhythmia, all claiming high success. They include activation mapping to define the earliest site of ventricular myocardial activation, the earliest Purkinje potential, the diastolic potential and pathway, and site of concealed entrainment. Concealed entrainment is extremely difficult because of the apparently small isthmus, but when accomplished is 100% successful. Ablation at the diastolic153–159 potential has also yielded excellent results. While Nakagawa et al.150 initially suggested ablation directed at the earliest Purkinje potential, this has neither been uniformly successful. I have seen absence of Purkinje fibers at successful ablation sites, and as mentioned above, successful ablation sites at the diastolic potential often do not record the earliest Purkinje potential, as by the earliest ventricular myocardial activation (± a Purkinje potential) and an excellent pacemap. Success of these various methods (i.e., based on Purkinje mapping, pacemapping, or ventricular mapping) may indicate different mechanisms and locations of circuits, but more likely, it suggests these methods target the area incorporating the exit site accurately enough to successfully ablate the VT.

The true accuracy of these latter methods cannot be determined since the number of lesions required for success is usually not reported.

Ablation of VT in Cardiomyopathy and Miscellaneous Disorders

Sustained monomorphic VT is an uncommon presenting arrhythmia in IDCM, but appears more common in Chagas disease, sarcoidosis, and myopathy due to echinocochosis cysts or trauma. As noted above, the sustrate of VT in patients IDCM can be located endocardially or epicardially which may produce reentrant circuits that are difficult to ablate from the endocardium. Sosa et al.80 developed and successfully used the intrapericardial approach to ablate VT in Chagas disease in which the critical components of the VT circuit were commonly subepicardial. Another reentrant VT initially described in cardiomyopathy and other conditions with severe LV dysfunction, was bundle branch reentry.160–163 This VT circuit most commonly used the RBBB antegradely and the LBBB retrogradely, but the reverse could also be seen. Ablation of the RBBB or LBBB could cure this arrhythmia. More recently this VT has been noted in myotonic dystrophy and coronary disease, where it is usually confined to the fascicles, typically in patients with anterior infarction and bifascicular block. Unfortunately, in most patients,
other myocardial VTs are also present, mandating use of ICDs.

Discussion

Over the past 30 years electrophysiologic studies have been used to understand the mechanisms of a variety of VTs. They have also been pivotal in developing therapy for the arrhythmias. In recent years there has been a great interest in the molecular genetics of a variety of arrhythmias. Mutations responsible for the long QT syndromes, Brugada syndrome, ARVD, catecholamine induced polymorphic VTs, and high risk mutations with hypertrophic cardiomyopathy have been identified. The challenges for gene-based therapy for these disorders will be work for the next decade and is discussed elsewhere in this symposium.

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