Management of Cardiac Arrhythmias

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Preface

It is safe to say that few areas of medicine have moved faster than cardiac electrophysiology. In three short decades, our field has grown from its infancy to a highly sophisticated subspecialty of cardiology, complete with its own societies, scientific meetings, and board examination. Key to our successes has been a progressively more in-depth understanding of pathophysiology from our basic science laboratories. Burgeoning knowledge has been accompanied by a blitzkrieg of technology that has allowed us to treat what used to be lethal rhythm disturbances and to improve the quality of life of millions of people the world over. In 2010, we stand on the threshold of an even more impressive leap forward as we wrestle with defining how the genetic code predisposes to, or even causes, cardiac arrhythmias.

The price to pay for such rapid expansion of information is an ever-widening knowledge gap. It is obvious that practitioners who spend their time caring for patients find it difficult to keep up with the latest developments in our field. The number of articles and journals that come across our desks every month is mind numbing. And few have the sophistication to understand the myriad of discoveries that are unwrapped at each of our congresses. Clearly there is a need to have complex information presented in an efficient and user-friendly way.

We believe that condensed texts represent one of the best ways for colleagues to stay current. We also think that there are individuals in our field, as in any endeavor, who are particularly skilled in taking a complex mass of information, condensing and formulating it, and producing a state-of-the-art manuscript that makes clinical sense. Consequently, we agreed to recruit a stellar group of authors and edit the text you are about to read. Its organization is standard, proceeding from basic science to diagnostic and therapeutic techniques, before ending in a discussion of specific patient types and syndromes. We added an historical perspective that should be particularly gratifying to our younger readers. Since the time frame of development was short, the information is as current as possible and should bring the interested reader up to speed rather quickly. We have tried to feature issues that will be of continuing interest in our field over the next few years in order to provide a frame of reference for journal reading. Finally, we have kept the level of science high to appeal to physicians and health-care professionals, or those in training, who have a deep interest in cardiac arrhythmias.

There are several we would like to acknowledge and thank, including our colleagues who helped us with their knowledge and experience, our families who allowed us the time to write and edit, our staff who provided technical support, and the research foundations and granting agencies that keep us afloat. But most of all, we thank our patients who, by their courage and perseverance, inspire us to dig deeper so we can ultimately conquer the diseases that disrupt and end their lives.

Gan-Xin Yan, MD, PhD
Peter R. Kowey, MD

Acknowledgments

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I Introduction

1 Management of Ventricular Arrhythmias: An Historical Perspective

David J. Callans and Mark E. Josephson

CONTENTS

Abstract

The treatment of ventricular arrhythmias has undergone vibrant change in the last 40 years, evolving from a largely intellectual exercise to an evidence-based, guideline-supported set of patient care strategies. This progress have been fueled by basic and clinical science and by the initial application of randomized clinical trials to the study of electrophysiology. Along the way, several strongly held beliefs were reconsidered, most notably the use of programmed stimulation or serial Holter montoring to guide pharmacologic therapy for ventricular tachycardia. Although antiarrhythmic drugs are still considered useful in reducing the frequency of recurrent VT episodes, our loss of confidence in guided drug therapy led to the development of device, surgical ablation, and catheter ablation therapies, which form the mainstay of treatment today.

Key Words: Ventricular tachycardia; ventricular fibrillation; premature ventricular complexes; electrophysiologic study; implantable cardioverter defibrillators (ICD); antitachycardia pacing; catheter ablation; SCD-HeFT; Multicenter Automatic Defibrillator Trial; pace mapping.

> *A few hours before his death he told me . . . he did not feel any bodily ailments, and . . . without any sign of anything amiss, he passed away from this life.*
>
> *. . . through failure of the artery that feeds the heart . . . which I found to be very parched and shrunk and withered.*
>
> – Leonardo DaVinci

Interest in the management of ventricular arrhythmias developed with the understanding that ventricular tachyarrhythmias were responsible for sudden cardiac arrest (Table 1). Although sudden death has been recognized for many centuries, true sudden cardiac arrest was probably initially described by Leonardo DaVinci (see quote above). It was not until the second half of the twentieth century and the development of electrocardiographic monitoring that physicians recognized the initiation of ventricular fibrillation by premature ventricular complexes (PVCs), particularly in the early post-infarction period (Fig. 1) *(1)*. With the advent of Holter monitoring, several studies demonstrated that the risk of sudden death and cardiac mortality increased as PVC frequency increased (particularly at a

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Table 1
Strategies for Treatment of VT/VF

Pharmacologic
Empiric
Holter-guided
EPS-guided
Combination
Non-phamacologic
Antitachycardia pacing
Implantable cardioverter defibrillator (ICD)
Surgical ablation
Catheter ablation

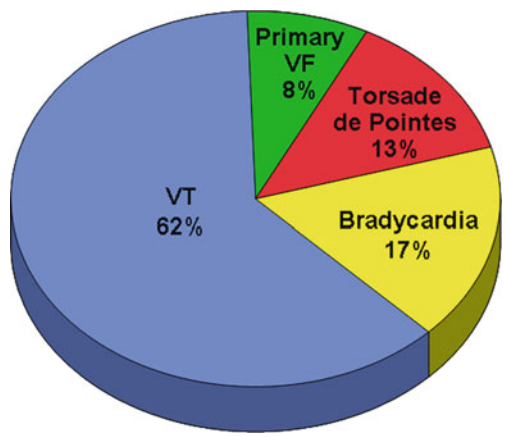

Fig. 1. Holter monitoring study demonstrating the rhythm recorded at the time of cardiac arrest in ambulatory patients. The vast majority of sudden death in this study was caused by ventricular tachyarrhythmias, with ventricular tachycardia (at least as this initial arrhythmia) being the most common. Adapted from Ref. *(1)*.

"threshold" of greater than 10 PVCs per hour) and/or the complexity of the PVCs increased *(2, 3)*. In fact, PVC grading systems were developed by Lown that attempted to signify an increasing risk of sudden death with more malignant ventricular ectopic beats *(4)*. This led to the PVC hypothesis that treating spontaneous ventricular arrhythmias would prevent the induction of sustained ventricular arrhythmias, resulting in a reduction of sudden death risk. Initially, therapy was empiric use of antiarrhythmic agents, particularly sodium channel blocking agents since these agents stabilized membranes and reduced the frequency of PVCs (Table 2). Unfortunately, as later trials would eventually demonstrate, none of these agents prevented sudden cardiac death, particularly in the post-infarction setting. Empiric use of beta-blockers, however, seemed to decrease mortality, both total and sudden in the Beta Blocker Heart Attack Study (BHAT) *(5)*. Because of the failure of empiric use of antiarrhythmic agents, Holter guided therapy was attempted. It was clearly realized, however, that Holter monitoring itself had many limitations. First of all, the frequency and complexity of arrhythmias could vary from hour to hour and day to day. The longer one was monitored, the more frequent arrhythmias were noted. This became even more evident when Holter monitoring was performed during the administration of antiarrhythmic drugs. Many studies showed that the frequency of spontaneous arrhythmias bore no relationship to the spontaneous episodes of sustained ventricular arrhythmias (Fig. 2). Thus, the following basic assumptions of Holter guided therapy were shown to be in error.

Table 2
Pharmacologic Therapy for Treatment of VT/VF

Advantages:
- Noninvasive
- No surgical morbidity or mortality
- Inexpensive in short run
- May be appropriate for certain subgroups:
  - Refused ICD
  - Multisystem disease
  - Poor overall prognosis

Disadvantages:
- Often empiric, even if EP-guided, since not all drugs can be serially tested due to expense
- Often associated with intolerable side effects, organ toxicity, and non-compliance
- Even if EP-guided, many patients remain non-suppressible and have a poor prognosis

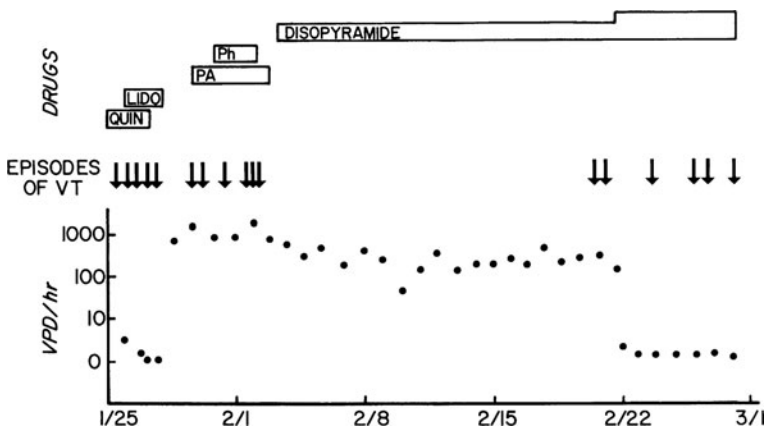

Fig. 2. The lack of ventricular ectopy and spontaneous episodes of sustained VT is one of the limitations of managing antiarrhythmic therapy guided by Holter monitoring. In this example, multiple antiarrhythmic drugs were used and treatment efficacy was assessed with monitoring. Despite a marked reduction of ventricular ectopy during quinidine and subsequently diisopyramide therapy, frequent episodes of sustained VT were observed. (From Ref. *(38)*).

1. Frequent and complex ectopy are specifically and causally related to VT/VF.
2. Holter monitoring reliably identifies these arrhythmias.
3. Elimination of PVCs prevents sudden death

This led to the demise of the use of Holter monitoring as a mode of prevention of lethal arrhythmias. Moreover, the Cardiac Arrhythmia Suppression Trial (CAST) demonstrated that in patients with coronary artery disease, moderately reduced injection fractions and chronic stable angina, use of 1C agents was associated with an increase in mortality *(6)*. The conclusions from CAST were that treatment of asymptomatic or mildly symptomatic arrhythmias with Class IC agents in such patients was associated with excess mortality and no benefit. Proarrhythmia caused by these sodium channel blocking agents

may occur late and elimination of ventricular ectopy did not provide protection against sudden cardiac death. It was the CAST Study that put an end to pharmacologic-directed therapy for the treatment of spontaneous ectopy.

In the early 1970s, clinical electrophysiology began to develop as a tool to investigate the mechanisms of arrhythmias. Wellens in 1972 first demonstrated that sustained ventricular tachycardia could be initiated by programmed electrical stimulation (Fig. 3) *(7)*. Shortly thereafter, Josephson and his colleagues from the University of Pennsylvania demonstrated that using aggressive stimulation protocols, sustained ventricular tachycardia and coronary artery disease could be reproducibly initiated in the vast majority of patients with healed myocardial infarction who presented with VT. Furthermore, VT could be reproducibly induced in patients who had more rapid arrhythmias, clinical arrhythmias associated with cardiac arrest and even those nonsustained ventricular arrhythmias, albeit in a much lower percentage of cases (Fig. 4) *(8)*. The sensitivity and specificity of programmed stimulation were validated in a number of centers. As a result, the concept of electrophysiologic testing of VT induction as a way to evaluate therapy was advanced *(9)*. In this philosophy, one considered that there needed to be a substrate in which spontaneous or stimulated extra beats could initiate lethal arrhythmias. Studies from Horowitz, Fisher, Mason and others demonstrated that one could use the response to programmed electrical stimulation to evaluate whether or not drugs could prevent spontaneous events *(9–11)*. In Fig. 5, a series of drugs was administered and the response to programmed stimulation evaluated. A variety of antiarrhythmic drugs were tested and it was established that the class 1A agents more frequently prevented induction than other agents. Moreover, noninducibility of arrhythmia was associated with

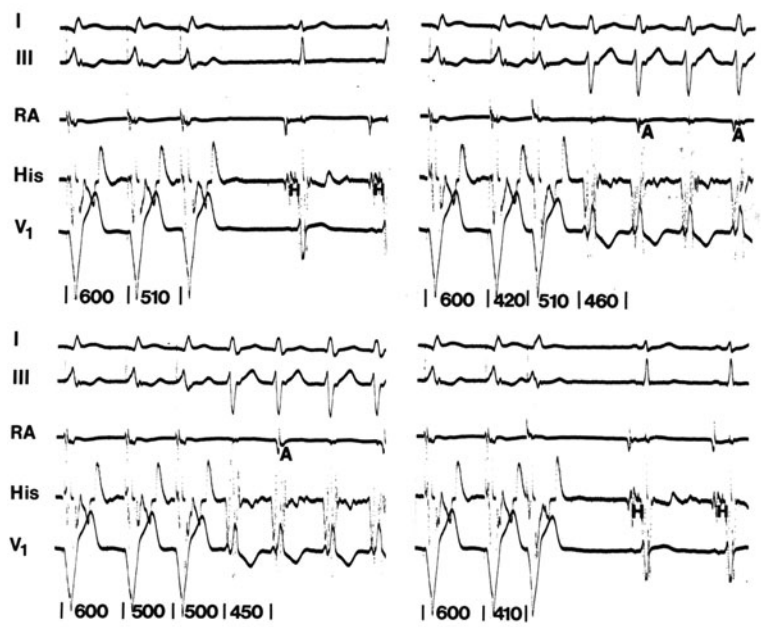

Fig. 3. Programmed ventricular stimulation for the induction of VT in one of Dr. Wellens' original patients. Following a drive train at 600 msec, an extrastimulus at 510 msec does not induce VT (*upper left*). When the extrastimulus coupling interval is decreased to 500, VT is induced and the interval to the first tachycardia beat is 500 msec (*lower left*). When the coupling interval is decreased to 420 msec (*upper right*), VT is induced and the interval to the first VT beat increases to 510 msec. Finally, when the coupling interval is decreased to 410 msec, VT is no longer induced. The observations of an extrastimulus coupling interval "window" which results in VT induction, and a reciprocal relationship between the extrastimulus coupling interval and the timing of the first tachycardia beat provide evidence for a reentrant mechanism for VT in the setting of healed infarction.

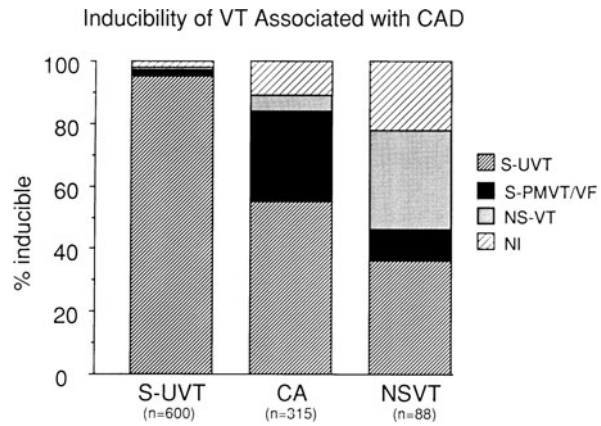

Fig. 4. The ability to reproducibly induce VT in patients with healed infarction varies according to their clinical presentation. In patients who present with tolerated sustained VT, VT is induced in over 95%. The frequency of VT induction is less in patients who present with cardiac arrest or nonsustained VT; in addition, the frequency is less in patients with non-infarct-related forms of structural heart disease. Reproduced from Ref. *(8)* with permission.

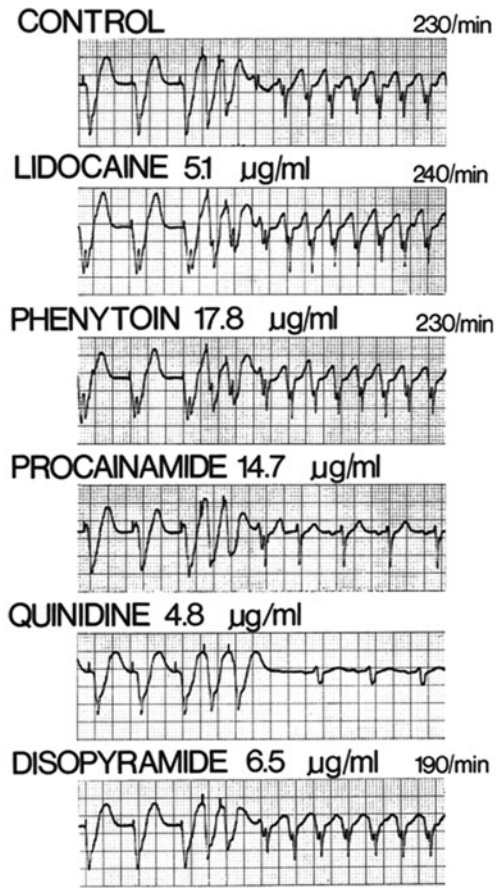

Fig. 5. The use of programmed stimulation to predict the efficacy of antiarrhythmic agents. A collection of separate electrophysiologic study data from the same patient being treated with different drug regimens is shown. Ventricular stimulation resulted in VT induction in the baseline state, which was not prevented by treatment with lidocaine, phenytoin or disopyramide, but was prevented by procainamide and quinidine. (From Ref. *(39)*).

freedom of events with a predictive accuracy of approximately 80% in a 2-year follow-up. Unfortunately, VT inducibility on a given antiarrhythmic regimen did not always predict recurrence. This was particularly true with amiodarone. Despite this limitation, it was also noted that these sodium channel blocking drugs could frequently slow VT, resulting in well-tolerated recurrent events as opposed to syncope or cardiac arrest *(12)*. Thus, such agents not only could prevent arrhythmia but could make it tolerated so that elective cardioversion or other stimulation techniques could be used to terminate the arrhythmia. While these findings applied to patients with VT in the setting of prior myocardial infarction, the ability to use programmed stimulation to predict successful antiarrhythmic therapy for nonischemic cardiomyopathy was unsuccessful. In such patients, reproducible initiation was less often noted, and response to drug therapy was not predictive of freedom from sudden cardiac death *(13)*.

The use of electrophysiologic guided therapy had limitations aside from the inability to use it in cardiomyopathy, however. First, none of the studies which demonstrated favorable outcomes were randomized. Secondly, most results were actually a combination of prospective and retrospective data (i.e., prior clinical drug failure associated with inducible VT and EP studies). Finally, the follow-up of all of these studies was short, somewhere between 1 and 2 years. Nonetheless, all studies showed a higher occurrence rate and/or mortality in those patients with persistently inducible VT.

The use of electrophysiologically guided antiarrhythmic drug therapy came to an abrupt halt with the Electrophysiologic Study versus Electrocardiographic Monitoring (ESVEM) Study. This was the first prospective randomized trial to evaluate the role of antiarrhythmic therapy guided by the results of programmed stimulation versus Holter monitoring. This was a highly selected patient population of patients with sustained VT (15 beats or more), cardiac arrest (less than 15% of patients) and syncope (15%). In addition, the inclusion criteria required patients to have both >10 PVCs per hour on Holter monitoring and inducible VT with programmed stimulation. The results of ESVEM Study showed that both methodologies, as applied, were not useful to predict drug efficacy; recurrence was frequent independent of which strategy was used *(14)*. Sotalol was a well-tolerated, moderately successful drug in patients with reasonable ventricular function who had not failed prior antiarrhythmic therapy. However, these results did not permit relative drug efficacy comparisons in untreated patients, since those effectively treated were excluded from the ESVEM trial. These results are also not applicable to cardiac arrest patients with VT in clinical settings besides healed infarction, as these patients were not well represented in this study. There were many limitations to the ESVEM Study. There was no placebo armed to access mortality of untreated patients. Because of the known risks of many of the antiarrhythmic agents that were used, it is not inconceivable that a placebo group may even have faired better. The data may apply to only 15% of patients who present with frequent ectopy and/or nonsustained VT on Holter who have inducible VT on EPS. There is a bias against EPS and a bias against type 1 agents, because patients with VT who were successfully treated with class 1 agents were excluded and patients with VT failing drug therapy (particularly class 1 agents) were included. This latter limitation is extremely important, since prior study suggested that failure of one or more class 1 agents (typically procainamide) predicted failure of any antiarrhythmic agent as assessed by programmed stimulation. In total, 2/3 of the patients had failed standard drugs. In our opinion, there were other limitations that prohibit generalization of the ESVEM trial. First, the stimulation protocol was inadequate and not uniform. The number of extrastimuli was never more aggressive than during stimulation in the baseline state; if three extrastimuli were not delivered at baseline, three extrastimuli would never be delivered in interpreting the efficacy of a drug regimen. Thus, what was considered successful may not have been. Second, the ability for a patient to tolerate sotalol, particularly with regard to absence of severe LV dysfunction, may have biased the apparent response to sotalol. Many patients had already failed class 1 agents, but none were included who had been successfully treated, a significant bias against class 1 agents. There is a very high recurrence rate despite "best" therapy, probably due to the prior failure of class I agents in many subjects (which predicts failure of other drugs, as discussed above). Finally, amiodarone was not included in this trial. Regardless of these limitations which we believe

Table 3
History of the Development of Nonpharmacologic Therapy for VT

- 1977–1985 – anti-tachycardia pacing for VT
- 1978–1985 – development of surgery for VT
- 1980–1999 – development and refinement of the implantable defibrillator
- 1984–1993 – refinement of mapping techniques and development of catheter ablation for monomorphic VT; change from direct current ablation (fulguration) to radiofrequency energy.
- 1998–2002 – application of catheter-based identification of the arrhythmia substrate to treat untolerated VTs by RF ablation

significant and biased against EP studies, the use of EP-guided pharmacologic therapy virtually ended following completion of the ESVEM study. The recognition of significant pro-arrhythmia also shifted the approach towards nonpharmacologic therapy (Table 3).

NONPHARMACOLOGIC MANAGEMENT OF VT/VF

The nonpharmacologic modalities that have been developed to treat VT/VF include:

1. antitachycardia pacing
2. antiarrhythmic surgery
3. implantable cardioverter defibrillators (ICDs)
4. catheter ablation

The concept of antitachycardia pacing was obvious at the time of the initial studies of programmed stimulation for ventricular tachycardia by Wellens and Josephson *(15, 16)*. Both labs demonstrated that reproducible termination of arrhythmias was possible in patients whose tachycardia could be reproducibly initiated. The group from The University of Pennsylvania demonstrated that the rate of tachycardia influenced the ability to terminate by programmed stimulation. The success of programmed stimulation (in the form of burst pacing, programmed stimuli or autodecrimental pacing) was high at rates <200 beats per minute or less; for more rapid VT, antitachycardia pacing was still successful in at least 50% VTs, but acceleration to ventricular fibrillation was more common. Furthermore, antiarrhythmic drug therapy, which consistently slows VT rate, also has a favorable influence on termination with overdrive pacing. Although there was a period of time in which specific antitachycardia pacing devices were used, the possibility of accelerating the tachycardia or producing ventricular fibrillation led to abandonment of this modality of therapy as a stand alone therapy.

Three forms of therapy eventually evolved. The earliest was antiarrhythmic surgery. Surgical procedures evolved initially in the mid-1970s and continued to the early 1990s. Catheter endocardial mapping was developed in the mid-1970s and demonstrated for the first time that the majority of arrhythmias in coronary artery disease originated on or near the endocardium *(17)*. Intra-operative mapping of the endocardium and epicardium confirmed these findings in coronary artery disease *(18)*. In addition, Cassidy et al. demonstrated that the substrate in which the tachycardia arose could be defined by abnormal electograms, those of low amplitude, broad width, fractionation and those which were late (i.e., recorded beyond the termination of the QRS complex) *(19)*. Studies by Kienzle in the operating room confirmed these findings *(20)*. Mapping in the catheterization lab could identify exit sites of early activation of the ventricular myocardium giving rise to specific QRS morphologies. These data were confirmed by mapping in the operating room. As a result of these mapping studies, the group at the University of Pennsylvania developed the subendocardial resection to remove the arrhythmogenic substrate responsible for ventricular tachycardia and ventricular fibrillation (Fig. 6)

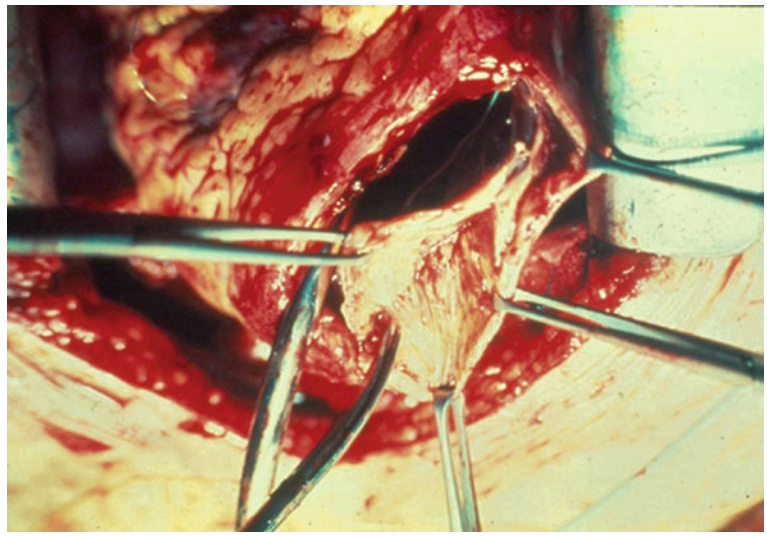

Fig. 6. The technique of subendocardial resection for surgical ablation of VT. The aneursymal segment of the left ventricle was opened, and after endocardial mapping, the subendocardial VT substrate was "peeled" from the surviving epicardial tissue. Ventricular stimulation was repeated, and if residual VT morphologies existed outside of the dense infarct, they were typically treated with focal cryoablation.

(21). These investigations demonstrated that map-guided endocardial resections could successfully prevent sudden cardiac death (4% in 5 years) or recurrent VT (8% in 5 years) *(8)*. The surgical procedure was successful in patients with recent or remote myocardial infarction. Other non-map-guided procedures such as encircling subendocardial resection or encircling cryoablation were developed by Guiraudon as a method to facilitate surgical procedures without the complexity of mapping equipment *(22)*. When map-guided and non-map-guided therapies were compared at the University of Pennsylvania, map-guided therapy appeared to have significantly better outcomes. While surgical therapy was successful for patients with coronary artery disease, there was a lesser experience and lower success rate in patients with cardiomyopathies. These patients appeared to have a lesser amount of endocardial electrical abnormalities and origins of VT and a greater amount of epicardial abnormalities. Not enough data were available to surgically address patients with cardiomyopathies and VT, and they continued to be considered nonsurgical candidates. Because of relatively high operative mortality (10–15%) and requirement for "a surgical electrophysiological team" the procedure was used minimally with the development of the ICD.

The implantable defibrillator was developed initially by Mirowski and colleagues despite initial deridement by many in the field *(23)*. Mirowski's persistence, however, led to the development of an implantable cardioverter defibrillator, which was initially improved in 1985 (Fig. 7). The initial devices required thoracotomy for the placement of epicardial patches. Since that time, the ICD has been miniaturized (20–25 cc) and has added an increasingly greater complexity in terms of number of leads (dual chamber or biventricular) or pacing (for rate support and antitachycardia pacing) as well as additional leads to assure adequate defibrillation thresholds (subcutaneous or dual coil leads in the SVC). The ability to implant these devices as simply as a pacemaker with transvenous leads led to the widespread application of this form of therapy throughout the world. The growth of ICD implantations has become exponential, such that more than 200,000 ICDs are implanted yearly in the United States alone. The Antiarrhythmic Versus Implantable Defibrillator (AVID) Study was the first to demonstrate that the ICD was superior to antiarrhythmic drugs (primarily amiodarone) in patients who had experienced a

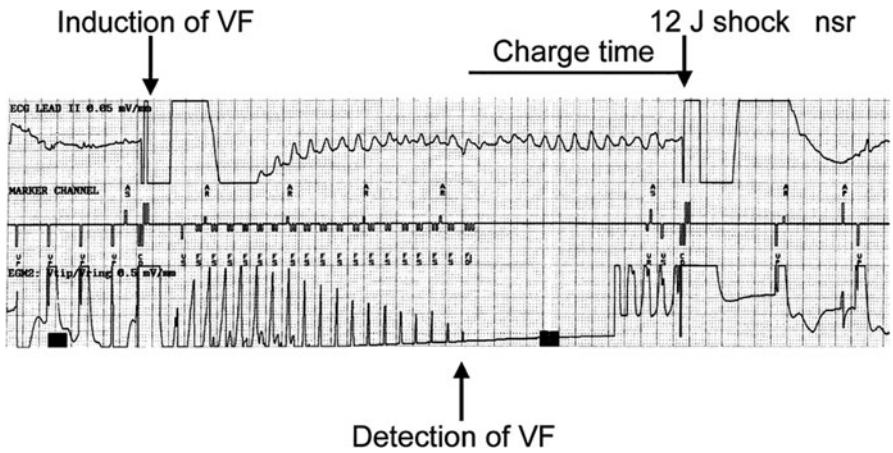

Fig. 7. Demonstration of efficacy in defibrillation during ICD testing. Surface ECG lead II, the electrogram recorded from the ICD lead and ICD sensing markers are recorded via the device. A low energy shock delivered at the crest of the T wave results in induction of ventricular fibrillation. This is promptly detected by the device, and sinus rhythm is restored with the delivery of a 12 joule shock.

cardiac arrest or untolerated VT *(24)*. The increase in survival was not impressive, but was diluted by cross over from initial treatment assignment. It was not very cost-effective ($125,000 per year life saved). Nevertheless, guidelines were established that suggested ICDs should be implanted in patients suffering from a hemodynamically untolerated VT or a cardiac arrest who had ejection fractions of less than 40%. Although limited data are available, ICD therapy has not been demonstrated to be effective (in terms of saving lives) in patients with ejection fractions of greater than 40% (except in specific clinical situations, such as long QT syndrome or hypertrophic cardiomyopathy). This demonstrates the inherent limitation of basing guideline recommendations on even well-constructed randomized controlled trials. Clearly, young patients without structural heart disease and high-risk channelopathies, whose only possible cause for death would be arrhythmic, require an ICD; however, these patients were underrepresented in the trials to make that point. In addition, the guidelines suggest that patients with well-tolerated VT also should receive devices because they had the same mortality as the untreated patients with poorly tolerated VT/VF. This conclusion is invalid since there has never been a trial assessing other strategies (pharmacologic, ablation) versus ICD therapy for tolerated VT. This is further attested to by the fact that surgical therapy for VT/VF was more effective than any ICD, yet the mortality was 50% at 5 years. As such, using total mortality as the primary endpoint, as was done in AVID as well as most contemporary randomized trials, carries with it significant limitations, particularly in patients with advanced structural heart disease. It is not reasonable to expect that ICD therapy would have any effect on mortality aside from sudden death mortality, and competing causes of death remain high, even with contemporary pharmacologic therapy for heart failure. Finally, an additional limitation of the AVID trial was that the control group received far less beta blockade than the ICD group. In fact, given the known benefit of beta-blockers in preventing both sudden and total mortality, it is conceivable that this difference could have been responsible for a majority of the difference in survival between groups.

More recently, the use of ICDs for primary prevention has been championed. Several studies evaluating ICDs alone versus paired with pharmacologic therapy or ICDs versus EP-guided therapy have demonstrated in patients with low injection fractions (less than 30%) and coronary artery disease (Multicenter Automatic Defibrillator Trial – MADIT II) *(25)*, less than 40% in coronary artery disease with nonsustained VT and inducible VTs (Multicenter Unsustained Tachycardia Trial – MUSTT) *(26)*,

less than 35% in coronary artery disease with nonsustained VT and failure to respond to intravenous procainamide (Multicenter Automatic Defibrillator Trial MADIT I) *(27)* and those patients with injection fractions of less than 35% who have class 2 or 3 heart failure (Sudden Cardiac Death in Heart Failure Trial -SCD-HeFT) *(28)* all demonstrated some benefit from ICD therapy. MUSTT and MADIT I, trials that by design enriched the arrhythmic risk in the studied population prior to enrollment by prior EP studies and the presence of spontaneous nonsustained VT, had a significant mortality reduction and good cost-effectiveness with number of needed to treat from three to fourpatients per life saved. However, MADIT II and SCD-HeFT had poorer number needed to treat parameters and lower absolute benefit. In fact in SCD-HeFT, the mortality benefit was 1.4% per year over 5 years. When one compares the noncoronary artery patients as a subgroup of SCD-HeFT as well as the noncoronary artery patients seen in the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) *(29)* trial and the Amiodarone Versus Implantable Cardioverter-defibrillator (AMIOVIRT) *(30)* trial, there has been no consistent benefit in survival from primary prevention ICD therapy. This was recently re-evaluated by Tung et al. and raises the prospect of potential overuse of the device in such patients. Of note is the fact that in Europe, the use of ICDs for primary prevention of cardiomyopathy patients is a class 2 indication, whereas it is a class 1 in the United States. Viewing the lack of striking benefit from the device as well as potential complications (which have been recently summarized by Josephson and coworkers) *(31)* many in the United States have reassessed device usage.

With the reduction of the use of surgery, and the simultaneous development of newer mapping tools, the possibility of catheter ablation to cure VT or abolish the substrate of arrhythmias has become a possibility. This is particularly true in the case of scar-related VT due to healed infarction but with the development of epicardial approaches, ablation for control of VT for patients with cardiomyopathy and in whom the substrate appears to be primarily epicardial or subepicardial. In addition, many other forms of ventricular arrhythmias which are highly symptomatic (RVOT and idiopathic LV tachycardia) and which can lead to cardiomyopathy can be cured by catheter ablation. Many of the mapping techniques established to localize critical areas of re-entrance circuits of scar-related VT were established in the mid-1970s and early 1980s by a group at the University of Pennsylvania. Resetting and entrainment were further designed by Almendal, Josephson, Morady, and Stevenson et al. in the 1980s to allow precise localization of critical components of re-entry circuits of scar-related VT that could be destroyed, eliminating the arrhythmia *(32–35)*. The findings during entrainment or resetting of VT which identify a critical isthmus through which an impulse must travel and is bordered by anatomic and/or functional barriers and is ideal for ablation and termination of VT include the following:

1. A paced QRS morphology which is identical to VT (concealed entrainment) which identifies that the paced site is in, attached to or just proximal to a protected isthmus
2. The stimulus to QRS is approximately equal to the electogram to the QRS during VT, which means that the paced LV site is not a dead end pathway attached to the circuit.
3. The return cycle measured at the pacing site is equal to the VT cycle length, which means that the site of pacing is within the tachycardia circuit.

These observations require pacing at rates not significantly faster than the VT cycle, to prevent slowing of conduction or using very premature stimuli to reset the tachycardia. In addition, it requires that the current used may not be too high to capture more distant tissues. An example of a perfect entrainment map with successful ablation is shown (Fig. 8). Failure to terminate a tachycardia, even when the entrainment map is apparently good may be related to a sub-epicardial location of the circuit, a wide isthmus or endocardial thrombus. Although dealing with insultating thrombus may be extremely difficult, the sub-epicardial location can be dealt with an epicardial approach and a wide isthmus can be dealt with by defining those sites which meet characteristics for an isthmus and ablating over a larger area.

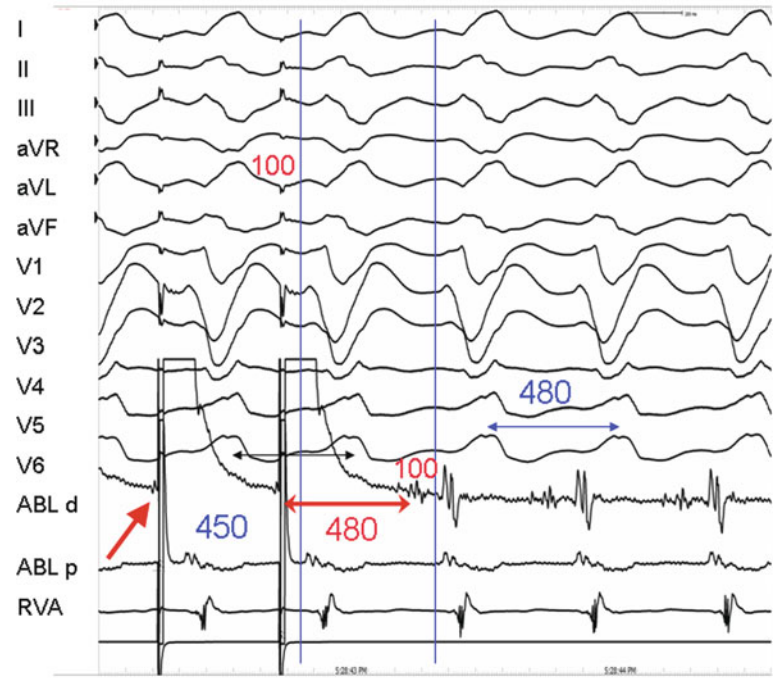

Fig. 8. Entrainment mapping for well-tolerated uniform VT. Surface leads and intracardiac recordings from the ablation catheter (ABL distal and proximal) and the right ventricle (RVA) are shown. Pacing is performed during an episode of VT. The following characteristics suggest that the ablation catheter is within a protected isthmus of the VT circuit: (1) pacing from the catheter results in a perfect match in all surface ECG leads, (2) the stimulus to QRS onset during pacing equals the electrogram to QRS onset during VT (100 msec) and (3) the return cycle (the first spontaneous VT beat after pacing) measured at the pacing site is equal to the VT cycle length (480 msec).

Although use of entrainment or reset mapping is useful for tolerated ventricular tachycardia, the majority of tachycardias occurring today are untolerated and cannot be mapped in detail by using these techniques. A different approach to those tachycardias is needed. Such an approach requires an understanding of the pathophysiological substrate of the arrhythmia. While the basic principles of substrate mapping were established in the mid-1980s by Cassidy et al., it was a development of electroanatomic mapping that allowed one to localize these electrograms in three-dimensional space and record them automatically, which allowed for the potential of ablating components of the substrate that were arrhythmogenic *(36)*. The approach to mapping and ablating the substrate involved finding potential channels of activation, which could form critical isthmuses responsible for arrhythmias within the scar *(37)*. The methods which are used include:

1. Pace mapping at a border zone to identify exit sites and isthmuses (long stimulus to QRS with the same morphology as the pacing is moved deeper into the scar).
2. Redefining voltage windows to find potential channels of viability within scar initially in scar defined by a voltage of 0.5 millivolts.
3. Pacing at high voltage to identify inexcitable tissue that could form barriers through which viable tissue is identified.
4. Identification of split potentials to define potential barriers of an isthmus

5. Define late potentials in order to identify critical isthmus sites leading to isolated mid-diastolic potentials.

Examples of pace mapping to define an exit site and an isthmus are shown in Fig. 9. Once these exit sites or channels have been identified, ablation perpendicular to the channel and into the channel can be used to prevent that channel from being used as an arrhythmia. Identifying channels of viable tissue either by changing the voltage definitions or by looking for an excitable tissue surrounding excitable pathways can identify channels that can also be ablated. Finally, ablating all late potentials is another potential methodology, but is much more difficult given the lack of ability for precisely identifying and ablating all existing late potentials.

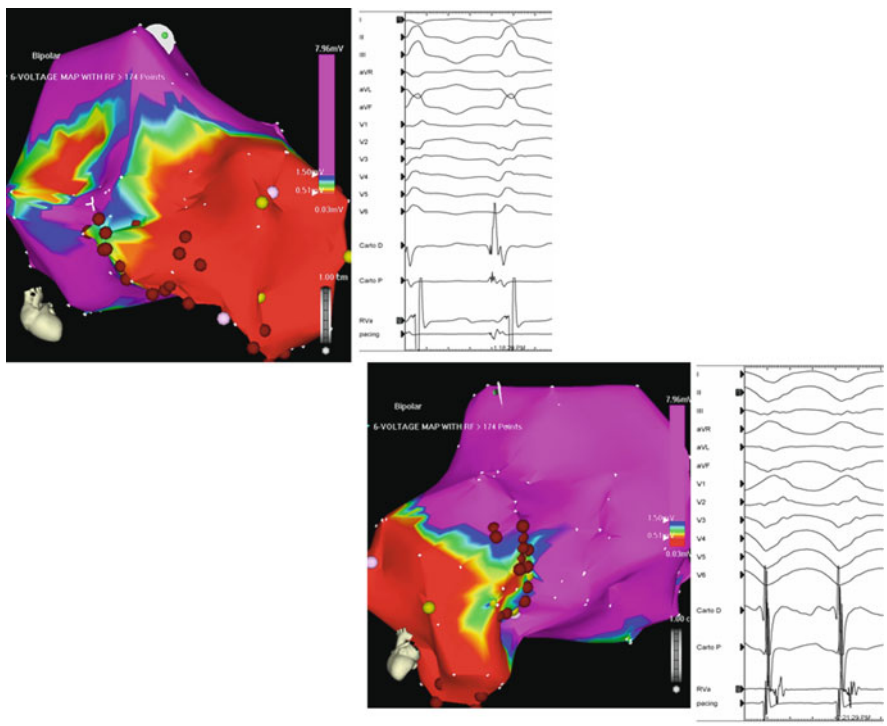

Fig. 9. Voltage mapping during sinus rhythm using electroanatomic mapping. A "shell" of the LV is made during sinus rhythm – each mapped point is assigned a location in three dimensional space, and information about the electrophysiologic characteristics of that point, in this case bipolar electrogram voltage, is presented in color coding: purple corresponds to normal, red to dense infarct (electrograms $\leq$ 0.5 mV) and the intervening colors to the intervening voltages. A large apical infarction is demonstrated, and two VT morphologies are mapped and ablated with substrate-based techniques. A right bundle right inferior axis VT (*top panel*) is mapped to the septal aspect of the infarct border, and linear ablation is performed perpendicularly to the presumed exit site (each *red icon* corresponds to a single ablation lesion), which was established as the site with the closest pacemap. A right bundle right superior axis VT is similarly mapped and ablated to the lateral aspect of the infarct (*bottom panel*).

There are limitations to all of these techniques that involve both false positive and false negative results. Many of these are related to using high current outputs at the pacing site, which leads to capture across circuit barriers, and effects more tissue than can be ablated with a single lesion. Despite these limitations, a recent randomized trial using a substrate-based ablation strategy in patients with prior ICD implantations for cardiac arrest or documented syncope with inducible VT demonstrated that this ablation strategy could reduce ICD therapies by nearly 70% in a 2-year follow-up period *(40)*.

Further work is necessary to demonstrate whether this is a valid approach with the implantation of devices for both secondary and primary prevention. However, since this ablation carries a risk, this strategy needs to be compared to standard antiarrhythmic therapies, beta-blockers and ace inhibitors, before widespread use is accepted.

CONCLUSIONS

The history of EP therapy has been one of continuous evolution for understanding of the mechanism and underlying physiological substrate of arrhythmias. The development of new technology to allow precise identification of arrhythmogenic sites has aided measurably to our ability to use catheter-based ablative procedures to treat these arrhythmias. It is our hope that with greater understanding of all the processes involved in development of the substrate may lead to improved antiarrhythmic agents which are less toxic and more targeted as well as better based techniques to treat these arrhythmias. Moreover, the role of surgery, which deals with the arrhythmogenic substrate of VT/VF, coronary artery disease, and adverse ventricular remodeling resulting in heart failure, needs to be reevaluated. Clearly, prevention of developing the physiological substrate by preventing infarction is the prime consideration. Regardless of the therapeutic modality used, it is important to treat every patient as an individual; since all trials have inherent limitations and biases, and one must recognize that one bullet does not fit all guns.

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2 History of Supraventricular Tachycardia

Yanfei Yang, Edmund C. Keung, and Melvin M. Scheinman

CONTENTS

Abstract

In this chapter, we will discuss the history of supraventricular tachycardia (SVT) that includes four sections: atrioventricular (AV) nodal reentry, AV reentry, atrial flutter (AFL), and atrial fibrillation (AF). We will focus on the historical evolution of the electrophysiologic study of the mechanism and the development of surgical and catheter ablation of these SVTs. We will also discuss potentially newer therapeutic approaches for these arrhythmias.

Key Words: Supraventricular tachycardia; atrioventricular (AV) nodal reentry; AV node; pre-excitation; accessory pathways; Wolf–Parkinson–White syndrome; atrial flutter; cavotricuspid isthmus-dependent atrial flutter; atypical atrial flutter; atrial fibrillation; catheter ablation; cardiac electrosurgery.

INTRODUCTION

We have divided the history of supraventricular tachycardia (SVT) into four sections: atrioventricular (AV) nodal reentry, AV reentry, atrial flutter (AFL), and atrial fibrillation (AF).

ATRIOVENTRICULAR NODAL REENTRY

The debate about precise anatomic boundaries of AV nodal reentry has been lasting for more than 60 years, since the first proposal that various mechanisms of SVT involve the region of the AV node *(1)*. This debate continues even though the vast majority of these patients are cured by standard ablative maneuvers.

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Anatomy of AV Nodal and AV Junction

The works by His *(2)* and Tawara *(3)* firmly established the electrical connection between the atrium and ventricle. The AV node consists of closely packed nodal cells in open contact with atrial muscle at its proximal end *(4)*. Its distal end is linked to the AV bundle which is normally completely insulated by the central fibrous body *(5)*. The AV bundle links with the specialized ventricular conduction system (Purkinje) which is likewise insulated from ventricular myocardium. The proximal portion of the compact node is coated with layers of transitional cells. These morphologically distinct cells have histologic features of both nodal and ordinary atrial myocardial cells. Of potentially great importance is the recent rediscovery of posterior extensions of the AV node *(6)*. These extensions may play a vital role in nodal reentrant circuits. One set of posterior extensions is covered by transitional cells over the left margin of the node in contact with the left atrial (LA) myocardium. More elaborate and extensive posterior extensions extend postero-inferiorly toward the area between the coronary sinus (CS) and tricuspid annulus (TA).

Strong evidence has been marshaled to place doubt on the existence of specialized atrial tracts *(7)*. Instead, input into the AV node is thought to consist of an anterior input from the septal atrial musculature and a posterior input emanating from the crista terminalis (CT) and skirting the inferior vena cava (IVC) to proceed into the region between the CS and TA (slow pathway area) *(8)*. The actual slow pathway may, in fact, be the nodal extension described above.

In a series of observations Moe and colleagues *(9, 10)* deduced evidence for dual AV nodal conduction in dogs and rabbits by using microelectrode recordings within the AV node. A critically timed premature beat was shown to block in one pathway (fast or beta pathway) but allowed for depolarization of a separate region (slow or alpha pathway). The latter was associated with slower conduction allowing for retrograde reciprocation into the beta pathway and producing an atrial echo (Fig. 1). These important concepts were rapidly assimilated into human studies and established the basis of our current understanding of AV nodal reentry in humans.

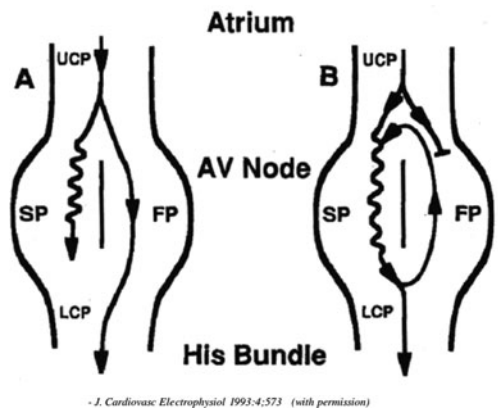

Fig. 1. "Classical" model of AVNRT. The AV node is "longitudinally dissociated" into a slow pathway (SP) and a fast pathway (FP). During sinus rhythm (**panel A**), impulses are conducted over the FP; in **panel B**, an atrial premature beat finds the FP refractory and is conducted over the SP. The conduction delay in the SP allows the FP to recover excitability; therefore, the impulse can conduct retrogradely via the FP and excite the upper end of the SP and initiate sustained reentry. Upper (UCP) and lower (LCP) common pathways of AV nodal tissue are present above and below the reentrant circuit. (Figure from J Cardiovasc Electrophysiol 1993; 4:573, with permission).

McGuire and colleagues *(11)* showed strong evidence that "AV junctional cells in the posterior AV nodal approaches appear to participate in slow pathway conduction." A later important study by Medkour et al. *(12)* described a combined anatomic and electrophysiologic examination of the

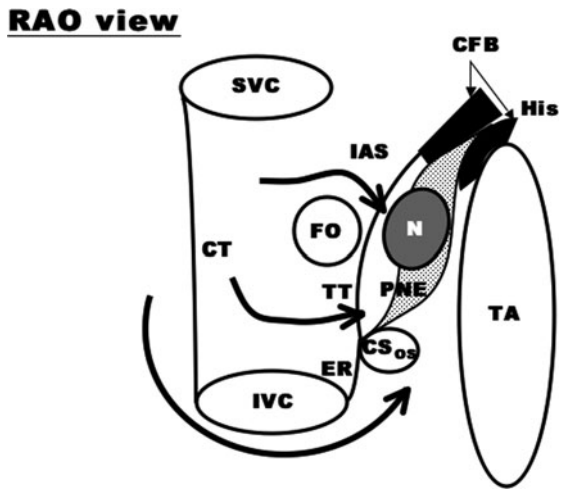

Fig. 2. A schema showing anterior (septal – 2 *upper arrows*) inputs into the AV node (N) and posterior inputs (*lower arrow*) into the node. SVC = superior vena cava; IVC = inferior vena cava; CT = crista terminalis; ER = eustachian ridge; TT = tendon of Todaro: FO = foramen ovale; IAS = interatrial septum; CS os = ostium of coronary sinus; PNE = posterior nodal extension; CFB = central fibrous body; His = His bundle; TA = tricuspid annulus.

posterior nodal extension (PNE) in the rabbit heart. As shown in Fig. 2, anatomically the extension appeared as a bundle of specialized tissues between the CS and compact node. They found no distinct separation between the compact node, lower nodal cell bundle, and the PNE. However, they found distinct differences in electrophysiologic properties between the PNE and compact node. The PNE showed cycle length-dependent slow conduction with its refractory period shorter than that of the node. Critically timed premature atrial depolorizations that blocked in the transitional cells could propagate in the PNE and thus explain the discontinuities in nodal conduction as well as in atrial echo beats (Fig. 3a and b). This study accumulated convincing evidence that the PNE provides substrate for slow pathway conduction.

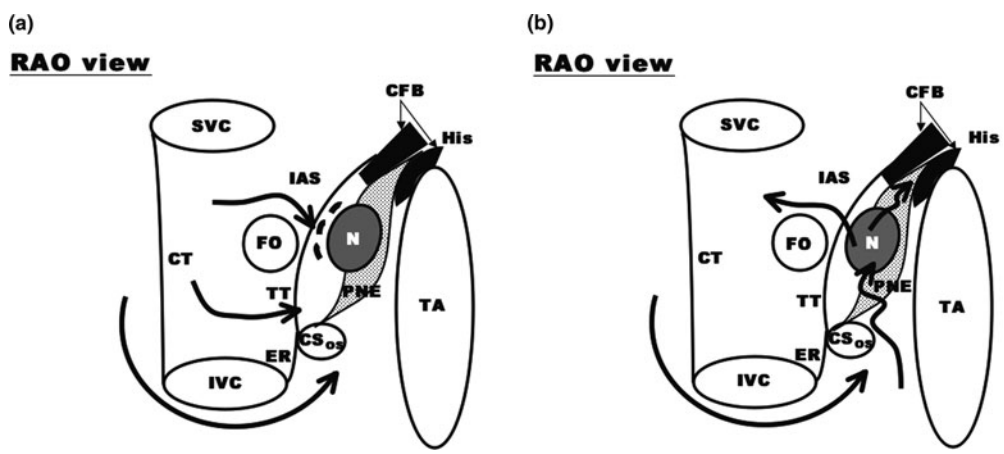

Fig. 3. (**a**) A schema showing a premature atrial complex that is blocked in the transitional cells surrounding the septal inputs to the node and the PNE as well as the node are engaged over the inferior inputs. (**b**) The pathogenesis of an echo beat. The impulse blocked in the septal inputs proceeds over the inferior input and activates the node via the PNE and is able to turn around in the node and reactivate the atrium.

Human Electrophysiologic Studies

As mentioned above, early observations by Moe and Menedez *(9, 10)* on reciprocal beats in rabbits were rapidly applied to humans. These seminal findings were introduced just as the field of clinical invasive electrophysiology began to emerge. Early invasive electrophysiologic studies *(13–16)* attributed AV nodal reentry as cause of paroxysmal SVT. Of particular note was the work of Dr. Ken Rosen and colleagues *(15)* who demonstrated evidence for dual AV nodal physiology manifest by an abruptly increase in AV nodal conduction time in response to critically timed atrial premature depolarizations. These data served as an excellent supportive compliment to the original observations of Moe and Menendez.

By the end of the 1970s, the concept of dual AV nodal conduction in humans had been well established.

However, the precise anatomic components of the AV nodal reentrant circuit remained controversial. Josephson and colleagues *(17)* showed impressive evidence that the circuit was intranodal and this concept was contested by Jackman et al. *(18)* and McGuire et al. *(19, 20)*. The newer anatomic understanding of the node has made this debate largely moot. If one accepts the concept that the posterior nodal extensions as well as the transitional cells are part of the node *(12)* then the debate is largely resolved. Current understanding suggests that most subjects with AV nodal reentry have a final common pathway within the AV node and an upper pathway involving the fast and slow pathways surrounding the compact node.

In 1993 McGuire et al. *(19, 20)* nicely summarized the available information and proposed various models for tachycardia mechanisms which involve right-sided atrial inputs. Lately Jackman and colleagues have expanded on various subforms of AV nodal reentrant tachycardia (AVNRT) *(21)*. These include slow–fast form (antegrade conduction over the slow pathway and retrograde conduction over the fast pathway) (81.4%), slow–slow form (both antegrade and retrograde conduction over the slow pathway) (13.7%), and fast–slow forms (antegrade conduction over the fast and retrograde conduction over the slow pathway) (4.9%). The differentiation among these subforms is made based on the location of earliest atrial activation. The slow pathway retrograde conduction is manifest over the CS ostium region while fast retro conduction occurs over the antero-septal area just superior to the His bundle-recording site. In addition, Jackman et al. *(22)* have suggested left-sided inputs as part of the AV nodal reentrant circuit. Recently Gonzalez et al. *(23)* proved the existence of LA input to the AV node in humans with structurally normal hearts.

In addition, there are several case reports that documented the need to ablate AVNRT from the left annulus or left posteroseptal area *(24–26)*. One source of LA input is via the left-sided posterior nodal extension. The hypothetical left-sided inputs to the AV node and possible tachycardia circuits are illustrated in Fig. 4.

Surgical Ablation of AVNRT

Ross et al. *(27)* first introduced a non-pharmacologic therapy of AVNRT that involved surgical dissection in Koch's triangle, of which the results were confirmed by a number of surgical groups *(28–30)*. This technique also led to a better understanding of this tachycardia. For example, high-resolution mapping of Koch's triangle showed two distinct types of atrionodal connections in patients with "typical" slow–fast AVNRT. In most patients the retrograde fast pathway (either during tachycardia or ventricular pacing) showed earliest atrial activation over the apex of Koch's triangle while in the minority earliest atrial activation occurred near the CS. This would nicely compliment the current designation of AVNRT subforms *(21)*.

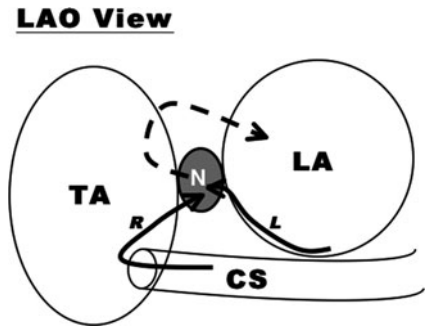

Fig. 4. Hypothesis of left-sided inputs to the AV node. In one iteration the coronary sinus musculature is involved with input into the region of the PNE. Ablation either within the coronary sinus or over the traditional slow pathway region (R) would be expected to ablate the circuit. Alternatively, the circuit may involve activation of the left atrium (LA) (shown by the *broken arrow*) either via the septum or Bachmann's bundle. Activation toward the AV node is through the tracts (L) along the mitral annulus. In the latter instance ablation over the putative left-sided inputs (L) will be required for arrhythmia cure.

Catheter Ablation of AVNRT

Catheter ablation of the AV junction using high-energy direct current (DC) shocks for control of drug-refractory SVT was first introduced in 1981 *(31)*. In 1989, two groups *(32*, *33)* almost simultaneously reported success using high-energy discharge in the region of slow pathway. The subsequent use of radiofrequency (RF) energy completely revolutionized catheter cure of AVNRT. The initial attempts targeted the fast pathway by applying RF energy superior and posterior to the His bundle region until the prolongation of AV nodal conduction occurred. Initial studies *(32–36)* showed a success rate of 80–90%, but the risk of AV block was up to 21%. Jackman et al. *(37)* first introduced the technique of ablation of the slow pathway for AVNRT. Among experienced centers the current acute success rate for this procedure is 99% with a recurrence rate of 1.3% and a 0.4% incidence of AV block *(38)* requiring a pacemaker.

Ablation of the slow pathway is achieved by applying RF energy at the posterior–inferior septum in the region of the CS. This technique can be guided by either via discrete potentials *(37*, *39)* or via an anatomic approach *(40)*; both have equal success rate. Radiofrequency energy is applied until junctional ectopics appear but at times successful slow pathway ablation may result without eliciting the junctional ectopic complexes. Final testing involves proof that either the slow pathway has been eliminated or no more than one AV nodal echo is present *(37*, *41)*.

More recently cryoenergy has been used for the slow pathway ablation *(42*, *43)*. The potential advantage of cryoenergy is the fact that the catheter sticks to adjacent endocardium during application of energy; hence, inadvertent catheter displacement and damage to the node are not possible. In addition, regions closer to the node may be explored since injury during the test procedure is reversible.

WOLFF–PARKINSON–WHITE SYNDROME

The Story of Wolff–Parkinson–White (WPW) Syndrome

The WPW syndrome holds particular interest not only for clinical cardiologists but also for anatomists, surgeons as well as clinical and experimental electrophysiologists. The definition of this syndrome was dependant upon a clear knowledge of both the normal conducting system and mechanism of reentrant arrhythmias.