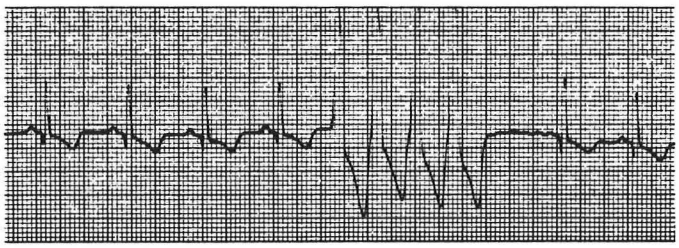
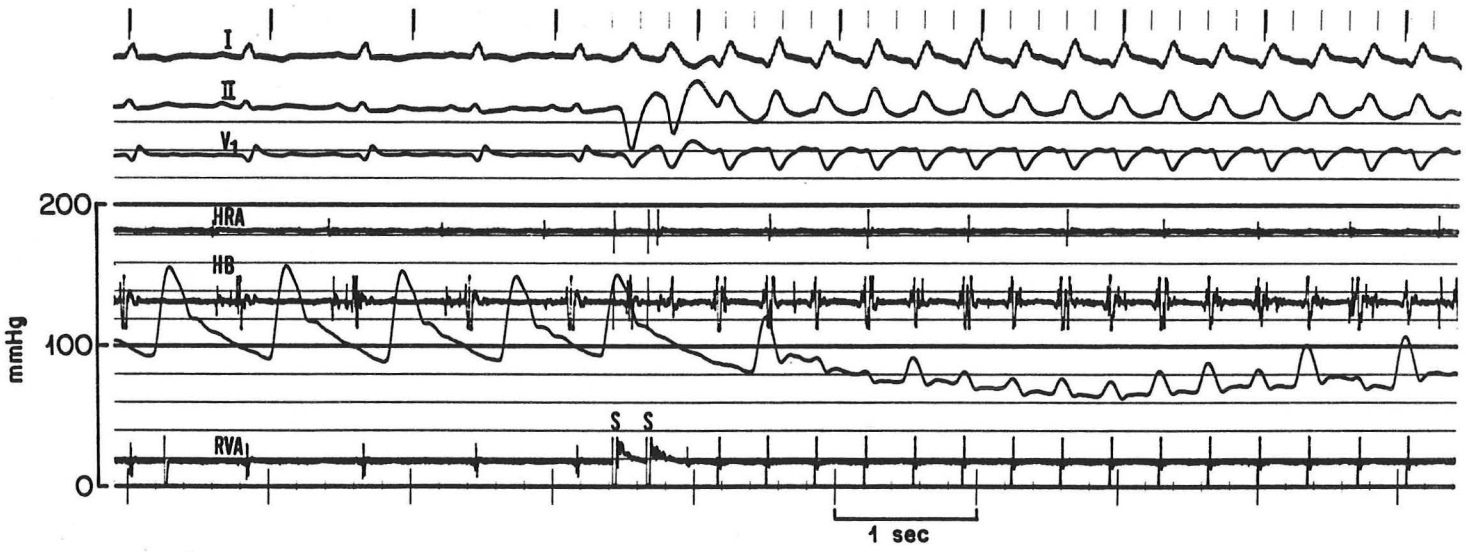
VENTRICULAR TACHYCARDIA





MEDICAL GRAND ROUNDS
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I. INTRODUCTION

A consideration of ventricular tachycardia (VT) at these exercises seems appropriate for a number of reasons.

First, the presence of this arrhythmia in the patient with heart disease is considered a marker of significant cardiac electrical instability, much more specific than the ubiquitous and frequently benign ventricular premature depolarization (VPD). Because VT may be a precursor of the ultimate ventricular arrhythmia, ventricular fibrillation (VF), its discovery in the individual patient marks a major point of departure in his management.

Second, alterations in medical practice patterns and technologic advances in ECG monitoring are bringing to attention increasing numbers of patients with various forms of VT. The physician is now called upon to manage not only VT associated with acute myocardial infarction and chronic left ventricular aneurysm (the most common clinical settings in which VT was recognized 10-20 years ago); he is also faced with patients varying from those with asymptomatic arrhythmias to survivors of out-of-hospital VF. Proper recognition of certain syndromes of VT can facilitate patient evaluation and management.

Third, a literal explosion of information about the electrophysiology of the normal and diseased human heart has become available from intracardiac electrode recordings during spontaneous arrhythmias and programmed cardiac extrastimulation. As such findings are coupled with data from experimental electrophysiologic studies, it becomes possible to begin to unravel the underlying mechanisms of repetitive ventricular arrhythmias in man.

Fourth, there have been major additions to the physician's options in antiarrhythmic therapy. Not only has the number of pharmacologic antiarrhythmic agents increased, but so has our knowledge of their salutary and adverse effects on the diseased human heart. Dramatic advances in pacemaker technology and cardiac surgery have allowed application of electrophysiologic principles to the treatment of very ill patients with recurrent VT and VF. The potential for future application of similar techniques to increasing numbers of patients is obvious.

II. ELECTROPHYSIOLOGIC AND ELECTROCARDIOGRAPHIC DIAGNOSIS

Most textbooks of electrocardiography define VT as three to five or more consecutive ventricular depolarizations at a rate which is both greater than 100 beats per minute (most commonly between 130 and 180 beats/minute) and greater than that of the previously dominant pacemaker of the heart. The classic ECG criteria of Robinson and Hermann (1921) are also well known, and include electrocardiographic similarity of the paroxysm to previously recognized VPD's, wide ($\geq$ 0.12 second) and notched QRS complexes, similar coupling intervals for single VPD's and the first beat of VT, and atrioventricular (AV) dissociation. Furthermore, capture and fusion beats (Cooksey et al., 1977), if present, aid in the diagnosis, as may a relatively long pause after termination of the arrhythmia (especially in the presence of atrial fibrillation). However, these rules and others which relate largely to QRS morphology, still do not allow definite distinction of VT from some supraventricular arrhythmias (Kastor et al., 1981).

A review of information obtained from intracardiac electrograms is now in order, both to understand the basis for their use in the diagnosis of VT, as well as to ensure understanding of future material dealing with electrophysiologic mechanisms of VT in man. In 1969, Scherlag et al. demonstrated that a bipolar electrogram, recorded from a catheter positioned in the low right atrium near the tricuspid valve, frequently included a high frequency potential identical in timing to that previously recorded directly from the Bundle of His in the conduction system of animals (Alanis et al., 1958; Scherlag et al., 1968). Multiple studies from different centers have confirmed that this high frequency deflection is a marker of depolarization in the His bundle region of the human conduction system (Damato et al., 1969; Narula et al., 1970; Roberts and Olley, 1972; Dhingra et al., 1973). The ability to record electrical activity in the infranodal part of the conduction system during a "silent" period of the surface ECG (the P-R segment) provided the opportunity to define the physiology and pathophysiology of AV nodal conduction in man (Kastor, 1975). When combined with the information available from the low right atrial electrogram and the high right ventricular electrogram which are recorded from the same catheter, conduction times across the AV node (the A-H interval) and the His-Purkinje system (the H-V interval) can be measured with great accuracy (Fig. 1). When multiple intracardiac electrograms, usually from standard positions in the high right atrium (HRA), right ventricular apex (RVA), and coronary sinus (CS) (a reflection of basal left ventricular and left atrial electrical activity) are recorded simultaneously, detailed information about the sequence of cardiac activation in sinus rhythm or during an arrhythmia becomes available (Fig. 2, 3). Such multiple lead intracardiac recordings have replaced the single-lead "His bundle study" of previous years.

FIGURE 1. (adapted from Narula et al., 1971)

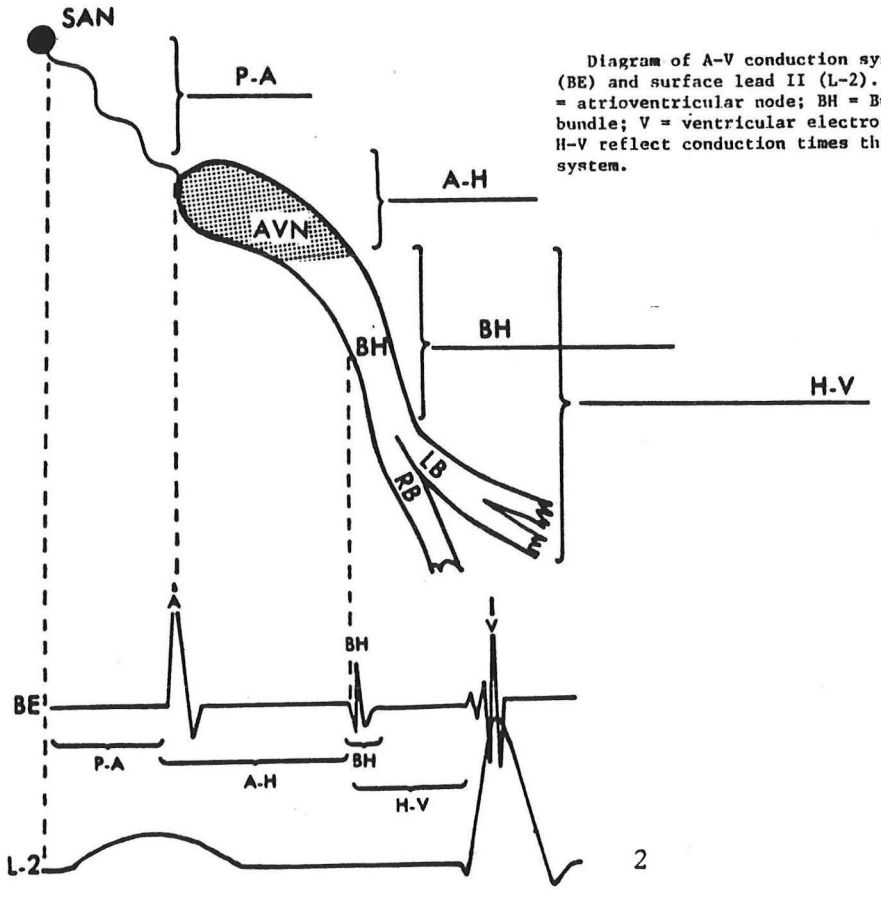
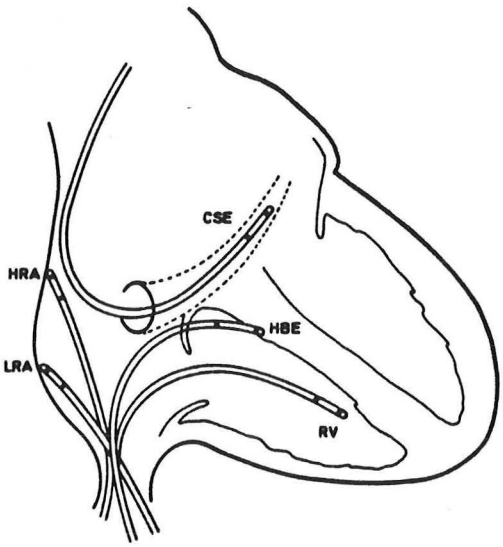


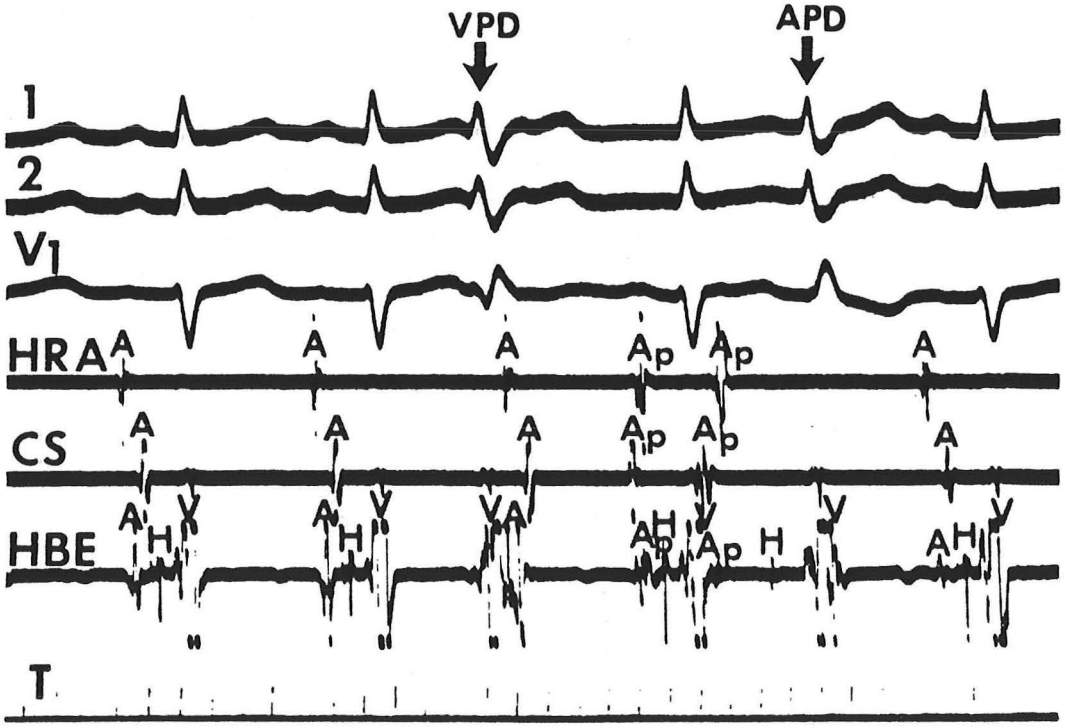
Diagram of A-V conduction system depicting Bundle of His electrogram (BE) and surface lead II (L-2). Abbreviations: SAN = sinoatrial node, AVN = atrioventricular node; BH = Bundle of His; RB = right bundle; LB = left bundle; V = ventricular electrogram; A = atrial electrogram. P-A, A-H, and H-V reflect conduction times through bracketed parts of the conduction system.

FIGURE 2. (from Curry, 1975)



Catheter electrode positions normally used for intracardiac recording. HRA = high right atrium; LRA = lower right atrium; HBE = His bundle lead; RV = Right ventricle; CSE = coronary sinus electrode representing, indirectly, left atrial and left ventricular sites.

FIGURE 3. (from Josephson and Seides, 1979)



Differentiation of ventricular premature depolarization (VPD) from an atrial premature depolarization (APD) with aberration. The third and fifth ventricular complexes both manifest a right bundle branch block pattern. The former is demonstrated to be a ventricular premature depolarization (VPD, arrow) because of the absence of a preceding His bundle deflection. The latter is aberrantly conducted (APD, arrow) from the second of two atrial premature depolarizations (A_p), which is not seen on the surface ECG (there is no clear P wave noted during the second A_p). Aberration is confirmed by a His bundle deflection's preceding the QRS complex which, in this case, is associated with H–V prolongation. The fact that clear His bundle deflections are recorded before and after the VPD rules out improper position of the catheter as the cause of failure to record a His bundle spike with the VPD.

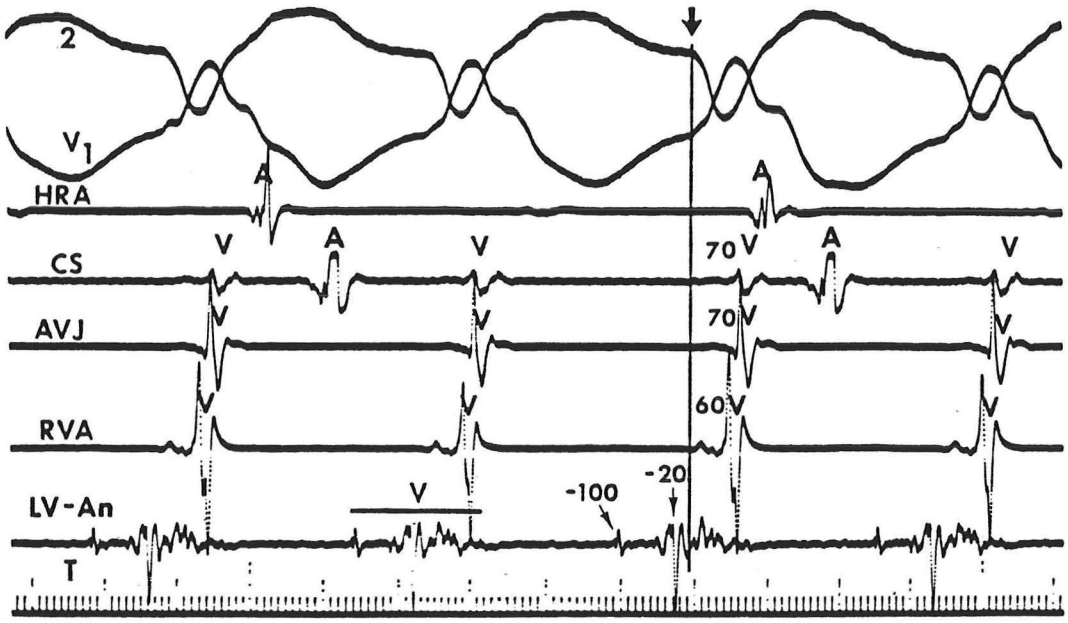
A large body of knowledge exists regarding the characteristics of cardiac activation during various arrhythmias. In general, ventricular depolarizations which are preceded by a His potential (H) in the His bundle electrogram (HBE) are considered supraventricular in origin, whereas those not preceded by an H are considered to be ventricular (Fig. 3). A major qualification of this definition is that one must be certain that failure to record a His potential does not result from catheter malposition; confirmation of adequate catheter position is usually obtained by recording a satisfactory His potential in sinus beats either before or after the occurence of the beat(s) in question (Josephson and Seides, 1979). A second qualification of this definition is that antegrade conduction through an atrioventricular bypass tract (which may result in ventricular activation before the H in response to a supraventricular impulse) is not present. There is one instance where ectopic beats arising within the ventricles may be consistently preceded by a His potential, thus constituting a third qualification of these guidelines for distinguishing supraventricular and ventricular beats. Fascicular rhythms and premature beats are thought to arise in the proximal conduction system or the bundle branches, just distal to the bundle of His. Because impulses arising in these parts of the conduction system may conduct in both antegrade and retrograde directions, it is possible for a propagating wave front to reach the nearby His bundle (resulting in an H) before it travels through the distal ramifications of the conduction system to ventricular myocardium (which must occur for production of a ventricular complex). His potentials may therefore be recorded shortly before the onset of the QRS complex. The correct diagnosis can usually be made, however, because the apparent H-V interval is much shorter (< 35 milliseconds) than during antegrade conduction through the His bundle (Castillo et al., 1971; Cohen et al., 1972). Fascicular beats are considered to be of ventricular origin because they arise below the bundle of His. When their origin is within the proximal conduction system (before division into right and left bundle branches), antegrade ventricular activation may be similar to that for normally conducted supraventricular impulses, and the QRS complex may therefore be similar in duration and axis to that recorded in sinus rhythm (Rosenbaum, 1969).

The differentiation of sustained VT from supraventricular tachycardia (SVT) hinges on the presence or absence of His potentials preceeding ventricular activation. His potentials during sustained VT may occur randomly, at fixed or variable ratios in relationship to the QRS complex, in a fixed relationship to atrial activity, or as a result of retrograde activation of the His bundle from ventricular depolarization. In many instances of VT, a retrograde His potential is probably buried within the high amplitude ventricular electrogram, and is thus not discernible. When retrograde His activation occurs during VT and is followed by retrograde AV nodal conduction to the atrium, ventriculo-atrial conduction has occurred. The absence of such a relationship confirms the presence of AV dissociation, which is highly suggestive of VT.

Another piece of information which can be used to infer the site of origin of an arrhythmia (and thus the diagnosis of VT) is the relationship of earliest site of endocardial electrical activity in reference to an observed wave form on the surface ECG. With regard to VPD's and VT, if ventricular electrograms begin simultaneously with or before the onset of the QRS complex, the ventricular electrogram is being recorded from a site with very early activation, before that of the bulk of the ventricular myocardium. Thus, recording of very early electrical activity within, for example, the border of a ventricular aneurysm (Fig. 4), implies that the aneurysmal tissue is the site of origin of the ectopic beat or

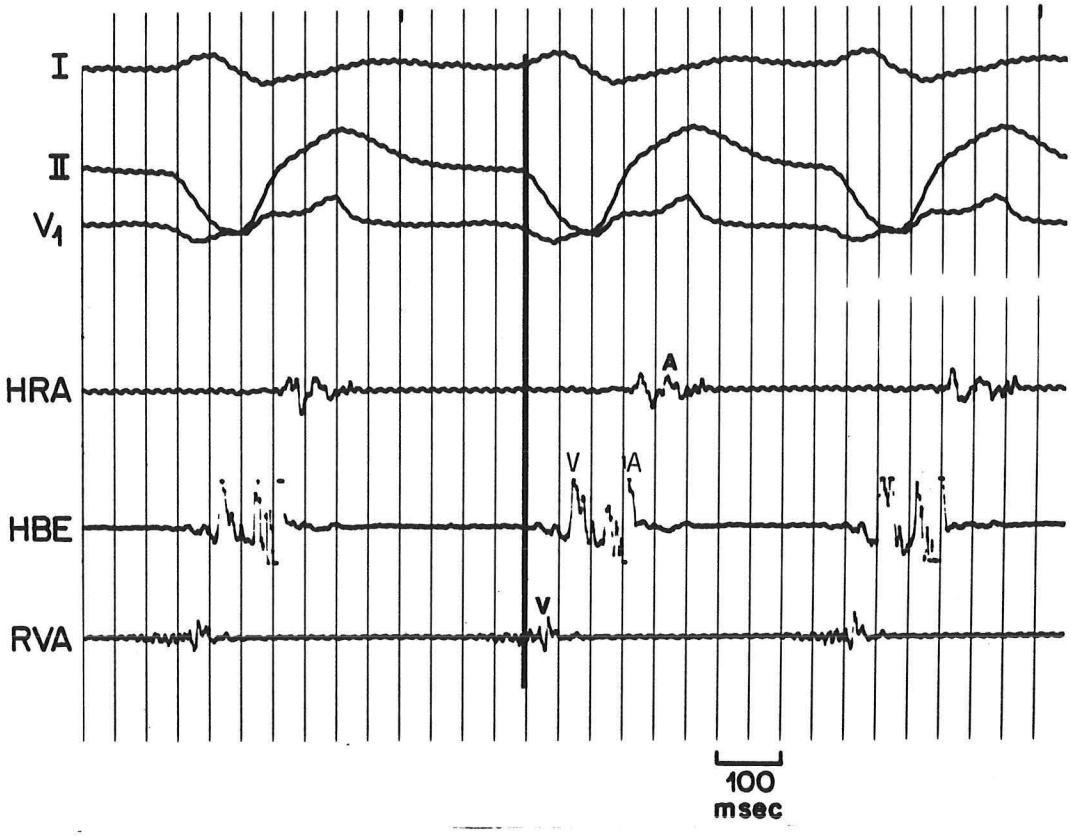
sustained tachycardia in question (Josephson et al., 1978b). On-line comparisons of activation times are easily made when multiple surface ECG and intracardiac leads are displayed simultaneously. The concept of earliest electrical activity (epicardial and endocardial) is the basis of mapping techniques to define the "site of origin" or "site of perpetuation" of various tachycardias (Fig. 5).

FIGURE 4.



Ventricular tachycardia with right bundle branch block morphology arising in a left ventricular aneurysm. From top to bottom: ECG leads 2 and V_1 and electrograms from the high right atrium (HRA), coronary sinus (CS), A–V junction (AVJ), right ventricular apex (RVA), and a left ventricular aneurysm (LV–An). T = time lines. The tachycardia originates in the LV–An, where fragmented diastolic activity is observed (From Josephson ME, et al: Circulation 57:440, 1978.)

FIGURE 5.



(PMH #79-33-50) Surface and intracardiac recordings during VT in a patient with arrhythmogenic right ventricular dysplasia. Electrical activity in right ventricle precedes onset of QRS by at least 50 msec, compatible with right ventricular origin of VT.

A frequently discussed topic, which seems to be taking on more importance as more specific antiarrhythmic therapy becomes available, is the differential diagnosis of the site of origin of a sustained wide-QRS tachycardia, i.e., VT versus SVT with aberrancy. This distinction has haunted electrocardiographers and clinicians for years, leading to scores of publications and suggestions of "rules" for differentiating "ectopic" VPD's from "aberrantly conducted" supraventricular impulses (Pick and Langendorf, 1960; Sandler and Marriott, 1965; Marriott and Sandler, 1966). The development of intracardiac recording techniques which allow determination of the chamber of origin of ectopic beats and sustained tachyarrhythmias provides a "gold standard" for evaluation of the validity of previously promulgated rules. A work of major importance in this area appeared in 1978 from the laboratory of Dr. Hein Wellens (Wellens et al., 1978a). One hundred forty episodes of sustained, wide-QRS tachycardia in 122 patients were characterized with regard to simultaneous intracardiac and surface ECG recordings. VT was diagnosed when a His potential failed to precede the QRS or preceded it at an interval shorter than in sinus rhythm. SVT with aberration was diagnosed when the H-V interval was present and equal to or longer than that observed in normal sinus rhythm. The findings confirmed and/or pointed out limitations of earlier touted rules for this distinction, and produced several others. The

following surface ECG findings, when present, were diagnostic of VT: a) QRS duration $\geq$ 0.15 seconds, b) evidence of AV dissociation, c) supraventricular capture beats during tachycardia, d) fusion beats during tachycardia. In addition, left axis deviation (< -30°) during tachycardia had a predictive value of 91% for the diagnosis of VT. Although simple notation of right bundle branch block (RBBB) or left bundle branch block (LBBB) morphology of the tachycardia was of no diagnostic significance, certain ancillary findings were of importance when considered along with the basic tachycardia morphology:

a) Right bundle branch block morphology

1) In lead V_1, a mono- or biphasic QRS complex (QRS types 1, 6, and 7 in Table 1), or a triphasic complex with a higher initial limb ("left rabbit ear" RsR', complex 5 in Table 1) were essentially diagnostic of VT (predictive value 97%)

2) A "classic" RBBB triphasic complex in V_1 (rSR' complexes 3 and 4 in Table 1), was highly suggestive of SVT (predictive value 91%)

3) In lead V_6, an R/S ratio of < 1.0 (QRS types 3-5 in Table 2) was indicative of VT (predictive value 94%)

4) If the ventricular rate was $\geq$ 170 beats/minute, SVT was more likely (predictive value 69%)

TABLE 1. (from Wellens et al., 1978a)

Configuration of Right Bundle Branch Block-Shaped QRS Complexes in Lead V_1 During Tachycardia

Type Complex	QRS Configuration in Lead V_1	
	Aberrant	Ventricular Tachycardia
1 	–	12
2 	7	9
3 	12	2
4 	28	2
5 	–	4
6 	1	12
7 	–	4
	48	45

TABLE 2. (from Wellens et al., 1978a)

Configuration of Right Bundle Branch Block-Shaped QRS Complexes in Lead V_6 During Tachycardia

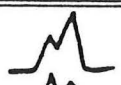
Type Complex	Aberrant	Ventricular Tachycardia
1 	31	2
2 	15	10
3 	2	18
4 	–	11
5 	–	3
6	–	1
	48	45

b) Left bundle branch block morphology

The only helpful lead was V_6, where the presence of an initial q wave (QRS types 3 and 4 in Table 3) was diagnostic of VT.

TABLE 3. (from Wellens et al., 1978a)

Configuration in Lead V_6 in Patients with Left Bundle Branch Block-Shaped QRS Complexes During Tachycardia

Type Complex	Aberrant	Ventricular Tachycardia
1 	10	11
2 	12	10
3 	–	3
4 	–	1
	22	25

Considerations of tachycardia regularity were not of great diagnostic importance, unless chaotic irregularity was present to suggest atrial fibrillation with aberrant ventricular conduction. Furthermore, the classic findings of AV dissociation, capture and fusion beats, although highly specific were not at all sensitive for the diagnosis of VT; indeed, 50% of patients with confirmed VT had evidence of ventriculo-atrial conduction during tachycardia, and fusion beats were present in only 4 of 70 episodes of VT (6%).

This study stresses the importance of recording multiple surface ECG leads during sustained tachyarrhythmias to derive the most diagnostic information, and emphasizes the limitations of the differential diagnosis of ventricular and supraventricular beats and tachycardias from single-lead ECG's or monitor strips. Furthermore, it points out that a secure diagnosis of VT vs. SVT from the surface ECG is frequently impossible. This important study has some limitations: 1) excluded from the study were patients who had pre-existing bundle branch block during sinus rhythm -- it is uncertain whether the same rules with regard to axis and QRS wave forms in V_1 and V_6 would apply to this group of patients, 2) patients with atrioventricular bypass tracts were excluded, 3) the study concerned itself only with wide QRS (0.12 seconds or more) tachycardias, therefore eliminating from consideration the unusual but important-to-recognize patient with ventricular or fascicular tachycardia with a narrow QRS complex (Cohen et al., 1972). 4) Finally, as the authors point out, these criteria were not tested by prospective application.

III. CLINICALLY RECOGNIZABLE SUBGROUPS OF PATIENTS WITH VENTRICULAR TACHYCARDIA

With the emergence of in-hospital, on-line ECG monitoring in coronary care units, and later developments in telemetry and Holter monitoring and computerized arrhythmia detection systems, it is more and more common for the physician to detect complex ventricular ectopy in patients with a wide variety of underlying cardiac conditions. Such monitoring has demonstrated that spontaneous VT may produce severe hemodynamic compromise and/or degeneration into VF. Monitoring may temporally correlate previously vague symptoms with the occurrence of arrhythmias, thus facilitating understanding of patients' symptoms and leading to proper therapy. Frequently, however, monitoring exposes high grades of ventricular ectopy, including VT, which are asymptomatic: the detection of such arrhythmias raises major questions with regard to proper management.

These advances in monitoring techniques have provided realization that "ventricular tachycardia" is not a single syndrome or disease entity, but rather an expression of multiple physiologic and pathologic conditions which cause alterations in cardiac electrical activity. An attempt at an etiologic or at least a syndromic classification of VT, therefore, seems desirable because of possible implications for better determining patient prognosis and management. Attempts at such classification are now in very early stages, and will doubtlessly undergo many changes during the next few years. Table 4 lists multiple clinical, etiologic, ECG and electrophysiologic variables which may be used to classify VT. Except for those electrophysiologic characteristics listed in the last column, all can be recognized by history, physical examination, and routine non-invasive diagnostic techniques (ECG monitoring, exercise stress testing, echocardiography, and radionuclide ventriculography). A complete classification of a patient with regard to presence or absence of these variables, many of which are not mutually exclusive, would create thousands of possible subgroups and would not be applicable for clinical purposes. Fortunately, it seems likely that the number of syndromes of VT which are commonly observed in clinical medicine is much smaller. The following paragraphs summarize the principal features of several common, well-defined and clinically relevant syndromes of VT:

TABLE 4.

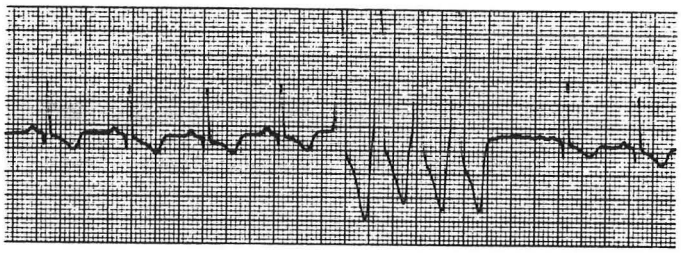
VARIABLE FEATURES OF VENTRICULAR TACHYCARDIA TO BE CONSIDERED IN CLASSIFICATION SCHEMES

Clinical Presentation	Underlying Cardiac Condition	Electrocardiography	Electrophysiologic Features
- Symptomatic - Asymptomatic - Sustained - Non-sustained - Ischemia induced - Exercise induced - Exercise suppressed - Stress related - Sleep related - Mechanically (catheter, pacemaker) induced - Bradycardia induced - Associated with marked metabolic or biochemical imbalance ($\downarrow pO_2$, $\uparrow K^+$, etc.) - Associated with toxins (digitalis, quinidine, tricyclic antidepressants, alcohol) - Degenerates to VF	- Heart disease a) CAD (acute MI, angina, old MI, aneurysm) b) Cardiomyopathy c) Valvular disease disease (incl. mitral prolapse) d) Congenital heart disease (incl. some long QT pts) e) Others - "Normal" heart	- Rates from 60-250 have been considered "VT" - Idioventricular - Regular - Irregular - Pleomorphic - Monomorphic - *Torsades de pointes* - RBBB form - LBBB form - Wide ($\geq$0.12 sec) QRS - Narrow QRS - Parasystolic - Fascicular - Bidirectional - Accelerating (R on T, or VT of "vulnerable period") - Repetitive (Parkinson-Papp)	- Inducible by PES - Not inducible by PES - Terminated by PES - Not terminated by PES - Single "site of origin" - Multiple "sites of origin"

A. Non-sustained Ventricular Tachycardia

This arrhythmia is most often detected by ambulatory Holter monitoring, by in-hospital telemetry monitoring, and occasionally on a routine ECG. Various authors differ in the exact duration of VT which they classify as non-sustained, but most definitions will classify up to several seconds of successive ventricular extrasystoles as non-sustained VT. The arrhythmia most commonly lasts for only 3-7 beats (Fig. 6). It may cause palpitations, but is commonly asymptomatic. Persons with impaired cardiac reserve or other conditions predisposing to cerebral hypoperfusion may develop lightheadedness as a result of this arrhythmia, particularly if they are in an upright posture when it occurs. In hospitalized patients at bed rest, it is very commonly asymptomatic. This arrhythmia is usually associated with complex VPD's, but may occur in their absence. It may occur in patients known to have had sustained VT or VF. With regard to our discussion here, it does not include those types of VT associated with prolongation of the QT interval. The successive QRS complexes may be identical or multiform.

FIGURE 6.



Non-sustained VT (asymptomatic) detected by Holter monitoring.

Although this arrhythmia, like most types of VT, usually occurs in patients with heart disease, there are multiple well-documented instances of its occurrence in normal, healthy subjects. Approximately 2% of subjects without evidence of heart disease have non-sustained VT on Holter monitoring (Winkle, 1980). The syndrome of "repetitive" VT, in which short paroxysms are separated by sinus beats, is a rare form of non-sustained VT most commonly seen in patients without obvious heart disease (Parkinson and Papp, 1947; Heger et al., 1980). Ambulatory monitor recordings in patients with heart disease (Winkle, 1980) have shown that 40-50% of episodes of VT are only three beats in duration, that they tend to occur at normal heart rates during ordinary activity, and that less than 10% of them are symptomatic. The sense of urgency felt by most physicians upon the detection of this arrhythmia most likely results from their experience with patients with acute myocardial infarction, where it is commonly taught that repetitive arrhythmia is a "warning" of potential VF. It is not clear that non-sustained VT in the absence of ischemia is a major separate risk factor for mortality above and beyond other clinical features (i.e., frequent complex VPD's and severe heart disease with left ventricular dysfunction) (Moss, 1980; Winkle, 1980; Califf et al., 1981).

B. Recurrent Sustained Ventricular Tachycardia

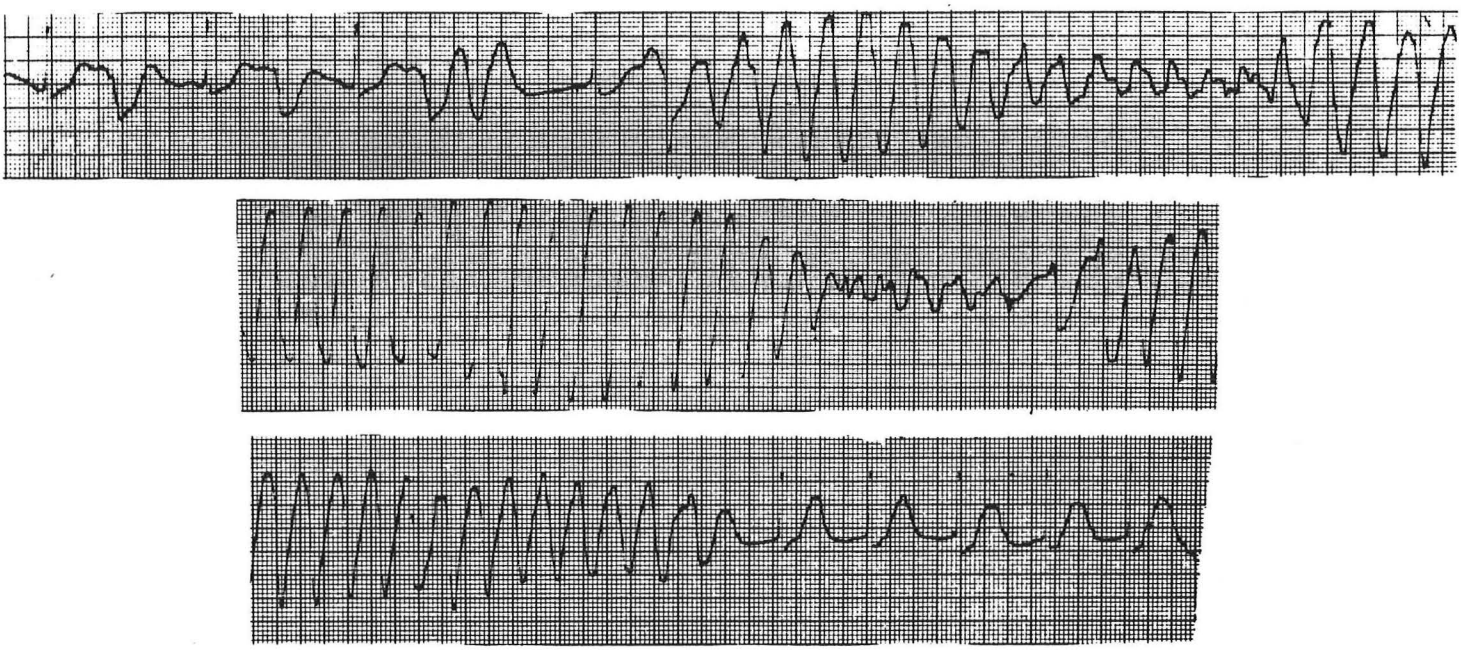
This syndrome is quite similar electrocardiographically to that described above except for the fact that runs of VT vary from minutes to days in duration. Such episodes of VT are almost always associated with structural heart disease,

most commonly coronary artery disease with either frank left ventricular aneurysm or major left ventricular segmental wall motion abnormality due to myocardial infarction. Patients with various forms of cardiomyopathy, valvular, and congenital heart disease, and those with ventricular injury resulting from cardiac trauma or previous cardiac surgery may also occasionally present with a syndrome of recurrent sustained VT. Episodes of symptomatic tachycardia may be widely separated in time, and precipitating factors, including QT interval prolongation and acute ischemia, are usually not obvious. These episodes of VT are symptomatic, except in occasional patients with excellent ventricular function or those in whom the rate of VT is dramatically slowed by antiarrhythmic drug therapy. Common symptoms include palpitation, dyspnea, lightheadedness, and syncope. Obviously, depending on the patient's residual ventricular function, the overall ventricular rate, and the level of perfusion pressure to vital organs, there is wide variability in the clinical severity of the patient's symptoms. Some episodes of recurrent sustained VT may ultimately degenerate to VF, while others may last long enough to produce a low cardiac output state, including pre-renal azotemia and biventricular heart failure. Hemodynamic sequelae may be worsened if the patient is on cardiodepressent drugs, if he is markedly volume overloaded or volume depleted, or if he develops angina or myocardial ischemia. The wide spectrum of response allows some patients to be no more symptomatic than many with paroxysmal SVT, and patients with recurrent sustained VT are sometimes able to walk into emergency rooms and seem in such mild to moderate distress that the possibility of VT is not considered by the physician. It is this subgroup of patients in whom classic physical signs of A-V dissociation may clinch the diagnosis of VT: a variable first heart sound, cannon A waves in the jugular venous pulse, and frequent variation in pulse pressure and amplitude are the most easily detectable of these features. It is also in this group that the clinical value of ECG rules for distinction of the "site of origin" of wide QRS complex tachycardias have obvious clinical significance. The syndrome of recurrent sustained VT is much less common than that of non-sustained VT, but has been discussed much more frequently in the literature because of its symptomatic nature and its frustrating tendency to recur despite antiarrhythmic therapy. It is in this group that pacemaker and surgical therapy have been considered for a number of years. Finally, it is in this subgroup of patients that invasive electrophysiologic testing has been most commonly performed, thus leading to major advances in the understanding of mechanisms and treatment options. The prognosis of recurrent sustained VT in the absence of acute myocardial infarction is bleak, and approaches a 50% mortality in 1-2 years (Armbrust and Levine, 1950; Hermann et al., 1959). It is generally agreed that this prognosis is much worse than that of asymptomatic or non-sustained VT. The fact that it is almost always symptomatic removes from consideration major questions about the need for therapy.

C. Ventricular Tachycardia Associated with Prolongation of the QT Interval

Repetitive ventricular beating associated with various syndromes of delayed myocardial repolarization usually has a characteristic polymorphic appearance which was first termed in the French literature *torsades de pointes* (Dessertenne, 1966). This nomenclature is being used in English-speaking countries in deference to the original French reports and because the translation "twisting of the points" is considered too clumsy for use (Smith and Gallagher, 1980). The arrhythmia is characterized by cycles of alternating electrical polarity in at least some of the standard ECG leads, such that the QRS complexes seem to be twisting around the isoelectric line of the recording (Fig. 7). The arrhythmia frequently terminates spontaneously after variable periods of time, but may also

FIGURE 7.



Torsades de pointes ventricular tachycardia. Monitor leads are continuous. Ventricular bigeminy with prolonged QT interval is followed by a ventricular couplet, then VT with twisting or "ballet" morphology. VT suddenly terminates and is followed by normal sinus rhythm.

deteriorate into VF. Because of its rapid rate, bizarre appearance, and tendency to terminate abruptly, *torsades de pointes* probably accounts for most reports of "spontaneously terminating" VF. It is almost always associated with prolongation of the corrected QT interval except in cases of extreme bradycardia when the QT_c may be at the upper limit of normal, but the absolute value of the QT interval is markedly prolonged. Prominent U waves and U or T-U wave alternans may precede episodes of *torsades de pointes*. Patients with these arrhythmias usually have symptoms which correlate with prolonged episodes. In most instances where the arrhythmia is recognized, an underlying cause can be identified; since many are either iatrogenic, self-limited or easily reversible, recognition of this type of VT is mandatory for proper management. The causes of *torsades de pointes* are essentially those of prolongation of the QT interval, and are listed in Table 5. The diagnosis of congenital QT prolongation (Jervell and Lange-Nielsen or Romano-Ward Syndromes) should be made only after a careful search for acquired causes of QT prolongation. The mechanism of the arrhythmia is not definitely known and may vary from case to case. A strong case has been made, in experimental models, for inhomogeneity of myocardial repolarization within the ventricles being responsible for QT prolongation (Yanowitz et al., 1966). An autonomic imbalance in favor of cardiac sympathetic stimulation, mediated through the left stellate ganglion, is certainly part of the pathophysiology of some episodes of *torsades de pointes*, and left stellate ganglion block or ganglionectomy has constituted a successful form of treatment for chronic or otherwise unmanageable cases (Moss and Schwartz, 1979). James and his associates have reported focal neuritis and neural degeneration within the cardiac conduction system and intracardiac nerves, and have raised the question of whether a chronic viral infection or some degenerative process might account for the substrate of autonomic imbalance in some cases (James et al., 1978).

TABLE 5.

CAUSES OF *TORSADES DE POINTES*

1. Drugs
   Cardiac: type I antiarrhythmics, phenylamine, lidoflazin
   Psychotropic: phenothiazines, tricyclic antidepressants
2. Electrolyte disturbances
   $\downarrow K^+$, $\downarrow Mg^{++}$, $\downarrow Ca^{++}$
3. Intrinsic heart disease
   Myocarditis, acute MI, angina (including Prinzmetal's)
4. Autonomic imbalance
5. Central nervous system disease
   Intracranial hemorrhage
   Post pneumoencephalogram
6. Complete or high-grade AV block
7. Liquid protein diets
8. R-on-T pacemaker depolarization
9. Organophosphorous insecticides
10. Congenital QT prolongation syndromes (with and without deafness)
11. Neck surgery
12. Hypothemia
13. Arsenic poisoning

Regardless of the multiple etiologies of this type of VT, it still seems wise to consider this one general syndrome until further pathophysiologic or etiologic distinctions are clarified. Management of the syndrome, in addition to identification and withdrawal of precipitating factors, may consist of treatment with beta blockers, lidocaine, phenytoin, isoproterenol, overdrive pacing, bretylium, phenobarbital, and left stellate ganglion block or ganglionectomy. Details of management have recently been reviewed by Smith and Gallagher (1980). It should be emphasized that type I antiarrhythmic drugs (especially quinidine and disopyramide) may precipitate the arrhythmia in susceptible patients, some of whom will not have QT prolongation before treatment, and that this arrhythmia is at least one of the mechanisms of syncope associated with quinidine. Precipitation of *torsades de pointes* may occur without "toxic" serum levels of the offending drug, and may appear after the patient has tolerated the agent for long periods of time. Failure to recognize *torsades de pointes*, whether it is due to type I antiarrhythmic drugs or not, may be lethal to the patient if *torsades de pointes* is "treated" with one of these agents which can further diversify myocardial repolarization and intensify electrical instability. Failure to recognize the situation is not always due to inattention to electrocardiographic detail, because the QT interval may vary from hour to hour, and changes are appreciated only by careful scrutiny of those ECG leads in which the offset of the T wave is most prominent. During evaluation of patients with "refractory ventricular arrhythmias" for either experimental drug therapy and/or electrophysiologic testing, we have identified seven patients with this subtype of VT in whom the first step was discontinuation of an antiarrhythmic drug, usually quinidine. This particular type of drug-induced arrhythmia is <u>not rare</u>, and increasing awareness of its ECG features should lead to both a healthy respect for potential lethal adverse reactions to antiarrhythmic drugs as well as proper management of patients with already prolonged QT intervals.

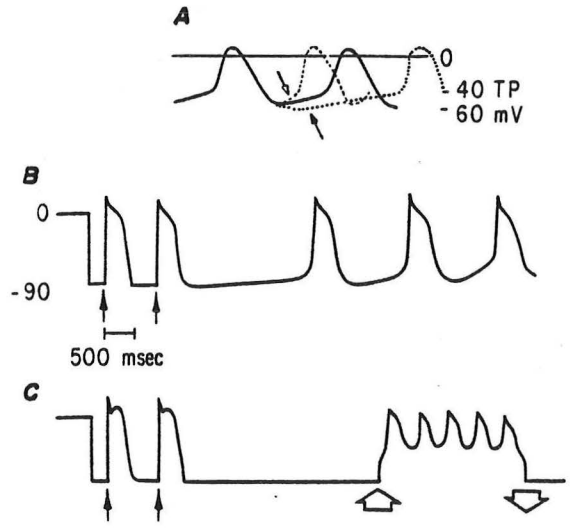
IV. MECHANISMS OF VENTRICULAR TACHYCARDIA

A. General Considerations

Three general types of mechanisms have been proposed for clinically observed VT (Wit and Rosen, 1981; Hoffman and Rosen, 1981):

1) Enhanced Automaticity. Automaticity is a normal property of several types of pacemaker cells, and may be observed in other types of cardiac cells under abnormal conditions. It is most simply defined as the capacity for initiation of cellular action potentials. In sinus rhythm, sinus node cells spontaneously depolarize at an interval which determines the heart rate; cardiac contraction and mechanical function depends upon an orderly propagation of this impulse throughout the heart. Other cardiac cell types which may normally possess automaticity are "specialized" atrial cells, cells in the AV junctional region (nodal cells), and cells in the specialized His-Purkinje system. Cells with automatic properties, whether normal or abnormal, have action potentials which demonstrate a slow diastolic depolarization during phase 4 of the action potential (Fig. 8). The firing rate of automatic cells is influenced by the time taken for diastolic depolarization to reach threshold potential, as well as by the absolute values of maximum diastolic potential and threshold potential. The rate of normally automatic cells may be decreased by vagal stimuli and increased by sympathetic stimuli or circulating catecholamines.

FIGURE 8. (from Wit and Rosen, 1981)



Automaticity in cardiac fibers. In (A) the solid trace indicates a sinus node transmembrane potential. There is a spontaneous decline in membrane potential during phase 4 (spontaneous diastolic depolarization) to the threshold potential (TP) causing normal automatic firing. The broken traces show how alterations in maximum diastolic potential (MDP) and in the rate of spontaneous diastolic depolarization alter the firing rate. The unfilled arrow indicates an acceleration in rate of impulse initiation caused by an increase in the rate of spontaneous diastolic depolarization. The filled arrow indicates a decrease in the rate of impulse initiation caused by an increase in MDP and a decrease in the rate of spontaneous diastolic depolarization. (B) shows transmembrane potentials recorded from a latent pacemaker cell (Purkinje cell) stimulated at the arrows. Spontaneous diastolic depolarization develops and normal automatic firing occurs when the cell is not stimulated. (C) shows transmembrane potentials recorded from a ventricular muscle fiber stimulated at the solid arrows. The muscle fiber does not develop normal automaticity when it is not stimulated. However, when the resting membrane potential is shifted toward zero, as can be done by passing a depolarizing current through a microelectrode (large arrow pointing upwards), abnormal automatic firing occurs at the low membrane potential. The current pulse is turned off (arrow pointing downwards) and automatic firing stops.

Under experimental conditions, cells which do not ordinarily possess automaticity may develop this property when their resting membrane potentials are reduced to approximately -60 millivolts. It is possible that such abnormal automaticity may occur as a result of multiple acute and chronic disease states, thus rendering many types of cells within the ventricles potential sources of automatic firing of either single or repetitive impulses, and thus the source of automatic arrhythmias.

2) Reentry. Reentry as a mechanism for cardiac arrhythmias requires simultaneous presence of several conditions (Table 6). Reentry is most simply defined as the failure of a propagated impulse to "die out" after activation of the heart -- the impulse persists (because of slow conduction) and is capable of reexciting part of the heart after the end of the refractory period. Thus more than one cardiac cycle may result from a single propagated wavefront. The original wavefront may be that of a normal sinus impulse, an "automatic" ectopic focus, or an artificially introduced electrical stimulus.

TABLE 6.

REENTRY

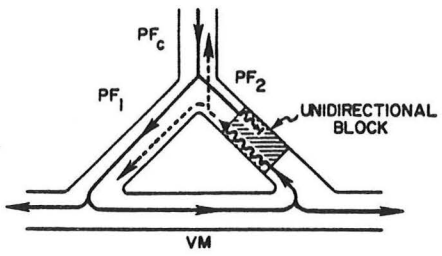
1. At least 2 functionally distinct pathways that join proximally and distally (initial and final common pathways)
2. Unidirectional block in one pathway
3. Slow conduction down the unblocked pathway, allowing previously blocked pathway time to recover excitability

Reentry mechanisms were described by Mayer following his studies of rings of excitable jellyfish subumbrella tissue and by Mines in 1912-1914 in studies of rings of atrial and ventricular muscles from the tortoise heart, and the principles derived from these experiments have been synthesized and embellished by multiple electrophysiologists (Wit and Cranefield, 1978). In general, a propagating cardiac impulse is thought to encounter a "branch point" with two discrete pathways for continued wavefront propagation; these pathways are joined both proximally and distally, thus forming a potential "reentrant circuit". Due to some physiologic or pathologic influence, unidirectional block for antegrade conduction of the impulse obtains in one of the pathways, and relatively slow conduction is present in the unblocked pathway. The slowly descending impulse traverses the unblocked pathway and begins to ascend the blocked pathway. If the block is indeed unidirectional, and if cells proximal to the block have had sufficient time to recover excitability (a function of their refractory period), the ascending impulse can reexcite these cells, propagate retrogradely to the initial common pathway, and then reenter the slowly conducting pathway for another attempt at traversal of the circuit. If conduction velocities, degree of unidirectional block, and refractory periods of those cells requiring critically timed reexcitation remain within certain limits, a perpetuating "reentrant rhythm" may occur (Fig. 9).

Wit and Rosen have calculated, on the basis of minimum normal refractory periods and conduction velocities in the heart (150 milliseconds and 0.5 meters/sec, respectively), that a reentrant pathway in cardiac fibers with normal conduction and refractoriness would have to be at least 7.5 cm long (Wit and Rosen, 1981). Because it is unlikely that such a large reentrant pathway could exist in an isolated or "protected" milieu uninfluenced by normal surrounding cardiac conduction, it is likely that a decrease in the conduction velocity is a very critical substrate of reentry. If conduction velocity were slowed to 0.05 m/sec (a value which can occur in diseased cardiac fibers or AV nodal tissue) the length of the reentrant circuit would be decreased to 7.5 mm in length, a distance which is probably much more obtainable in an intact heart.

Although the processes which result in relatively "isolated" and discrete pathways for conduction probably occur as a result of multiple congenital and acquired conditions, slowed conduction and unidirectional or transient conduction

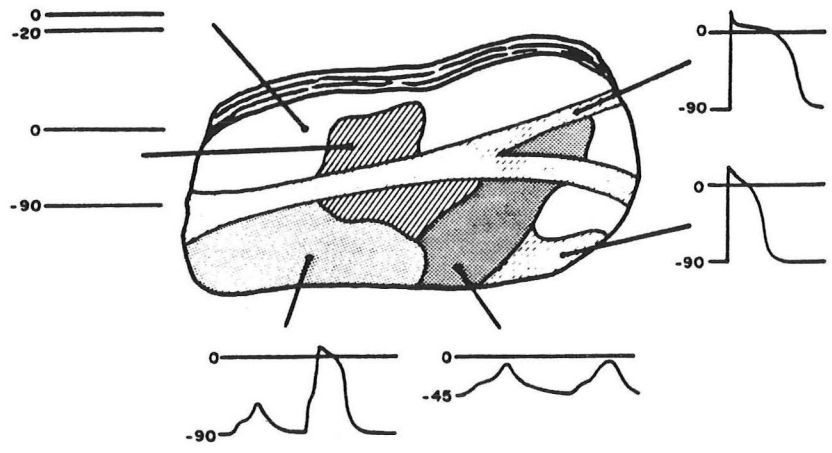
FIGURE 9. (from Arnsdorf, 1977)



Diagrammatic representation of the reentrant mechanism in terminal Purkinje fibers (PF) and ventricular muscle (VM). Normally, the impulse is conducted from the central Purkinje (PF_c) to the bifurcation where it continues down Purkinje fibers 1 and 2 (PF_1, PF_2) to the ventricular muscle. In this figure, a segment with unidirectional block and slow retrograde conduction is established in PF_2. The impulse descending from the central Purkinje finds antegrade conduction through the depressed segment in PF_2 blocked, but normally traverses PF_1 and enters the ventricular tissue from where it may enter PF_2 distally and conduct slowly in a retrograde manner through the depressed segment. As indicated by the dashed lines, if the conduction has been sufficiently slow in the depressed segment to allow the bifurcation and PF_1 to recover their excitability, the impulse may reenter this portion of the circuit, once more reaching the ventricular tissue or even traveling in a retrograde manner up the central Purkinje branch. Not only a reentrant beat, but a reentrant rhythm could be established by such a circuit.

blocks are readily explicable on the basis of well established electrophysiologic principles. The speed of cell-to-cell conduction (except in nodal fibers) is heavily dependent upon the amplitude of the cellular action potential and upon the rapidity of cell depolarization (V_{max} of phase 0). Any physiologic or pathologic condition which decreases the amplitude or V_{max} of phase 0 of the action potential may result in some slowing of conduction from cell to cell. Lowering of the resting membrane potential is thought to result in fewer open "sodium channels" for rapid sodium entry into the cell during phase 0 and to be a major final pathway by which multiple influences effect slowing of conduction. Also, the number of sodium channels available for depolarization is decreased during the cell's relative refractory period, and premature stimulation at this time results in an action potential with a depressed phase 0 amplitude and V_{max}. Variable levels of resting potential and refractory periods of cells in the pathway of a propagated impulse may, therefore, result in localized areas of slow conduction or functional unidirectional block (Moore et al., 1978) (Fig. 10).

FIGURE 10. (from Moore et al., 1978)



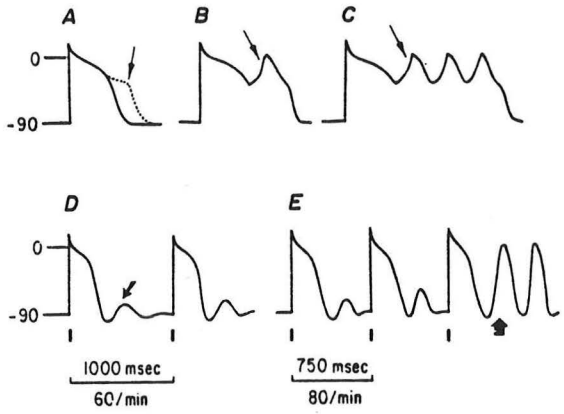
A schematic illustration of a human aneurysm preparation and the various action potentials that can be recorded. On the right are normal transmembrane potentials (−90 mV resting potentials) recorded from areas within the Purkinje system (upper right) and ventricular muscle (lower right). The action potentials presented below the drawing are the two types of abnormal action potentials recorded. On the left are slow potentials developing from normal resting potentials, while on the right are slowly rising low-amplitude potentials developing from low resting potential of −45 mV. On the upper left it can be seen that some cells with either normal (−90 mV) or abnormally low (−20 mV) resting potentials were totally electrically inexcitable.

During recent years, electrophysiologic studies have demonstrated anatomic feasibility of reentrant pathways in certain arrhythmias in man. Examples of reentry within anatomically identifiable pathways include reciprocating tachycardias associated with pre-excitation syndromes (e.g., antegrade conduction through AV node and retrograde conduction through an atrio-ventricular bypass tract) and bundle branch reentry following premature ventricular stimulation (Wellens and Durrer, 1975; Akhtar et al., 1974). These examples of reentrant arrhythmias have been termed "macro-reentry" because they involve identifiable structures of the conduction system. Ventricular arrhythmias and other types of atrial arrhythmias due to reentry occur in much less well defined and smaller circuits, and are thus defined as "micro-reentrant" circuits. Because of their lack of anatomic definition and the likelihood of their extreme variability from patient to patient and disease to disease, micro-reentry is still a much more theoretical concept than macro-reentry (Fig. 9).

A major feature which characterizes reentrant arrhythmia is that successive activation of the chamber or chambers in which the reentrant circuit exists occurs because that chamber is essentially a "passive bystander" being activated by a continuously propagating wavefront. If the cycle length of this wavefront is less than the interval required for spontaneous pacemaker depolarization, the reentrant rhythm (usually a tachycardia) will override activity of the dominant pacemaker. Automatic arrhythmias, on the other hand, result from continuous firing from an automatic focus at a rate greater than that of the previously dominant pacemaker. It therefore seems more appropriate to speak of "sites of origin" for automatic tachycardias and "sites of perpetuation" for tachycardias due to reentry.

3) Triggered Arrhythmias. Much more recent studies have demonstrated a third possible mechanism for tachyarrhythmias in the intact heart (Wit and Cranefield, 1976; Cranefield, 1977) (Fig. 11). The observation that, under certain experimental conditions, a second depolarization could result during partial repolarization has resulted in the term "afterdepolarization." Because such afterdepolarizations generally occur at a time during repolarization when the membrane potential is very low and the fast sodium channel is inactivated, they are thought to result from changes in membrane potential associated with the slow calcium current. Such afterdepolarizations are said to be "triggered" because they can occur only as the result of a previous, relatively normal action potential. If afterdepolarizations reach threshold potential, single or successive triggered afterdepolarizations might result in tachycardia. Experimental conditions known to result in triggered automaticity include the infusion of catecholamines and digitalis, hypoxia, and elevated carbon dioxide tension (Wit and Rosen, 1981; Wit and Cranefield, 1976). Hence, digitalis intoxication, myocardial ischemia, and stress-induced catecholamine release might be expected to precipitate arrhythmias due to triggered automaticity. Some investigators have suggested that afterdepolarizations which do not reach threshold may do so when the driving rate is increased, thus resulting in attainment of threshold and sustained arrhythmia as the result of premature stimulation or fixed rate pacing. It is now recognized that induction of sustained arrhythmia by pacing may not be specific for reentry as a mechanism. The most persuasive evidence against triggered afterdepolarizations as a mechanism of common types of VT in dogs (Garan et al., 1980) as well as in patients (Wellens et al., 1977) is that VT is not prevented by slow channel calcium blockers. In summary, the exact role of triggered afterdepolarizations in arrhythmogenesis in man is even more unclear than that of automaticity and reentry. If clinical arrhythmias are due to this mechanism, it is most likely that certain ectopic atrial tachycardias and arrhythmias due to digitalis intoxication are the prime examples.

FIGURE 11. (from Wit and Rosen, 1981)



In (A) an early afterdepolarization is indicated by the arrow. In (B) a single triggered action potential caused by this afterdepolarization is shown, while in (C) a train of triggered action potentials is shown (arrows in (B) and (C)). In (D) and (E) action potentials caused by propagating impulses (indicated by vertical lines) are followed by delayed afterdepolarizations (arrow in (D)). In (E) triggered activity caused by the afterdepolarizations occurs at the arrow.

B. Mechanisms of Ventricular Arrhythmias in Myocardial Ischemia

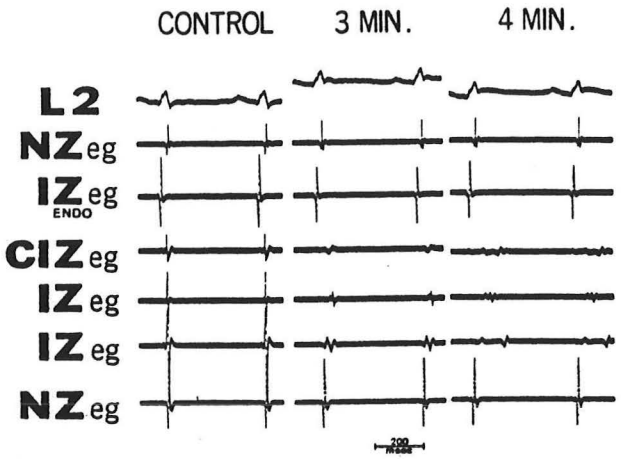
The largest body of data concerning mechanisms of VT has been collected in animal models of acute and chronic myocardial ischemia and in humans with various manifestations of coronary artery disease. Therefore, the data which we will review pertain almost exclusively to electrical instability resulting from either myocardial ischemia or from structural damage associated with myocardial infarction. It is generally thought that other disease processes which affect the ventricles produce a similar anatomic-electrical substrate, although there is very little experimental or clinical data to support this assumption.

The electrophysiologic consequences of coronary artery occlusion in the dog have been characterized over the past 30 years (Harris, 1950; Harris et al., 1951; Boineau and Cox, 1973; Williams et al., 1974; Scherlag et al., 1974; El-Sherif et al., 1977a and b; Lazzara et al., 1978; Garan et al., 1980; Michelson et al., 1980; Garan et al., 1981). Within five minutes of coronary occlusion in the anesthetized dog, multiform, frequently rapid VPD's and bursts of VT frequently occur and have a tendency to degenerate to VF. This first phase of electrical instability tends to last for about 30 minutes, and animals which survive it frequently enter a quiescent period of approximately 15 hours' duration. A second phase of manifest arrhythmia may then be observed which is characterized by much slower repetitive ventricular depolarizations which are not frequently associated with VF. Finally, between the third and seventh days, some animals enter a third phase of electrical instability characterized by few spontaneous repetitive ventricular arrhythmias, but by susceptibility to induction of VT or VF by programmed electrical stimulation or pacing techniques.

Intramural electrograms from the ischemic zone of the left ventricle have demonstrated fragmentation of electrical activity and marked heterogeneity of the timing of activation within minutes of coronary occlusion (Fig. 12). These fragmented electrograms are thought to represent the product of slow and fractionated conduction within the ischemic zone, and a reentrant mechanism for these early ventricular arrhythmias has therefore been proposed (Boineau and Cox, 1973; Waldo and Kaiser, 1973). It is thought that the ischemic process produces regional abnormalities in the electrical function of cell membranes (of both myocardial cells and Purkinje fibers), thus accounting for chaotic reentry over

dynamically changing pathways which results in multiform ventricular arrhythmias and VF. Indeed, "random" reentry within ventricular muscle has been proposed as the mechanism for VF (Hoffman and Rosen, 1981). Basic electrophysiologic studies in various models of the early ischemic setting have demonstrated decreases in cellular action potential amplitude and action potential duration and in the rate of cellular depolarization (Wit and Bigger, 1975; Lazzara et al., 1978).

FIGURE 12. (from Williams et al., 1974)

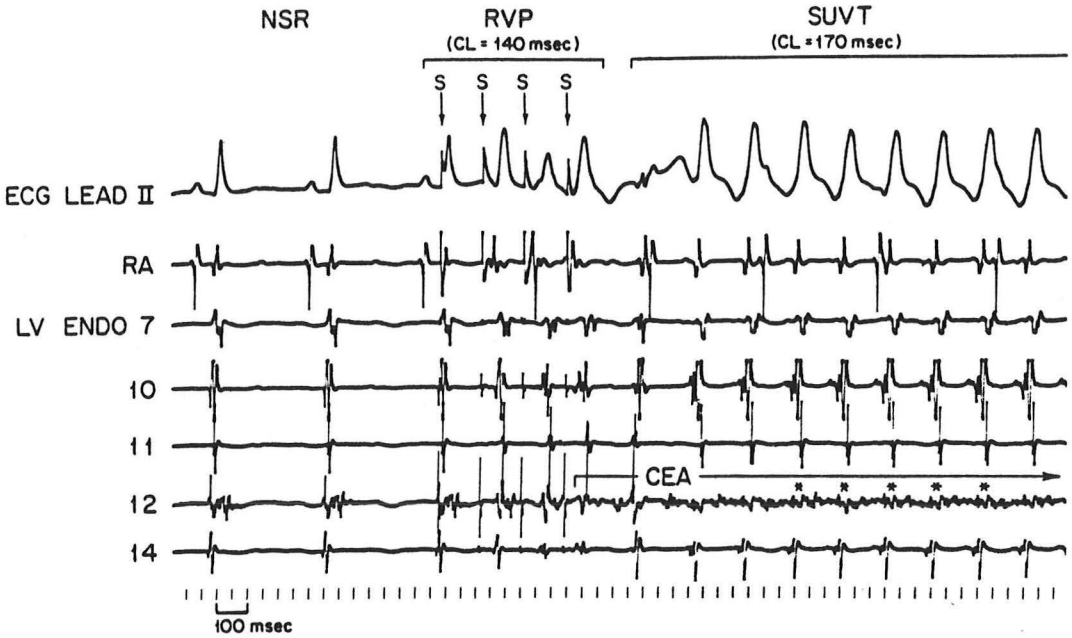


Records before (control), 3, and 4 min after coronary occlusion. Recordings from standard lead II (L2), two epicardial electrograms from a nonischemic normal zone (NZ eg), two electrograms recorded from bipolar wires from ischemic zones (IZ eg), one electrogram recorded with the composite electrode from ischemic zone (CIZ eg) and one endocardial ischemic zone electrogram (IZ eg ENDO). Progressive decrease in amplitude, increase in duration and fractionation is seen in the IZ eg recordings.

The second phase of ventricular arrhythmia following coronary occlusion in the dog is characterized by electrophysiologic inactivity of most myocardial cells (presumably because of cell death), but continued electrical activity in surviving Purkinje fibers (Friedman et al., 1973a). It is likely that some Purkinje fibers undergo delayed injury during this second phase of electrical instability, and that they will ultimately either regain normal electrical activity or die (Lazzara et al., 1974). These ischemic, damaged, but not yet dead subendocardial Purkinje fibers have been characterized by Friedman and Horowitz and their associates (Friedman et al., 1973b; Horowitz et al., 1976), who consider it possible that many arrhythmias in the second phase of post infarction electrical instability result from enhanced automaticity of these Purkinje fibers.

The third phase of electrical instability has been recognized more recently (El-Sherif et al., 1977a and b; Michelson et al., 1980; Garan et al., 1980). Studies in the intact animal demonstrate more localizable and stable fragmentation of electrical activity and slowed conduction than in the immediate post infarction period, and reproducible changes in these features occur in response to premature stimulation and increases in heart rate. In general, localized conduction delay and fractionation of electrical activity is exposed and maximized at rapid heart rates or during premature stimulation at short cycle lengths, until essentially continuous electrical activity is recorded at some sites in the ventricular myocardium (Fig. 13). Such continuous diastolic electrical activity is frequently observed at the onset of the type of pacing-induced VT which characterizes this phase of electrical instability following myocardial infarction. Continuous diastolic activity during VT has been recorded on both the epicardial (El-Sherif et al., 1977a and b) and endocardial (Garan et al., 1980) surfaces of the dog heart during these arrhythmias, and is thought to represent the heterogeneity of a conducting wavefront through well defined reentrant circuits. It is the general consensus that fixed reentrant pathways with anatomic reality do form during the healing phase of myocardial injury. Reentry over such fixed pathways

FIGURE 13. (from Garan et al., 1981)

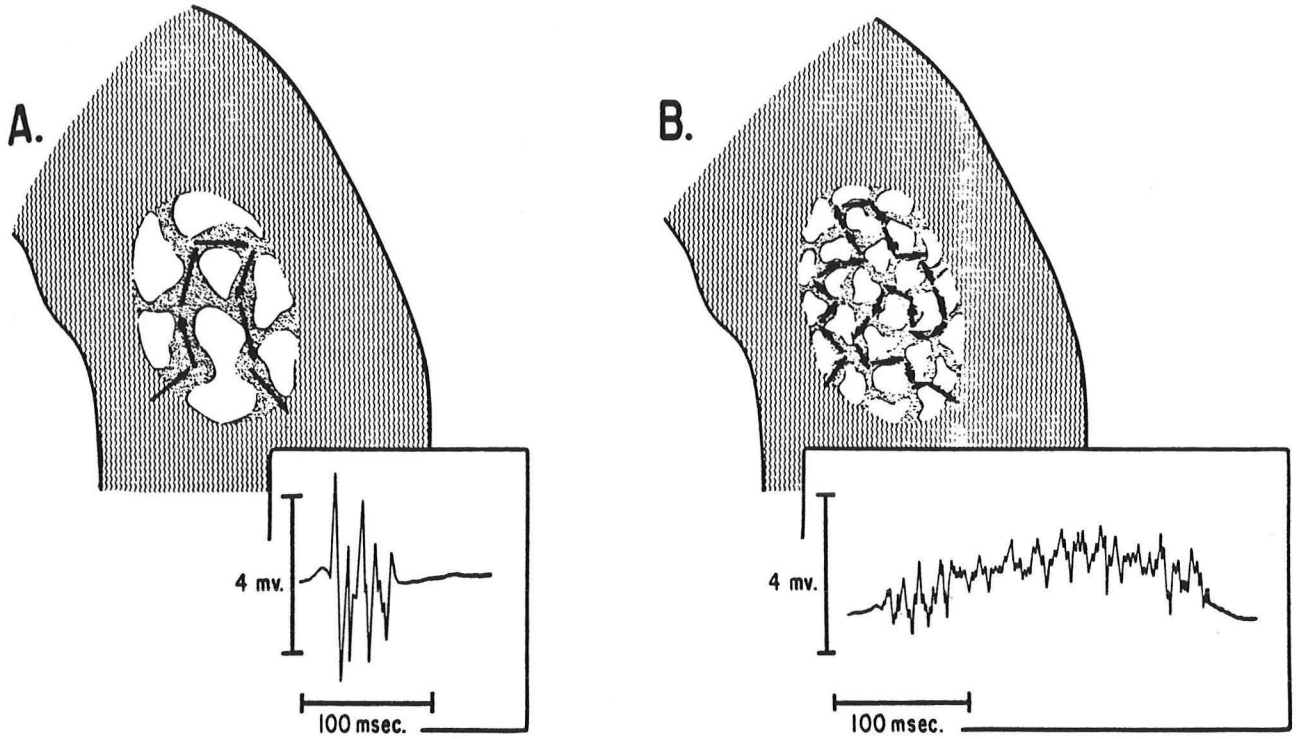


An episode of sustained uniform ventricular tachycardia (SUVT) initiated by a burst of rapid ventricular pacing (RVP) at a cycle length (CL) of 140 ms. Note the continuous electrical activity (CEA) recorded from LV-ENDO 12 (inferoseptal border of the left ventricular infarct zone). Note also that the continuous electrical activity demonstrates a reproducible repeating pattern (asterisks). LV-ENDO sites 7, 10 and 14 were recorded from the superior and septal borders of the infarct zones; LV-ENDO 11 was recorded from normal inferior wall. S = stimulus artifact.

has been called "ordered reentry" (Hoffman and Rosen, 1981). Although the exact anatomic features of these pathways are not well defined, it is not difficult to imagine how regional variations in patterns of myocardial injury might lead to different conduction velocities and localized conduction blocks in a complicated syncytium of surviving myocytes and Purkinje fibers. Such regionally damaged muscle and conduction system tissue may form a potential pathway which has all of the properties considered necessary for reentry as defined earlier. A reentrant circuit is thought to exist in the edge of the infarct in which frankly necrotic and viable myocardium interdigitate in an extremely complicated fashion (Fig. 14) (see page 21). Damage with similar regional characteristics might be produced by other myocardial diseases, thus allowing similar reentrant circuits to be established.

The three phases of electrical instability following experimental coronary occlusion may correspond to some of the arrhythmias seen in man following acute myocardial infarction. During the early hours of infarction, unpredictable, multiform and repetitive VPD's occur, and frequently degenerate to VF (Adgey et al., 1974). Beginning later during the first day, a better tolerated "accelerated idioventricular rhythm" or "slow ventricular tachycardia", which rarely leads to VF, may occur (Norris and Mercer, 1974). These sharply contrasting dysrhythmias may be the product of different mechanisms, i.e., disordered reentry and enhanced automaticity, respectively. Finally, late ventricular arrhythmias in the dog model are similar in timing, ECG characteristics, and modes of induction and termination, to VT occurring during the healing phases of myocardial infarction. It therefore seems likely that a second phase of reentry, indeed a more "ordered" reentry (Hoffman and Rosen, 1981), may be responsible for late in-hospital VT, and VT complicating ventricular aneurysm and healed infarcts. This last phase of electrical instability is probably the most important to understand for clinical purposes because it is likely involved in the majority of serious ventricular arrhythmias seen in patients with coronary artery disease, and because it is the best characterized phase of electrical instability in patients.

FIGURE 14. (from Boineau and Cox, 1973)



Suggested Mechanism of Complex Desynchronization and Slow Propagation. *In this schematic figure the white areas represent severely depressed (unexcitable) myocardium. The stipled areas represent less severely depressed, nonhomogeneously excitable myocardium. The area of wavey lines represents normally excited myocardium in the absolute refractory period. In A, the more coarsely distributed nonhomogeneity results in fewer spikes of larger amplitude, and a shorter duration of the activity than in B. In B, the more finely distributed nonhomogeneity of depressed excitability results in more complex and effectively longer pathways. The greater degree of asynchronous excitation in B results in a larger number of spikes of smaller amplitude, and a markedly prolonged duration of the circuitous activity confined to this region. The activity is confined by the absolute refractory state of the surrounding myocardium which has previously been excited by the normally propagated wavefront through this region. In this example there is interplay between the duration of persistent desynchronized activity and the duration of the recovery period of the surrounding myocardium, a factor which determines whether re-entrant PVCs are generated or not.*

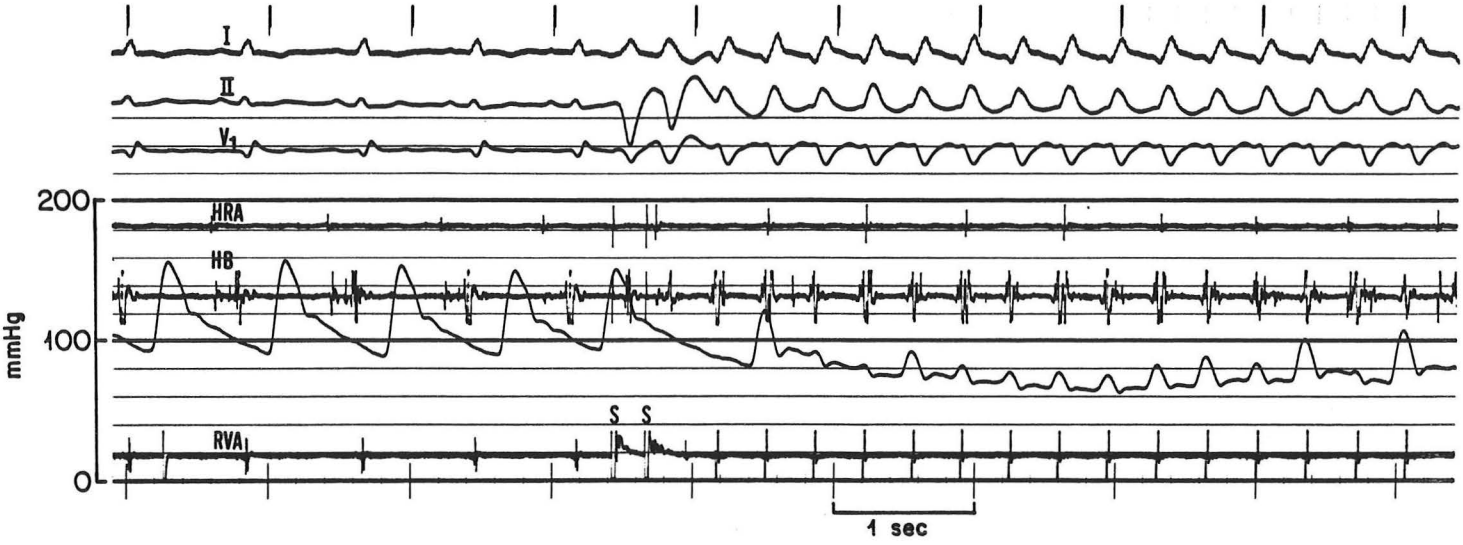
C. Mechanisms of Ventricular Tachycardia in Man

Much of what we know today about the mechanisms and clinical electrophysiology of VT in patients has resulted from the pioneering clinical studies of Dr. Hein Wellens in the Netherlands (Wellens et al., 1972; Wellens et al., 1974; Wellens et al., 1976; Wellens et al., 1978b). After he and others had shown the utility and safety of atrial pacing and programmed stimulation in the induction and termination of various supraventricular tachycardias and the reciprocating tachycardias associated with pre-excitation syndromes (Durrer et al., 1967; Bigger and Goldreyer, 1970; Goldreyer and Damato, 1971; Coumel and Attuel, 1974), Wellens and his associates showed that VT could also be induced and terminated safely in patients with syndromes of recurrent sustained VT.

We will first review some observations from electrophysiologic studies in patients with VT that are of great interest with regard to arrhythmia mechanisms, and will then review how VT induction may be of help in patient management. I cannot emphasize enough that most of the clinical data on mechanisms of VT have been obtained in patients with the syndrome of recurrent sustained VT associated

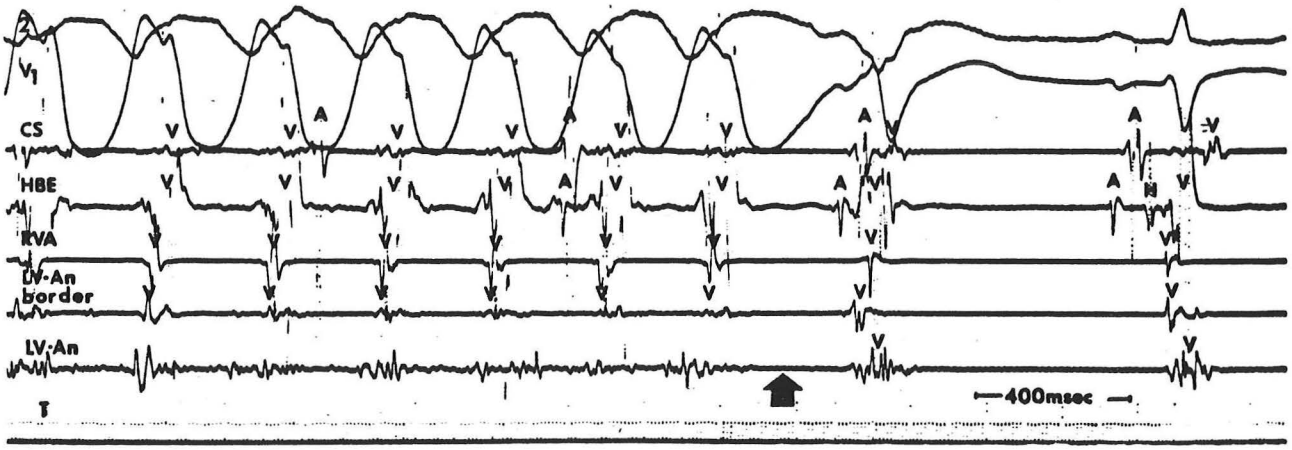
with coronary artery disease (frequently with ventricular aneurysm). Much less information is available on patients with non-sustained VT or sustained VT secondary to other disease processes. The most sophisticated studies of mechanisms of VT in man come from the laboratories of Dr. Wellens and of Dr. Mark Josephson at the University of Pennsylvania (Wellens et al., 1976; Josephson et al., 1978a-d). Considered as a whole, these investigators have amassed a large body of data to show that the clinical syndrome of recurrent sustained VT is due to intraventricular reentry. First, as in human reentrant SVT, and as in animal models of sustained VT, the arrhythmia may be reproducibly induced and terminated by programmed stimulation of the ventricles (Fig. 15). Pacing at rates greater than the spontaneous heart rate and premature extrastimuli are thought to maximize dispersion of refractoriness in potential reentrant circuits, thus creating inhomogenous conduction and unidirectional block which are substrates of reentry. Extrastimuli during tachycardia are thought to interrupt VT when they affect critical relationships between conduction time and block in the reentrant circuit. Electrograms recorded from endocardial sites ultimately confirmed (by cure of the arrhythmia after surgical excision) to be involved in the perpetuation of VT, frequently demonstrate fractionated electrical potentials and continuous diastolic electrical activity in response to programmed cycle sequences close to and including the ones which initiate VT (Josephson et al., 1978c). With termination of VT, localized continuous electrical activity terminates, thus implying strongly that the presence of this electrophysiologic signal is mechanistically associated with the arrhythmia (Fig. 16). The site of arrhythmia perpetuation has been localized to ventricular myocardium or terminal branches of the His-Purkinje system: evidence for such "micro-reentry" includes the fact that initiation and termination of VT is not dependent upon critical activity in the proximal His-Purkinje system, as reflected by inconsistent His potentials during induction and termination of VT. The micro-reentrant circuit is further characterized as "protected", because ventricular capture (resulting in contractile activity of the ventricle and a QRS complex on surface ECG) of the bulk of the ventricular myocardium may occur without termination of VT (Fig. 17). It is, however, not possible to state that reentry has been irrevocably proven to be the mechanism of sustained VT in man, because of recent findings that rhythms due to enhanced afterdepolarizations can be triggered by pacing or programmed extrastimulation; similarly, "protection" from interruption by extrastimuli or spontaneously conducted beats is also a feature of parasystolic rhythms which are thought to result from enhanced automaticity (Schamroth, 1971). Nevertheless, the concept of "ordered" reentry through fixed pathways best explains the bulk of observations in patients with recurrent sustained VT. The anatomic validity of the concept has been strengthened by the success of surgical procedures designed to incise, but not resect, reentrant pathways within the ventricles (Guiraudon et al., 1978; Fontaine et al., 1981); such procedures do not remove the "site of origin" of an arrhythmia, but probably interfere with the "site of perpetuation" of a reentering wavefront which can originate from different types of inherent or artificial (paced) extrastimuli. Based on comparisons of epicardial and endocardial mapping studies in patients undergoing cardiac surgery for VT, it seems likely that most VT reentrant circuits associated with coronary artery disease exist within or on the border of damaged areas of the left ventricle. Furthermore, the fact that electrical activity during VT is almost always recorded earlier from endocardial sites indicates that the bulk of the reentrant circuit exists deep within the myocardial wall rather than near the epicardial surface (Horowitz et al., 1980a) (Fig. 18).

FIGURE 15.



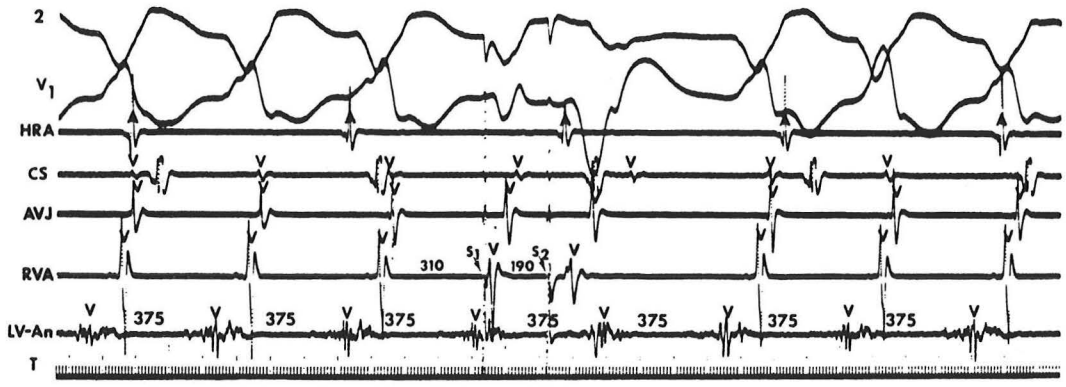
(PMH #46-53-19) Induction of sustained VT by double right ventricular extrastimuli in a patient with a large left ventricular aneurysm. Twelve-lead ECG demonstrated identity of this episode to spontaneously observed arrhythmia.

FIGURE 16. (from Josephson et al., 1978c)



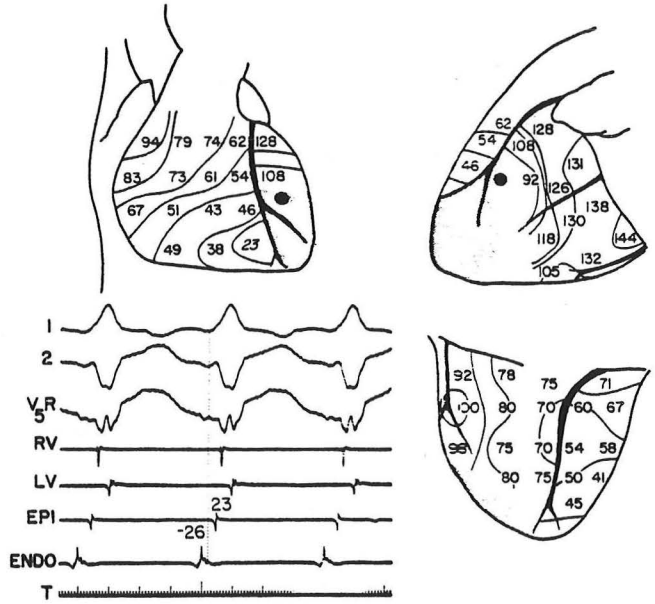
Spontaneous termination of ventricular tachycardia (case 2). Spontaneous termination of the tachycardia appears coincident with cessation of continuous activity (arrow). The last ventricular ectopic impulse results from block in the re-entrant circuit and exit via another pathway. Note the flat LV-An baseline subsequent to termination of the tachycardia.

FIGURE 17.



Mechanism of protection during ventricular tachycardia (VT). The panel is organized as is Figure 12–15, except that the left ventricular catheter has been moved to within an aneurysm (LV–An) and the ECG leads are 2 and V_1. A high right atrial electrogram is also present (HRA). During VT, two right ventricular extrastimuli are delivered, resulting in capture (note the changed QRS complex) without terminating the tachycardia. Continuing activity within the LV–An is seen despite biventricular capture. However, slight changes in ventricular activation have occurred. (From Josephson ME, et al: Circulation 57:431, 1978.)

FIGURE 18. (from Horowitz et al., 1980a)



Data from epicardial and endocardial mapping during ventricular tachycardia. Epicardial surface of both ventricles in the anterior *(upper left)*, left lateral *(upper right)*, and inferior *(lower right)* projections. The apical aneurysm is shaded, and endocardial site where ventricular tachycardia originates is indicated by solid circles. Analog records made in mapping ventricular tachycardia during surgery are shown at lower left. The earliest epicardial *(EPI)* electrogram corresponds to the site in upper left diagram indicated by the *23;* the endocardial activity *(ENDO)* electrogram corresponds to the solid circle.

V. ELECTROPHYSIOLOGIC TESTING AS A GUIDE TO ANTIARRHYTHMIC THERAPY

Provocative electrophysiologic testing of patients with ventricular arrhythmias has evolved as a method for determining, in the individual patient, the presence or absence of some abnormal response to programmed electrical stimulation which is used for prognostic purposes and more commonly as a guide to patient management.

These clinically applicable procedures are not the same as laboratory testing for a "ventricular fibrillation threshold" (Moore and Spear, 1975). The latter technique measures the electrical current required to induce VF when it is applied through stimulation during the "vulnerable period" of the cardiac cycle. VF can almost always be induced, even in the normal heart, if enough current is applied. The technique is of some value in experimental electrophysiology to assess changes in VF threshold which occur with antiarrhythmic drugs or other electrophysiologic alterations, but has not been applied to man except in a few intraoperative studies where VF is induced for the performance of cardiac surgery.

Programmed stimulation of the human heart by transvenous pacing electrodes is performed to elicit either 1) a "repetitive ventricular response" or 2) a ventricular arrhythmia which is identical to that which constitutes the patient's clinical problem. Repetitive ventricular response (RVR) testing, although simpler and theoretically safer to perform than induction of VT, is considered by most clinical electrophysiologists to be invalid because of its lack of specificity and sensitivity in patients with electrical instability. Although early reports (Greene et al., 1978) suggested that the RVR was specific for patients with heart disease and that it predicted future VT and sudden death in patients with recent myocardial infarction, other workers (Mason, 1980; Farshidi et al., 1980a; Ruskin et al., 1981) have pointed out that techniques used in the original studies could not distinguish whether RVR were due to reentry within the bundle branches (a normal physiologic response [Akhtar et al., 1974]) or within myocardium and/or the terminal portion of the His-Purkinje system (presumably a pathologic response). Furthermore, others have not been able to confirm the predictive value of either the presence or absence of RVR (Mason, 1980; Ruskin et al., 1981).

In contrast, electrical induction of VT during electrophysiologic study of patients with the clinical arrhythmia is a widely accepted technique with much more established indications and recognized limitations. Scheinman has summarized, in a recent editorial (Scheinman, 1978), the reaction of many physicians upon their first exposure to this technique: "One of the most deeply ingrained tenets of contemporary medical practice is the prevention or abolition of ventricular tachycardia. Medical personnel throughout the world have been trained to approach this arrhythmia with both awe and alarm for the patient's safety. The necessity for its prompt eradication has been unanimously proclaimed from the highest cardiologic pulpits. The introduction of laboratory techniques ... to provoke ventricular tachycardia in man appears at first appraisal to violate fundamental medical tenets". Scheinman goes on to conclude, however, that the benefit/risk ratio of electrophysiologic testing to define efficacy of therapy is favorable enough to recommend the technique for routine use in certain subgroups of patients with VT. Many other authorities have reached the same conclusion, and programmed ventricular stimulation to induce VT has become a standard part of the approach to complicated arrhythmia patients in many major cardiologic centers in Europe, North America, Australia, and the Middle East (Spurrell et al., 1973; Denes et al., 1976; Fontaine et al., 1976; Hartzler and Maloney, 1977; Fisher et al., 1977; Benditt et al., 1978; Mason and Winkle, 1978 and 1980; Wellens et al.,

1978b; Josephson and Horowitz, 1979; Ross et al., 1980a; Foster and Simpson, 1980; Ruskin et al., 1980; Reddy et al., 1980; Farshidi et al., 1980b; Breithardt et al., 1980; Meyerburg et al., 1980; Heger et al., 1981; Belhassen et al., 1981). Some modification of such an electrophysiologic study is necessary for safe determination of the efficacy of pacemaker interruption of VT; it is also useful for determining the adequacy of pharmacologic antiarrhythmic therapy and in selecting patients for surgical treatment of VT. Performance of these studies requires a fluoroscopy unit and moderately sophisticated and costly multi-channel electrophysiologic recorders and stimulating devices. The studies are best carried out by a team of physicians with varying responsibilities during the study for catheter placement and maintenance, for pacing and programmed stimulation, and for observation of the patient. Vital to such studies are the presence of a cardiac technician/electronic engineer who is prepared to "trouble shoot" the multiple electrical artifacts and recording problems which can hamper efficient performance of a study, and a catheterization laboratory nurse who is well-versed in ECG monitoring and administration of drugs used in cardiac emergencies. Resuscitation equipment and experience in both catheterization techniques and electrophysiologic principles are vital to the safe and efficient performance of such studies. Probably because such studies have usually been limited to referral centers able to sustain such a team approach to their performance, patient death complicating invasive electrophysiologic study for VT induction has never been reported, even though patients by definition are "high risk" for an invasive cardiac procedure because of recurrent VT or VF prior to the study.

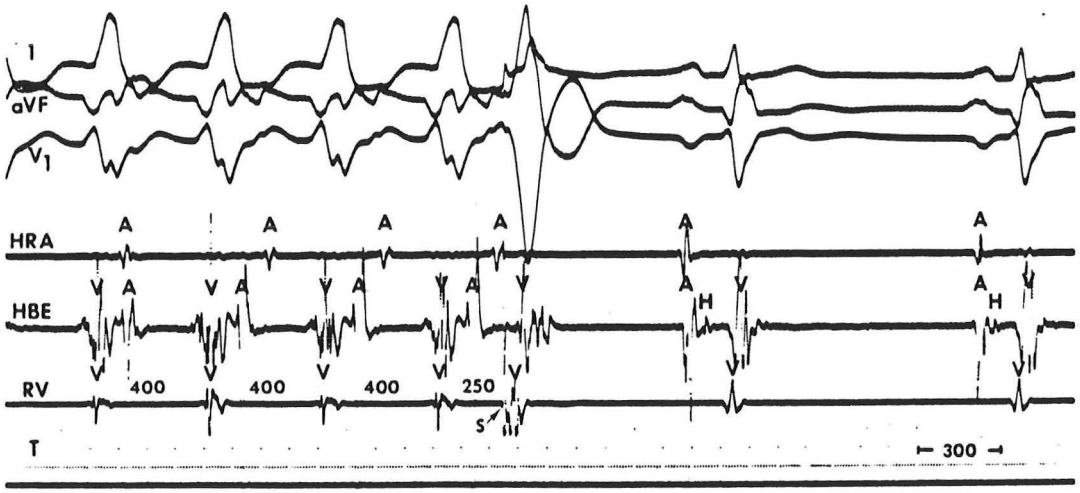
Multipolar electrode catheters (4-6 French) are positioned by standard percutaneous and cutdown techniques in the desired positions for electrophysiologic recording and stimulation. A system of switches allows recording and/or pacing from a wide variety of combinations of electrode sites. An arterial monitor line is frequently used for constant measurement of blood pressure during the procedure to further ensure patient safety and to assess the hemodynamic response to induced arrhythmias. Left heart catheterization, with its increased risk of peripheral vascular and embolic complications, is not routinely required unless induction of VT from the right ventricle is impossible, or an endocardial map of the tachycardia is desired for planning surgical therapy.

All antiarrhythmic drugs are discontinued before the original baseline study. After catheter placement, recordings in sinus rhythm are obtained prior to attempts to induce VT, and the effective refractory period of the atrium to progressively premature extrastimuli is determined. The capacity of the AV node to conduct during rapid atrial pacing is then defined, and screening procedures to exclude the presence of pre-excitation syndromes or SVT with aberrancy, both of which may simulate VT, are carried out. Programmed extrastimuli are then performed from the right ventricular apex during sinus rhythm to determine the ventricular effective refractory period. If VT is not induced by single or double extrastimuli (Fig. 15), progressively premature terminal extrastimuli during a "drive cycle" of ventricular pacing at different basic cycle lengths is then performed. Double, and in some laboratories, triple extrastimuli at the end of several basic drive cycles, and then short bursts of rapid ventricular pacing are performed in an attempt to induce VT. If VT cannot be induced from the right ventricular apex, a similar sequence of extrastimulation procedures is carried out from other parts of the right ventricle (free wall, outflow tract, mid-septum). In patients with the syndrome of recurrent sustained VT, approximately 80% will have their clinical arrhythmia induced by such right ventricular pacing protocols. Another 10% will have inducible VT if left ventricular stimulation is

performed (Robertson et al., 1981). Therefore, up to 90% of patients with the syndrome of recurrent sustained VT can be expected to have inducible VT during an electrophysiologic study off antiarrhythmic drugs.

Most patients with induced VT will tolerate it relatively well for at least short periods of time, and the electrophysiologist will be able to confirm the surface ECG identity of the induced arrhythmia to that which occurs clinically and determine the clinical and hemodynamic effects of VT. Then he will be able to determine how the tachycardia is best terminated. Sinus rhythm can be restored in the majority of patients by either programmed stimulation of the ventricles during VT (Fig. 19) or by "burst" or "over-drive" ventricular pacing. Synchronized cardioversion is quickly performed if the patient loses consciousness, becomes markedly hypotensive, or develops a complication of pacing such as acceleration of VT. In most large series, only about one-quarter of patients have required cardioversion or defibrillation, and it is frequently possible to predict who they will be from historical features of spontaneous episodes (history of immediate syncope or VF are, of course, clinical clues that severe hemodynamic or electrical instability may complicate an induced arrhythmia).

FIGURE 19. (from Josephson and Seides, 1979)



Termination of ventricular tachycardia (VT) by a single VPD. The figure is organized from top to bottom: ECG leads 1, aVF, and V_1 and electrograms from the high right atrium (HRA), His bundle region (HBE), and right ventricle (RV). VT is terminated by a single VPD (S, arrow) delivered at a coupling interval of 250 msec.

The rationale for the use of electrophysiologic testing to guide antiarrhythmic therapy is based upon several assumptions:

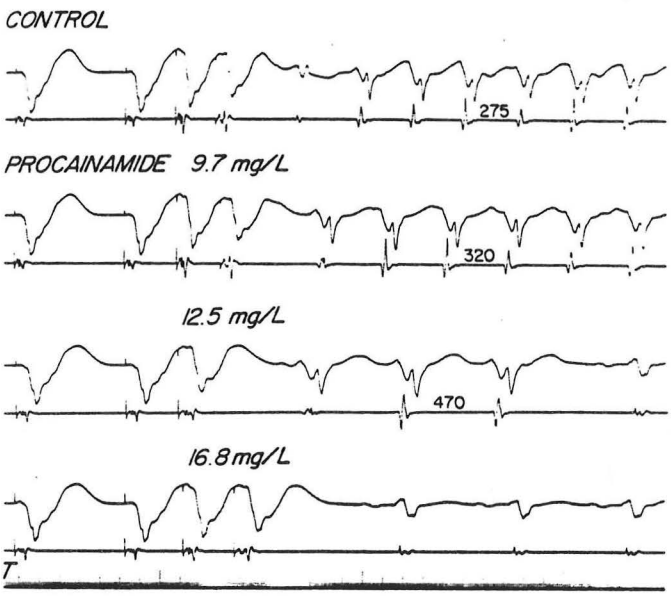
First, that induction of sustained VT is specific for patients with the clinical arrhythmia, and second, that the induced arrhythmia is identical to the clinically observed arrhythmia in the patient at hand. The data of Vandepol et al. (1980), in over 500 patients undergoing electrophysiologic study for various indications, indicate that a standard ventricular pacing protocol essentially never produces VT in patients without clinically observed VT. Furthermore, many investigators have repeatedly shown that the majority of induced VT is identical, by 12-lead ECG, to clinically observed episodes in patients with the syndrome of sustained recurrent VT (Fisher et al., 1977; Mason and Winkle, 1978; Vandepol et al., 1980). Third, it is assumed that the efficacy of pharmacologic intervention

in acutely preventing VT predicts the response to chronic oral antiarrhythmic treatment for recurrent sustained VT and possibly for VF. Earlier data from Wu et al. (1977) suggested the efficacy of such a protocol for determining optimal therapy for certain supraventricular arrhythmias. Fourth, it is assumed that VT is a reentrant rhythm, and that disruption of the functional capacity of the reentrant circuit (which is tested by stimulation protocols) rather than suppression of all ventricular "ectopy" (not tested by this technique) is the goal of management.

A relatively standard protocol for assessment of pharmacologic agents in preventing induction of VT during serial electrophysiologic testing has emerged from several major electrophysiologic centers (Fisher et al., 1977; Mason and Winkle, 1978; Josephson and Horowitz, 1979; Ruskin et al., 1980). It should be stressed that patients most commonly included in these studies have been those with the syndrome of recurrent sustained VT; those with VF (some of whom doubtlessly had sustained VT before degeneration to VF) form the next most common subgroup. Induction of VT, as described above, with the patient off all antiarrhythmic drugs, is performed to confirm the diagnosis, its identity to the clinically observed arrhythmia, and the mode of induction and termination. Laboratories vary with regard to the number of "control" VT inductions which they demand for a definition of reproducibility. If the patient does not have inducible VT, empiric chronic antiarrhythmic therapy is necessary. Patients who do not have inducible VT during electrophysiologic study frequently include those in whom some other factor (ischemia, autonomic imbalance, "stress") other than extrastimulation is necessary for the arrhythmia to occur.

If reproducible VT occurs with programmed electrical stimulation, a number of antiarrhythmic drugs are administered on separate occasions in order to define whether they prevent induction of VT and, if not, whether they affect the resulting tachycardia. The standard approach is to test single agents at maximally tolerated doses at time periods separated by several half-lives of the drug so that any improvement or worsening of the resulting arrhythmia can be inferred to result from a single drug (Fig. 20). Lidocaine, because of its short half-life, and one other drug can usually be tested during the same electrophysiologic study, but other agents must be tested singly on separate days. If single antiarrhythmic agents at "adequate" plasma levels and/or maximally tolerated doses do not prevent VT induction, combinations of drugs or experimental antiarrhythmic agents are then usually tested. If an effective drug or combination of drugs is found, the patient is treated with the oral agent(s) in an attempt to produce plasma levels similar to those which were obtained by intravenous infusion. Some laboratories perform a final electrophysiologic study several days after institution of chronic oral therapy in order to confirm that there are no major differences between oral and intravenous therapy in that particular patient. Some laboratories also attempt to define two effective pharmacologic regimens, so that, if after discharge, one proves to be intolerable or ineffective, the patient can be changed to another potentially useful drug regimen without further electrophysiologic testing; this approach is particularly useful if the patient has been referred from a great distance.

FIGURE 20. (from Horowitz et al., 1980b)



Dose-dependent effects of procainamide on initiation of VT. In each panel ECG lead V_1 and a right ventricular electrogram are shown. In the control study, VT was initiated by two premature stimuli during ventricular pacing. The tachycardia cycle length was 275 msec. After 1000 mg of procainamide was administered intravenously, the plasma level was 9.7 mg/liter. VT could still be initiated by two premature stimuli, and the tachycardia cycle length was increased to 320 msec. After an additional 250 mg of procainamide, the plasma level was 12.5 mg/liter. VT was then inducible by single stimuli; however, the VT was nonsustained and the cycle length was increased to 470 msec. No stimulation protocol could induce sustained VT at this plasma level. After an additional 250 mg of procainamide, the plasma level was 16.8 mg/liter. VT could not be initiated by any stimulation protocol at this plasma level.

Although successive electrophysiologic studies are certainly arduous for both the patient and the electrophysiologic team, there is no question that they can be performed safely and rather expeditiously in centers with appropriate committments of space and personnel. Although the initial electrophysiologic testing session usually requires three or four hours, sessions on future days are much shorter, with the period for safe drug infusion frequently requiring more time than programmed stimulation. Ross et al. (1980b) have studied the time and equipment costs for electrophysiologic testing of patients with tachycardias (Table 7), and have demonstrated an average cost of 21 man-hours and $800 for initial "complete" studies.

TABLE 7. (from Ross et al., 1980b)

	Number of cases	Range	Mean	SD
Catheterization time (minutes)	33	24–105	63	20
Fluoroscopy time (minutes)	33	6–67	22	15
Stimulation time (minutes)				
All cases	33	12–210	87	38
Cases with tachycardia	27	12–210	93	38
Cases in whom no tachycardia could be initiated	6	22–96	60	27
Cases with tachycardia and without research drug study	19	12–210	86	41
Research drug study time (minutes)	8	22–73	47	20
Analysis time (hours)	31	1–11	5	2.5
Length of paper recorded (feet)	33	360–2100	1260	390

Catheterization times and length of paper required for investigation of patients with paroxysmal tachycardias.

Follow-up studies are routinely done with only one catheter which is positioned at the site known to be most likely to induce VT. This site is most commonly the right ventricular apex, thus allowing repeated stimulation by means of a temporary pacing wire inserted through a subclavian vein and left in place for several days, obviating the need for venipunctures or cutdowns for each testing session. Furthermore, it is quite common not to have a full choice of standard antiarrhythmic drugs which are reasonable to test in an individual patient. Most patients referred for such involved studies have either failed some conventional antiarrhythmic drugs, have had major adverse reactions to one or more agents, or have relative contraindications to certain drugs which make long-term tolerance unlikely (the most common being left ventricular dysfunction which precludes long-term therapy with either disopyramide or beta-adrenergic blockers).

Important findings with diagnostic and therapeutic implications, other than the design of a therapeutic treatment regimen, frequently result from serial electrophysiologic testing. First, certain drug (or pacemaker) interventions may have deleterious effects, thus allowing their avoidance in chronic therapy and reducing the chance for life-threatening adverse effects when the patient is not under medical supervision. Probably the most unpredictable and potentially serious adverse effect of an antiarrhythmic drug is the actual induction of VT or VF which can occur after the administration of quinidine. It is interesting to note that of Ruskin's series of 31 patients who underwent electrophysiologic study because of out-of-hospital cardiac arrest not associated with acute myocardial infarction, two had no inducible arrhythmia off antiarrhythmic drugs, but had inducible VT on the same doses of quinidine they had been taking at the time of their cardiac arrest; discontinuation of quinidine was successful in preventing recurrent arrhythmias in these patients (Ruskin et al., 1980). Quinidine has also been implicated as a cause of ventricular arrhythmias in approximately one-quarter of patients with high grade ventricular arrhythmias undergoing electrocardiographically guided acute drug testing (Gaughan et al., 1976). The relationship of these findings to the dramatic and apparently idiosyncratic reaction of "quinidine syncope" is not entirely clear at this time; certainly quinidine-induced ventricular ectopy may occur without prolongation of the QT interval, and at "therapeutic" plasma levels. A major point which is not frequently emphasized does seem obvious: antiarrhythmic drugs, through complex electrophysiologic effects on hearts which are usually already diseased, may actually provoke arrhythmias, some of which are potentially lethal. Another Type I antiarrhythmic drug, procainamide, often has a curious effect on the induction of VT: as procainamide levels resulting from acute intravenous infusions are increased, VT will actually become easier to induce, although the resulting tachycardia is frequently slower, and therefore better tolerated hemodynamically than the original arrhythmia (Greenspan et al., 1980). This slower VT is sometimes characterized as being "incessant", because it is not as easily interrupted by pacing techniques (Horowitz et al., 1978). Further dosing with procainamide usually achieves a plasma level which prevents induction of VT (Fig. 20). Whether these findings during acute intravenous loading with procainamide can be directly extrapolated to the clinical setting of chronic oral procainamide therapy is not certain. Another clinically relevant acute drug testing finding which may be of significance is potential acceleration of VT by lidocaine. Lidocaine, although obviously not practical for chronic oral therapy, is usually tested in referral centers because it simulates the electrophysiologic activity of its oral congeners, tocainide and mexilitene, which are available for compassionate investigational use in selected patients. Horowitz et al. report a 25% incidence of

acceleration of VT by lidocaine, although the magnitude of acceleration is not hemodynamically significant in the majority of patients (Horowitz et al., 1978). Phenytoin may have similar effects on the rate of VT. Finally, antiarrhythmic agents may impair the hemodynamic stability of the patient in whom arrhythmia induction is not prevented. Probably the most likely agent to result in such an effect is propranolol, which through its depressant effects on myocardial function, the peripheral vasculature, and the autonomic nervous system, impairs the reflex mechanisms and "cardiac reserve" which are necessary to maintain adequate cardiac output during VT.

The power of serial electrophysiologic tests in predicting response to chronically administered antiarrhythmic drugs is fairly well documented in highly selected subgroups of patients with serious ventricular arrhythmias. Horowitz et al. (1980b) have recently reviewed the results of serial electrophysiologic testing for pharmacologic suppression of recurrent sustained VT. Of 232 reported patients, induction of VT was acutely prevented in 128 (55% of the total group), and chronically prevented in 108 (84% of those acutely responsive, 47% of the entire group studied). Of the 104 patients in whom VT induction was not prevented, 25 (11% of total group) had chronic suppression of VT on a therapeutic regimen usually selected because it rendered VT induction more difficult. The average follow-up on chronic therapy is about 12 months. Although randomized studies of patients treated by empiric antiarrhythmic therapy and passive observation versus electrophysiologically guided therapy have not been performed, it is unlikely that 47% of empirically treated patients would respond. Indeed, the patients reported in these 6 studies had usually already failed empirical drug therapy, thus making the nearly 50% success rate in the entire group even more impressive. It should be pointed out that prompt recognition of patients who do not respond to conventional pharmacologic agents is also of significance, because it provides an immediate clue that innovative and experimental pharmacologic, pacemaker, or surgical treatment should be considered. Thus, it is my conclusion that serial invasive electrophysiologic testing for definition of effective antiarrhythmic therapy should be routinely considered for patients with the syndrome of recurrent sustained VT when severe hemodynamic compromise or deterioration to VF results (leaving little room for error in empiric therapy).

The results of such "electropharmacologic" evaluation have also been reported in smaller numbers of patients with VF. The classic work in this area has been performed by Ruskin and his associates (1980) in 31 survivors of resuscitation from out-of-hospital cardiac arrest. Twenty-three of these patients had documented VF at the time of resuscitation, and 17 of these had inducible arrhythmias (usually sustained or non-sustained VT) at electrophysiologic study: antiarrhythmic therapy based on electrophysiologic testing limited mortality in the patients with VF to 4% in the first year, approximately one-sixth of that reported from Seattle by Cobb et al. (1980). Thus, it seems reasonable to consider invasive electrophysiologic testing for survivors of out-of-hospital VF without obvious precipitating causes; this is a patient subgroup with an approximately one in four chance of recurrence in the first year (Cobb et al., 1980), and one in which there is no room for error. Relative indications and contraindications to electrophysiologic study with programmed electrical stimulation (EPS-PES) are listed in Table 8.

TABLE 8.

EPS - PES IN VENTRICULAR ARRHYTHMIAS

Relative Indications
(for assessment of drug/pacemaker Rx)

1. Recurrent sustained VT
2. Aborted sudden death (VF or VT) not 2° to acute MI or reversible/avoidable factors
3. ? symptomatic non-sustained VT

Relative Contraindications

1. Recent MI, ongoing ischemia, or hx of angina during VT, especially if coronary anatomy is unknown or Rx of ischemia (medical or CABG) inadequate during rapid heart rates
2. "Stenotic" hemodynamic problems, e.g., AS, IHSS
3. Settings in which neural influences may act as independent uncontrolled variables, e.g., long QT syndromes, mitral prolapse, coronary spasm
4. Other contraindications to cardiac catheterization (except contrast allergy)

A full review of the complex stimulation protocols required for electrophysiologic evaluations of patients with VT is beyond the scope of this review, as is a detailed consideration of the mapping studies which are necessary for localizing the site of arrhythmia perpetuation prior to surgical interruption or excision. Certain technical and operational differences exist among different institutions and may be one source of variability in results; these are summarized in Table 9.

TABLE 9.

PROBLEMS IN STANDARDIZATION OF EPS FOR VT

- Reproducibility
- Aggressiveness
  (number of stimulation sites, basic cycle lengths, and extrastimuli; ? isoproterenol)
- Definitions of
  a) sustained vs. non-sustained VT
  b) bundle branch reentry vs. intraventricular reentry
  c) drug response
- Stimulus strength and duration
- "Non-clinical" tachycardia

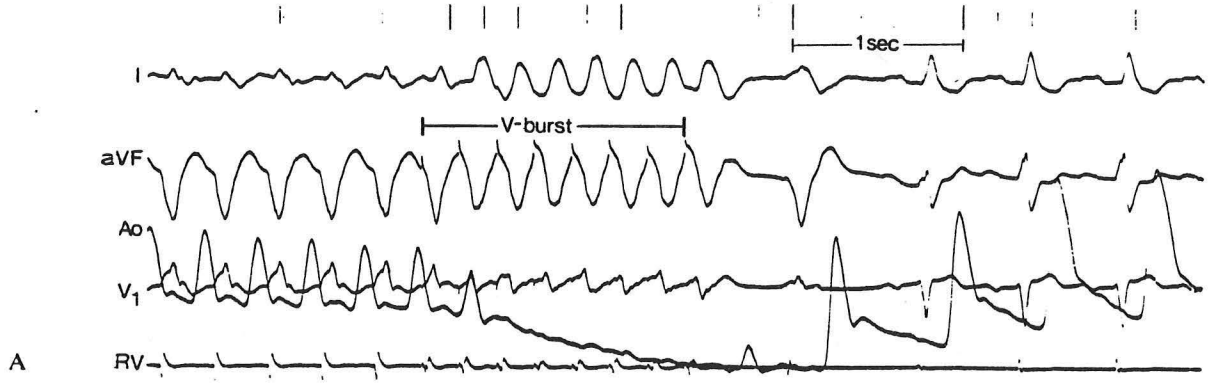
A brief review of the modes of cardiac pacing which may be utilized as an adjunct to pharmacologic treatment or as a primary antiarrhythmic therapy is in order (Fisher, 1981). From a prophylactic viewpoint, some types of VT may be prevented by chronic "overdrive" pacing. Just as critical degrees of tachycardia may promote dispersion of refractoriness and altered conduction velocities on a regional basis, thus serving as substrates for reentry, so can varying degrees of bradycardia. Avoidance of critical prolongation of ventricular cycle lengths may be all that is necessary to prevent the occurrence of these substrates of reentry or the emergence of subsidiary pacemakers which serve as the initiating stimulus for sustained VT. The role of electrophysiologic testing in exposing this mechanism of VT induction is limited, because of the lack of reproducible methods for slowing the heart rate without concomitant changes in autonomic tone or hemodynamics. Therefore, the success of chronic overdrive pacing can usually be gauged only by several days of temporary pacing. It should be emphasized, that in some patients, the heart rate need not be depressed to frankly bradycardic levels for such a mechanism to obtain; indeed troublesome recurrent VT may be

eliminated in an occasional patient by simply raising the average heart rate from 70 to 90 beats/minute. Patients with any degree of bradycardia preceding the onset of VT should be carefully evaluated for long QT interval syndromes.

A second broad category of antiarrhythmia pacing modes is that of arrhythmia interruption. In common terminology, there are both "underdrive" and "overdrive" pacing modes for this purpose. Underdrive interruption of VT is most commonly performed with a simple transvenous right ventricular pacemaker, which fires (usually activated with a magnet) in an asynchronous fixed rate mode (at a rate less than VT) after the onset of VT. Random discharge of the pacemaker at various parts of the cardiac cycle is purposefully allowed to occur until a beat achieves a critical coupling interval which interrupts the reentrant tachycardia. This mode of pacing is most likely to be successful in patients with a relatively slow VT rate who have reproducibly demonstrable interruption of VT with single ventricular extrastimuli during electrophysiologic testing.

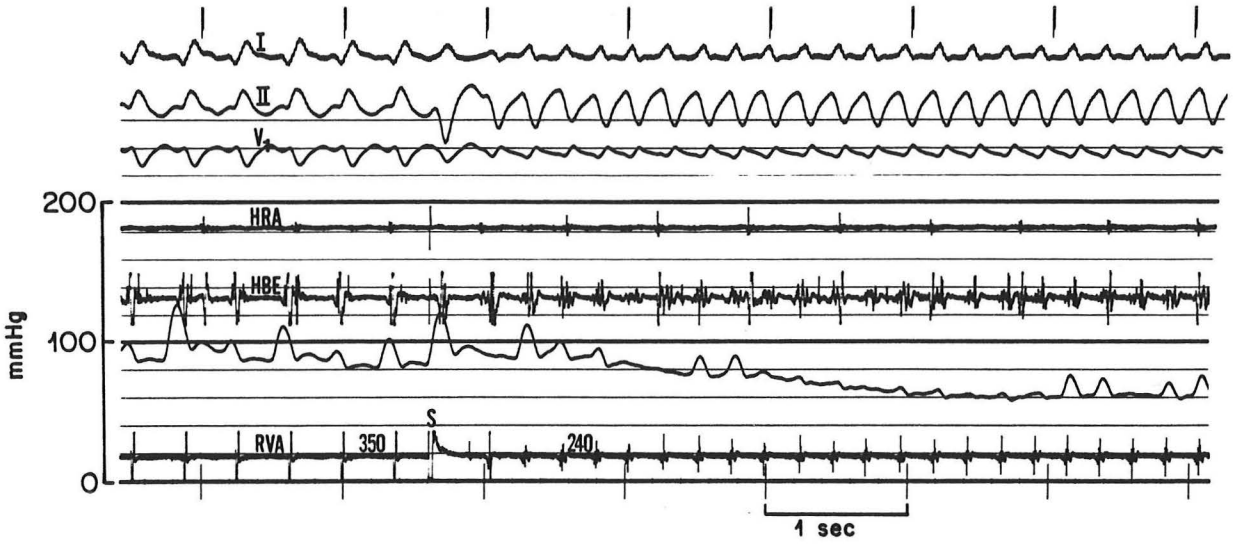
More innovative modes of pacemaker interruption therapy have evolved from the demonstration in recent years that VT can be terminated by pacing at rates greater than that of the tachycardia (Fig. 21). Pacemakers which are patient- or physician-activated to pace the ventricles at critical cycle lengths as well as pacemakers to sense the onset of VT and deliver burst pacing automatically have been used with excellent results in small numbers of patients (Fisher, 1981). A radiofrequency sensing device may be the only option in patients who develop immediate syncope or hemodynamic compromise with VT. The simpler device, requiring activation by a conscious patient or physician, is probably preferable from a safety standpoint. Both underdrive and overdrive pacing interventions have definite risks for induction of accelerated VT (Fig. 22) or VF, and should ideally be used only during ECG monitoring where immediate defibrillation is possible. Before patients are allowed to interrupt their tachycardia without medical supervision, it is recommended that multiple episodes of VT be broken safely under ECG monitoring (Fisher, 1981). The complexity of managing such patients is obviously immense; such interventions, as well as the recently reported implantable defibrillator (Mirowski et al., 1980), can only be supervised adequately by experts in the rapidly changing technology of invasive electrophysiology and pacemakers (Fisher, 1981). Unless dramatic simplification of such modes of therapy becomes available, it is unlikely that they will be useful for all but a handful of patients.

FIGURE 21. (adapted from Mason and Winkle, 1978)



The use of V-burst in attempted termination of ventricular tachycardia. In panel A surface leads I, aV_F and V_1 are displayed with right atrial, (RA) and right ventricular (RV) electrograms and the aortic pressure (Ao). The left side of the illustration shows ventricular tachycardia. In the middle of the illustration a burst of stimuli, labeled V-burst, with interbeat cycle length of 220 msec, results in termination of ventricular tachycardia (patient 16).

FIGURE 22.



Acceleration of VT by single right ventricular extrastimulus. Same patient as shown in Fig. 15. VT is converted from a cycle length of 350 msec to one of 240 msec, and the patient became significantly hypotensive. Rapid ventricular pacing restored sinus rhythm. This patient had been converted to sinus rhythm by similarly timed extrastimuli on five other occasions.

Advances in cardiac surgery to eradicate the "site of origin" of ventricular arrhythmias has occurred in recent years. Electrophysiologic testing is usually performed prior to antiarrhythmic surgery to confirm the diagnosis of VT, to test the efficacy of alternative medical or pacemaker therapy, and, in some institutions, to localize the site of perpetuation of VT at which the surgical procedure is directed. Antiarrhythmic surgical procedures for VT associated with coronary artery disease have recently been reviewed by Horowitz et al. (1981), and broader overviews of the topic have also been supplied by Waldo et al. (1981) and Engel (1981). Of particular importance in the unusual but very interesting patients with recurrent VT associated with structural heart diseases other than coronary disease are the writings of Fontaine and his associates in France (Giraudon et al., 1978; Fontaine et al., 1981). Various types of surgical procedures seem better suited to different disease processes, and require either preoperative catheter and/or intraoperative mapping studies of varying levels of complexity. On this continent the most publicized surgical procedure for VT is that developed by Harken at the University of Pennsylvania, in which preoperative left ventricular catheter endocardial maps (Fig. 4) and intraoperative epicardial and endocardial maps during VT are used to define a small area of damaged myocardium containing the reentrant circuit (Harken et al., 1979; Horowitz et al., 1980a) (Fig. 18). This site of reentry, localized by techniques outlined earlier in the discussion of mechanisms of VT, is usually found along the endocardial rim of a left ventricular aneurysm. The operation performed is a standard left ventricular aneurysmectomy with extension of the procedure to include a partial subendocardial resection ("peeling") in the area of identified reentry (Fig. 23). Patients are generally tested with programmed stimulation after the surgical procedure while the chest is open, and several days post-operatively by catheterization techniques. The operation has resulted in eradication of recurrent sustained VT in over 80% of patients; those who are not completely free of VT after

the procedure usually are more easily controlled with drug therapy. The operative mortality is less than 10%. This technique, although very instructive in the mechanism of VT, has to date been almost exclusively used in patients with coronary disease and left ventricular aneurysms. A disadvantage of this procedure is that VT must be induced intraoperatively for full intracardiac mapping; because hypothermia (used routinely for myocardial preservation) is a powerful antiarrhythmic factor, warm hearts must be allowed to have sustained VT for varying periods of time early in the operation, and must then survive extensive cardiac surgery, which is, of course, performed with standard preservation techniques.

FIGURE 23. (from Harken et al., 1979)

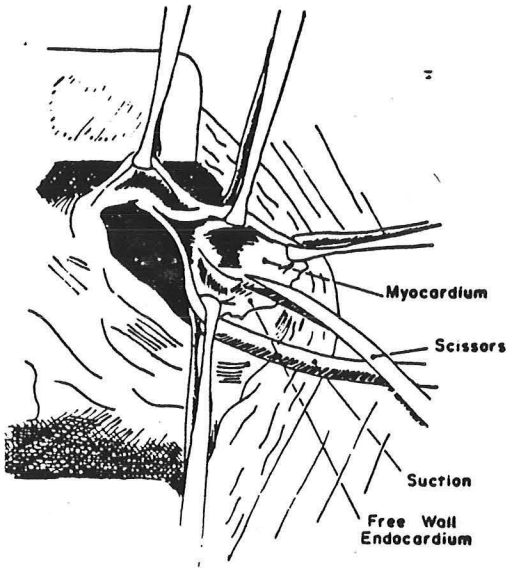


Diagram depicts "peeling" away of subendocardium in a perianeurysmal area identified by mapping as being the site of VT perpetuation.

A potentially more widely applicable technique for patients with coronary disease and other obviously regional processes is called encircling endocardial ventriculotomy (EEV) (Giraudon et al., 1978; Engel, 1981). This procedure, which may be performed either with or without mapping guidance, is aimed not at excision of the site of arrhythmia perpetuation but rather at electrical isolation of grossly abnormal tissue from the more normal parts of the ventricular myocardium. As unbelievable as it may sound, the surgeon opens the ventricle, and widely incises the ventricular wall (to a depth which avoids transmural incision by only one or two millimeters), and he does this in an encircling fashion around visible subendocardial scars or other regional processes (Fig. 24). He then sutures the wall back together and closes the ventriculotomy. Controversy exists as to how impaired the ventricle may be hemodynamically after such a procedure. Long-term successes in patients with VT, quite similar to those obtained by Harken's group in patients with aneurysms, have been reported. A modification of this type of approach is an epicardial ventriculotomy, which is frequently based on the results of epicardial mapping studies during induced VT. This is a particularly useful procedure for arrhythmias associated with processes other than coronary disease, particularly arrythmogenic right ventricular dysplasia (Fontaine et al., 1981; Marcus et al., 1980).

FIGURE 24. (from Waldo et al., 1981 and Guiraudon et al., 1978)

Diagrammatic illustration of the endocardial encircling ventriculotomy of Guiraudon. Note that a perpendicular incision is made in the endocardium to, but not through, the epicardium. This incision is then extended to encircle the edge of the endocardial fibrosis.

Another form of ablative surgery which has not enjoyed wide use is a cryosurgical procedure developed at Duke University (Gallagher et al., 1978). The site of perpetuation of tachycardia, as identified by various mapping procedures, is cooled with a cryoprobe, so that conduction through this area may be altered dramatically. If VT is interrupted, it is assumed that the reentrant circuit has been affected in a critical way, and a lethal freezing injury of the localized zone is then produced. Follow-up in an adequate number of patients to form even a preliminary opinion of this surgical procedure is not available at the present time.

All surgical procedures are at present limited to extremely ill patients with VT refractory to standard medical treatment and usually to investigational antiarrhythmic drugs. Although room for improvement in surgical procedures obviously exists, there can be little question that further advances in mapping techniques to define ever smaller and more critical limbs of the presumed reentry circuit, and advances in surgical techniques for controlled excision or damage of such circuits, holds great potential for patients with cardiac arrhythmias. Furthermore, "electrically guided" procedures are more effective than such procedures as coronary bypass surgery and "blind" aneurysmectomy for recurrent sustained VT (Harken et al., 1980). It should be emphasized that, just as for extensive electrophysiologic studies of pharmacologic and pacemaker interventions, successful antiarrhythmic surgery requires costly equipment and personnel as well as an extremely close working relationship between the cardiac surgeon and the cardiac electrophysiologist.

VI. SELECTED ASPECTS OF MANAGEMENT

Regardless of whether a patient presents with an asymptomatic or symptomatic arrhythmia, an attempt to characterize the arrhythmia electrocardiographically and to detect important reversible causes is always in order before long-term empirical treatment. In the absence of hemodynamic collapse, the few seconds required for a cardiac examination directed at detecting signs of AV dissociation and for recording a 12-lead ECG may be of key importance in confirming the diagnosis and defining the clinical subgroup into which a patient best fits. For patients with asymptomatic VT, a careful history directed at detecting subtle symptoms and manifestations of underlying heart disease is in order. A careful drug history (including prescription, non-prescription, and illicitly used items) should be obtained. In patients with symptomatic arrhythmias, a history of precipitation of symptoms by exercise, emotion, sleep, and changes in body position may be particularly helpful. All patients should have routine blood chemistries, and patients with any suggestions of marked metabolic imbalances should have arterial blood gases and serum magnesium levels measured. An attempt at syndromic classification, particularly into those of non-sustained, recurrent sustained, and *torsades de pointes* VT is easily accomplished after this clinical and laboratory examination. Because of the frequent subtlety of QT prolongation and its tendency toward variable expression, a review of previous ECG's and Holter monitors, with actual calculation of the corrected QT interval, is vital if one expects to detect less than flagrant QT prolongation. In patients with histories suggestive of recent onset of VT or other changes in cardiopulmonary function, serial ECG, enzymatic and scintigraphic evaluation for recent "silent" myocardial infarction is in order.

In asymptomatic or questionably symptomatic patients, the next step in evaluation will consist of continuous Holter monitoring to define the frequency of VT, the severity of associated ventricular ectopy, and whether reported symptoms indeed correlate with a documented arrhythmia. Some authors recommend 48 hours or more of Holter monitoring sessions before attempts at long-term pharmacologic suppression, the major purpose being to define the degree of spontaneous variation in frequency of ectopy and VT which might later simulate a therapeutic effect (Winkle, 1980). When possible, such pretreatment monitoring sessions should be done under conditions that most simulate the ambulatory conditions under which post-treatment monitoring sessions will be conducted. If the patient is hospitalized, he should be encouraged to be physically active while he wears the monitor. At some institutions, attempts are made to perform a formal exercise test during Holter monitoring, to characterize both those arrhythmias associated with exercise as well as those which sometimes occur during the late post exercise period. Holter monitoring may also indicate that a bradyarrhythmia or an ischemic event (marked by ST segment depression or elevation) precedes VT.

In all patients with VT, a complete anatomic and physiologic evaluation for structural heart disease is in order. Clinical, echocardiographic and scintigraphic evaluation will usually identify major valvular, congenital, and cardiomyopathic conditions, and certain sequelae of myocardial infarction. Most patients will also come to hemodynamic and angiographic evaluation at cardiac catheterization.

Exercise stress testing is important in all patients with VT who do not have physical impairments or severe cardiac failure. First, exercise testing may

define whether VT is associated with acute myocardial ischemia (detected electrocardiographically or by a scintigraphic technique). This is an extremely important finding, because it implies that a major focus of management should be to eradicate, through medical or surgical treatment, the ischemic response which precipitates the arrhythmia. Secondly, exercise testing will identify another subgroup of patients in whom higher grades of ventricular ectopy, and occasional VT, will be precipitated by exercise without evidence of ischemia. These patients may or may not have coronary artery disease, and antiarrhythmic drugs are the cornerstone of their management. Third, an occasional patient will be identified in whom acceleration of the heart rate with exercise is associated with abolition of both VPD's and VT. Such patients should be carefully reevaluated for evidence of ventricular parasystole and QT prolongation syndromes associated with slower (though not necessarily frankly bradycardic) heart rates; many cardiologists do not feel that patients with exercise-suppressed ventricular ectopy or VT require antiarrhythmic drug therapy unless they have severe underlying heart disease.

Electrophysiologic testing is in general reserved for special problems in the VT patient (Table 10). Such testing can provide valuable information early in the evalution of patients when there is doubt regarding the correct diagnosis (VT vs. SVT with aberrancy or fascicular tachycardia). It is considered by many cardiologists to be indicated during the initial hospital admission in patients who have been resuscitated from out-of-hospital cardiac arrest due to VT or VF which is not associated with acute MI, the goal of such testing being to establish that antiarrhythmic drug therapy is adequate in protecting the patient from electrically induced VT or VF. Invasive electrophysiologic testing to guide pharmacologic treatment is not always necessary in the patient with the new onset of sustained VT, but is recommended when severe hemodynamic instability has occurred or the patient develops angina as a result of hypotension during VT. Both of these circumstances make survival of repeated episodes of VT less likely, and thus constitute a relative contraindication to "trial and error" antiarrhythmic drug therapy. Such patients, as well as those with multiple episodes of recurrent sustained VT refractory to ordinary antiarrhythmic drug therapy, should have electrophysiologic testing in order to define an effective pharmacologic regimen as well as to assess the feasibility of pacemaker and surgical therapy.

TABLE 10.

EPS-PES INDICATIONS - GENERAL POINTS

- Very helpful if diagnosis of VT uncertain
- Useful only in reentrant arrhythmias
- Required when pacemaker or surgical Rx contemplated
- More useful when
  - other "markers" of electrical instability (e.g., spontaneous or exercise-induced arrhythmia) are absent or infrequent
  - symptomatic arrhythmia is catastrophic, leaving little room for error in empirical Rx
  - arrhythmias occur in absence of identifiable provoking factors
  - findings interpreted in context of hemodynamic, angiographic, and other clinical data
- Studies are complex, lengthy, expensive, and inefficient. They require a patient and referring M.D. willing to cooperate with a series of tests with intervening changes in therapy, and a patient likely to comply with the therapeutic program which seems most efficacious

A detailed review of pharmacologic therapy of patients with VT is beyond the scope of today's presentation. Both conventionally available antiarrhythmic drugs and those available for investigational use on a "compassionate" or "emergency use" basis for individual patients, have been discussed recently by Singh et al. (1980). The important issue of effective combinations of drugs has been discussed by Fisher (1977) and Lown and Graboys (1977). The efficacy and relative safety of "high dose procainamide" in patients with recurrent sustained VT has been outlined by Greenspan et al. (1980). It is possible that, within the next two years either mexilitene or tocainide will be available for general use in the United States, thus adding a totally different class of antiarrhythmic agent to the physicians' armamentarium, and making multiple new combinations of drug treatment possible. An intense interest has recently developed in amiodarone, a pharmacodynamically odd and complicated drug whose half-life is measured in weeks; this agent seems to be remarkably effective in patients with recurrent VT refractory to other antiarrhythmic drugs. The efficacy of the agent in the long-term prevention of refractory VT and VF seems relatively well established by uncontrolled studies (Nademanee et al., 1981; Kaski et al., 1981; Heger et al., 1981). It is unlikely, however, that amiodarone will be generally available in this country in the near future because of the lack of controlled studies documenting efficacy, a bizarre constellation of non-life-threatening adverse effects, and complicated patent laws which make it economically unattractive for a pharmaceutical company to attempt to develop the agent in the United States. There seems to be little question that by the end of this decade, multiple new pharmacologic agents and classes of agents will be available for use in the critically ill patient with VT. Although the search continues for a "perfect" antiarrhythmic drug without adverse effects, with a sufficiently long half-life to allow dosing at infrequent intervals, recent developments in the pharmacologic treatment of ventricular arrhythmias are quite encouraging (Zipes, 1981).

One general aspect of antiarrhythmic drug therapy which demands special attention has recently been discussed by Winkle (1980), and it seems to be generally accepted among arrhythmologists and biostatisticians. This involves the issue of variability of chronic ventricular arrhythmias in untreated patients from day to day, and the amount of suppression of ventricular ectopy or VT which is necessary to prove drug effect in an individual patient. Based on concordance analyses of paired Holter monitors done at varying intervals in untreated patients with frequent simple and complex ventricular ectopy, it seems that up to approximately 80% reduction of ventricular ectopy frequently may be explained by patient variability rather than by a drug response, thus making it necessary for an 80-90% reduction in ectopic activity to occur before one can be reasonably certain, in an individual patient, that an administered antiarrhythmic drug has definitely had an effect (Winkle, 1980). Such realizations have a major impact on clinical trials of new antiarrhythmic agents, and for the clinical use of generally available antiarrhythmic drugs. It is unfortunate that they have not been heeded by many ECG laboratories which do not provide a referring physician with enough quantitative information to assess the degree of ectopic suppression which has occurred between two Holter monitoring sessions. There is essentially no available data on a corollary problem which the clinician frequently faces; that is the question of how frequently Holter monitors should be repeated to assure continued efficacy of a chronically administered agent already "proved" to suppress ectopy in an individual patient.

An even more haunting question which revolves around ambulatory monitoring and pharmacologic treatment of ventricular ectopy and VT (particularly the non-

sustained variety) has recently been discussed (Winkle, 1980). Although not frequently emphasized by proponents of aggressive antiarrhythmic therapy and representatives of the pharmaceutical industry, it remains an unproven hypothesis that pharmacologic suppression of asymptomatic ventricular ectopy or VT can prolong life in any subgroup of patients with or without heart disease. The uncontrolled studies of antiarrhythmic therapy guided by electrophysiologic testing in patients with sustained VT and in survivors of out-of-hospital cardiac arrest, reviewed above, and two similarly uncontrolled studies of non-invasively guided drug therapy for patients with VT and VF (Myerberg et al., 1979; Lown and Graboys, 1977), suggest that pharmacologic therapy may improve the prognosis of these extremely complex and very ill patients, but it is not valid to extrapolate these findings to patients with simple or complex ventricular ectopy, or even non-sustained VT. These considerations, as well as lethal and non-lethal adverse effects of antiarrhythmic drugs, should be kept in mind whenever one attempts to suppress chronic ventricular ectopy (Wanowicz and Denes, 1980); when pharmacologic suppression requires complex regimens involving multiple antiarrhythmic drugs, the cost and risk to the patient may begin to outweigh any proven benefit, and the physician may best serve his patient by accepting some ambient (even complex) ectopy.

Even in the patient with recurrent sustained VT or VF, there appears to be a wide spectrum of the amount of ventricular ectopy which can be tolerated while risk of recurrence of these major symptoms is still reduced by antiarrhythmic treatment. This is not a question of only academic interest, because in the complex arrhythmia patient, it is common to find that total suppression of VPD's and sometimes even repetitive arrhythmias is impossible. Available evidence suggests that antiarrhythmic therapy sometimes prevents the occurrence of catastrophic arrhythmias without having much effect at all on the level of ambient ectopy (Meyerburg et al., 1979; Myerburg et al., 1981); it may be that alteration of a fixed reentry circuit by antiarrhythmic drugs, without major alteration in the frequency of VPD's, accounts for the observed clinical improvement. At the other end of the spectrum, patients may develop recurrent VT or VF in the absence of intervening complex ventricular ectopy (Herling et al., 1980). These studies illustrate the frustrating practicalities of attempts to manage individual patients by "passive-objective" approaches (Fisher, 1978); even though successful pharmacologic suppression of ventricular ectopic activity generally correlates with prevention of recurrent VT and VF, sole reliance on such methods will result in unnecessarily complicated treatment regimens in some patients and in even more dangerous inadequate therapy in others (20-30% of Herling's series). The only methods which begin to define truly adequate therapy are provocative exercise or invasive electrophysiologic testing in patients in whom similar studies off antiarrhythmic therapy have demonstrated reproducible "markers" of electrical instability.

The general principles of pacemaker and surgical treatment of VT have been reviewed above. There seems to be little question, that just as we are improving methods for individualization of pharmacologic antiarrhythmic therapy, we are experiencing a noisy and exciting infancy of pacemaker and surgical treatment of ventricular arrhythmias. As with most new invasive and surgical procedures, these techniques have been first applied to critically ill patients without other therapeutic options. It is hoped that the lessons learned from these patients and from those in whom electrophysiologic testing is used to guide pharmacologic treatment of VT may ultimately lead to an ability to define "electrical instability" in more precise terms, allowing definitive treatment early in the course of its development and a favorable effect on patient longevity.

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