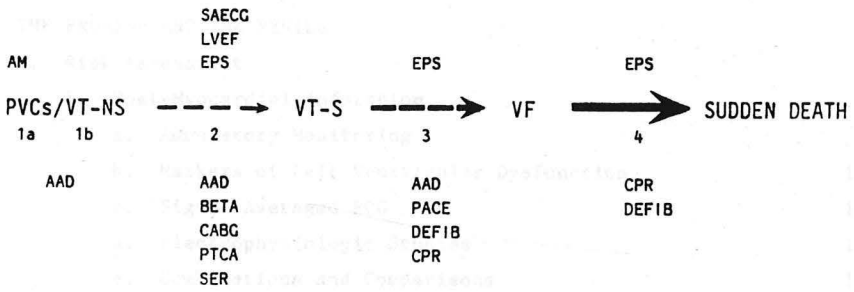
THE PREMISE, PROMISE, AND PERILS OF THE PREVENTION OF LETHAL VENTRICULAR TACHYARRHYTHMIAS



MEDICAL GRAND ROUNDS

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I. INTRODUCTION

Sudden unexpected death claims an estimated 400,000 lives per year in the United States. When death occurs within 1 hour of symptoms, 90% are cardiac in origin and are usually the result of ventricular tachyarrhythmias (1). The overwhelming majority of victims have coronary atherosclerosis, but there is no distinctive coronary pathoanatomy predictive of sudden death (2). However, multivessel disease is present in about 65% of victims. In 50-75%, there is evidence of previous myocardial infarction, but in approximately 25%, sudden death is the presenting manifestation of their disease (3). Despite the strong association with coronary disease, a minority of patients suffer an acute myocardial infarction as their precipitating event (4). Overall, about 60% of all mortality due to coronary artery disease is the result of sudden death.

Survival has improved with the initiation of bystander cardiopulmonary resuscitation (CPR) (5) and early defibrillation (6), but even when these techniques are promptly applied, 65% of patients still die with their initial episode. Therefore, prevention of sudden death is clearly preferable to resuscitation. Unfortunately, while populations at elevated risk can be clearly identified, our ability to sensitively and specifically predict which patients will die suddenly is imperfect. The major purpose of this Grand Rounds will be to review our current understanding of the mechanism and pathogenesis of sudden death due to ventricular tachyarrhythmias and to establish a framework upon which a logical approach to risk assessment and management can be based.

II. THE PREMISE -- PATHOGENESIS OF VENTRICULAR TACHYARRHYTHMIAS

A. Mechanisms

Recordings of the terminal rhythm at the time of sudden cardiac death reveal that 85-90% are due to ventricular tachyarrhythmias (7,8). Although ventricular fibrillation (VF) is the most common initial rhythm documented by rescuers (9), it is rarely present from the onset. Rather is is almost always preceded by ventricular tachycardia (VT) of a variable duration (10-12). In the electrophysiology lab, sustained ventricular tachycardia (VT-S) has been defined as VT that lasts >30 seconds or produces hemodynamic collapse. Therefore, the VT that precedes VF will be considered VT-S in this presentation.

Several studies have shown that in the period immediately preceding sudden death, there is an increase in the frequency of ambient ventricular arrhythmias (10-12). However, the underlying mechanism for this increase and its relationship to the subsequent development of VT-S and VF are unclear. While early cycle (R-on-T) premature ventricular complexes (PVCs) in the setting of acute infarction are legendary in their role of precipitating VF, VT-S and VF, in reality, can be initiated by early or late cycle PVCs and are frequently initiated by the latter (13). Based on the above data, a first approximation of the pathogenesis of tachyarrhythmic sudden death can be represented by the following relationship:

PVCs ⇢ VT-S ⇒ VF → SUDDEN DEATH (1)

This schema will be used throughout the remainder of this Grand Rounds as a shorthand graphic representation of the pathogenesis of tachyarrhythmic death and will be referred to as the "Tachyarrhythmia Equation". It is hoped that this will facilitate understanding of the pathogenesis, evaluation, and management of ventricular arrhythmias. In this schema, the mechanism of pathogenesis will be presented on the main line. The role of prognostic tests will be shown above the line in relation to the component of the equation they address and the site of action of therapeutic intervention will be shown below the line in a similar fashion. Equation 1, as shown, suggests only that the arrhythmias listed are interrelated in a fashion that is as yet undefined (dotted arrows). The increasing potential of each arrhythmia to progress to sudden death is indicated by the increasing arrow width. Thus, the "rate-limiting step" is the progression of PVCs to VT-S.

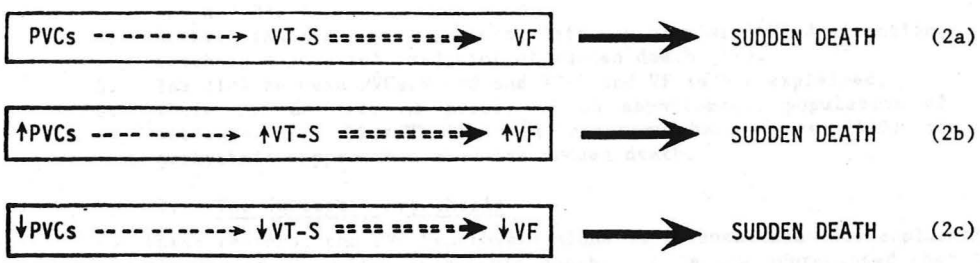
B. Theories of Pathogenesis

1. The PVC Hypothesis

The appearance of "warning arrhythmias" in some patients developing VF in the setting of acute myocardial infarction and the frequent occurrence of PVCs in patients who subsequently developed sudden death led to the formulation of the PVC Hypothesis (14). The major tenets of this theory are as follows:

1. PVCs are a marker of myocardial "electrical instability" and the propensity to develop life threatening arrhythmias. In essence, they are the tip of the iceberg of a larger electrical problem (see Eq. 2a)
2. An increase in frequency of these arrhythmias imparts a greater risk of developing a lethal arrhythmia (see Eq. 2b)
3. Suppression of these non-lethal arrhythmias will lead to a decreased risk of VT-S and VF (see Eq. 2c).

These are graphically summarized below.



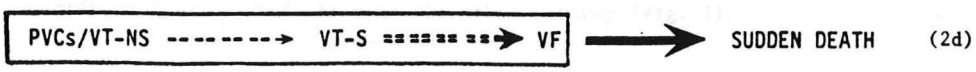
In these modifications of the Tachyarrhythmia Equation, PVCs, VT-S, and VF are enclosed in a square to demonstrate that they are considered by this hypothesis as part of the same pathophysiological process (i.e., "electrical instability").

The Lown grading system attempts to codify arrhythmias by frequency (Grades 1 and 2) and complexity (Grades 3, 4a, 4b, and 5) into categories of differing risk (Table 1). In this system, grades are mutually exclusive, and an increase in grade implies an increase in risk. Patients are graded by the highest arrhythmia they manifest.

TABLE 1 LOWN GRADING SYSTEM

Grade 1	< 30 PVC/hr
Grade 2	> 30 PVC/hr
Grade 3	multiform PVC
Grade 4a	couplets
Grade 4b	VT-NS
Grade 5	R-on-T

Bigger et al. (15) confirmed that risk for sudden death increased with increasing frequency of PVCs. The greatest increment in risk occurred between ∿3 and 10 PVCs/hr and appeared to level off at ∿30/hr. The risk in patients with Lown Grade 1 arrhythmias, therefore, varies from very low to very high. No additional risk exists for patients with Grade 2 arrhythmias. The complexity grades are similarly flawed (16). Grades 3 and 5 rarely exist in isolation, and Grades 4a and 4b are correlated with arrhythmia frequency. Therefore, the arrhythmia grades are not independent and several categories contribute little to risk. It has been found, however, that arrhythmia frequency and repetitiveness act independently to increase risk (17). The equation will therefore be modified to include non-sustained VT (VT-NS) as an indicator of PVC repetitiveness.



(2d)

While this hypothesis is conceptually attractive and logically appealing, it has several limitations:

1. Tachyarrhythmic death can occur in the absence of ambient PVCs.
2. The risk relative to PVC frequency is highly non-linear.
3. Even frequent PVCs and VT-S may be associated with a benign prognosis (18).
4. Arrhythmias are associated with left ventricular (LV) dysfunction, which is a powerful predictor of sudden death (19).
5. The link between PVCs/VT-NS and VT-S and VF is not explained.
6. There is, as yet, no proof, in an asymptomatic population of patients with PVCs/VT-NS, that antiarrhythmic drugs (AAD) or arrhythmia suppression prevents sudden death.

2. The Substrate Hypothesis

For these reasons, the PVC Hypothesis alone is an unsatisfactory explanation of the pathogenesis of sudden arrhythmic death. It is now appreciated that the presence and severity of underlying structural heart disease is the single most powerful predictor of sudden death (20-25). The presence of ventricular dysfunction increases the risk of arrhythmic death by 3-4 fold. To integrate this data into the equation, a Substrate Hypothesis has been proposed:

1. Sustained ventricular tachyarrhythmias occur because of an abnormal electrophysiological milieu or substrate that allows the initiation and maintenance of lethal arrhythmias.
2. This substrate is usually a manifestation of clinically demonstrable structural heart disease.
3. Ambient ventricular arrhythmias may be important not because they are a manifestation of the substrate, but because they may "trigger" sustained arrhythmias if the substrate is present.

This theory can be demonstrated with the following series of modifications to this equation:

PVCs/VT-NS ⟶ VT-S ⟹ VF ⟹ SUDDEN DEATH (3a)

± PVCs/VT-NS ⟹ VT-S ⟹ VF ⟹ SUDDEN DEATH (3b)

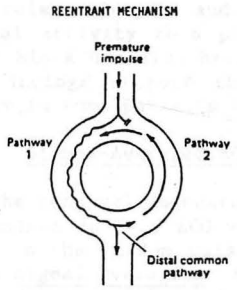
The square has been removed to demonstrate the independence of the arrhythmias from each other. The arrows between them have been converted from dotted (unexplained by the PVC Hypothesis) to solid to show that the substrate is the link between them. The magnitude of the potential for developing VT-S (width of substrate arrow) is shown to be independent of PVC/VT-NS frequency.

a. Electrophysiology of the substrate

Most arrhythmias are believed to be due to a reentrant mechanism. Therefore the electrophysiologic substrate is usually the substrate for reentry. The prerequisites for reentry are

1. two linked pathways with different electrophysiologic properties (i.e., a potential reentrant circuit),
2. unidirectional conduction block in one pathway, and
3. critically slow conduction in the other pathway (Fig. 1).

FIGURE 1



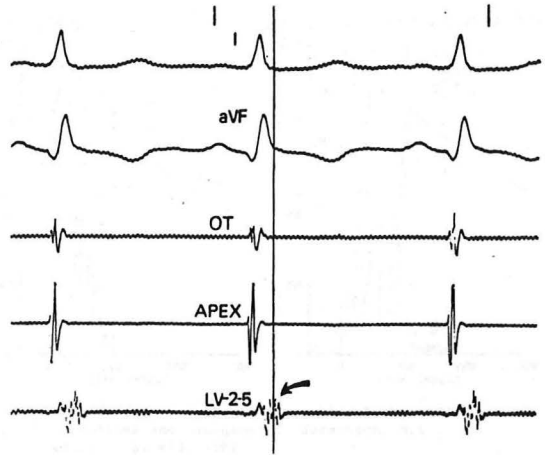
In healthy myocardial tissue, the rapid and uniform tissue activation provided by the specialized conduction system and tight cell-cell electrical coupling precludes reentry. Therefore, some form of structural heart disease is implied, although it may be clinically occult.

The following evidence supports the Substrate Hypothesis.

1) Endocardial mapping data

Endocardial catheter mapping during sinus rhythm in normal patients shows rapid discrete electrograms that terminate before the end of the surface QRS (24). However, in patients with previous myocardial infarction and inducible VT-S, the endocardium frequently shows areas with low amplitude, fractionated (multi-component) electrograms that extend beyond the end of the surface QRS (25) (Fig. 2). These electrograms are thought to be due to slow, delayed, and inhomogeneous conduction in the underlying tissue. With further critical slowing of conduction, activation could span electrical diastole and reexcite (reenter) proximally recovered tissue.

FIGURE 2



Josephson et al. (26) have recorded continuous electrical activity that spanned diastole in association with the initiation and maintenance of VT-S. With termination of this continuous electrical activity, VT-S terminated. Patients with left ventricular aneurysms and VT-S have more endocardial border zone with abnormal electrical activity than patients with an aneurysm without VT-S (27). Local conduction block has also been observed during human VT-S by Miller et al. (28). These findings support the presence of the electrophysiologic requirements for reentry in some patients with scar-related VT-S.

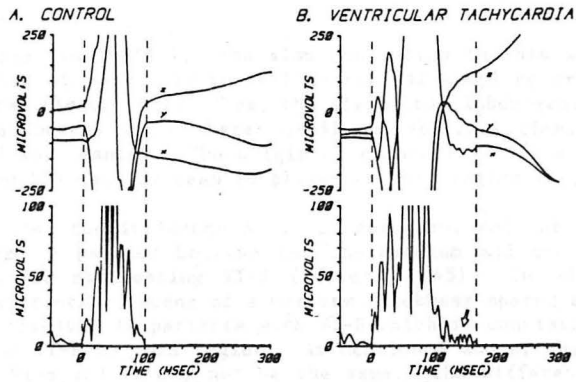
2) Signal-Averaged ECG (SAECG)

The detection of the abnormal endocardial electrical activity noted above is not possible using standard surface ECG recordings because the signals are low amplitude and are lost in the random noise of the recording. However, using a computer process called signal averaging, these signals can be extracted from the noise (29). In this process, multiple analog QRS signals are recorded, digitized, and summed. An averaged QRS signal is then derived by dividing by the number of signals recorded. Because random signals will tend to sum to zero over time, the signal-to-noise ratio is enhanced proportionately to the square root of the number of complexes averaged (i.e., 10-fold decrease in noise with averaging 100 complexes). Using this approach, ECG recordings with noise levels of <1 μV (1/1000 of a centimeter on standard ECG paper) can be derived and the low amplitude signals can be appreciated (30).

The SAECG usually records leads X, Y, and Z, which demonstrate smooth analog QRS contours and frequently show evidence of low amplitude activity in the initial portion of the ST segment. The X, Y, and Z signals are then further processed by squaring, summing, and taking the square root of the sum ($X^2+Y^2+Z^2$) to give a mean QRS vector magnitude. Final processing involves digital high pass filtering at 25-100 Hz to eliminate low frequency signals. This results in the filtered mean QRS complex.

FIGURE 3

SAECG



from Simpson, et al in Ventricular Tachycardia; Mechanisms and Management. Josephson, M.E., editor. p. 413, 1982.

Simpson et al. (31) at the University of Pennsylvania showed that the duration of endocardial activation and the duration of the SAECG were highly correlated. These same authors found that after an infarction, patients with sustained and inducible VT-S had longer SAECGs (139±29 msec) than patients with infrequent arrhythmias (95±10 msec) (Fig. 3). The amplitude of the signal in the last 40 msec was significantly less in the VT group (14.9±14.4 μV) than in the control group (73.8±47.6 μV) (32). Therefore, the presence of either an abnormally long SAECG QRS duration or a high-frequency, low-amplitude late signal (delayed potential, late potential, or "tail") is a marker for slow and delayed conduction and suggests the presence of the substrate for reentry.

3) Electrophysiologic Studies (EPS)

If a sustained arrhythmia occurs because of reentry in an anatomically fixed electrophysiologic substrate, then it should be provocable with extrasystoles. Sustained arrhythmias can be induced in 60-100% of patients with VT-S (33-36) and 60-80% of patients with sudden death (36-39). However, the arrhythmias induced in these two populations are not identical. The induced arrhythmias in patients with sudden death are more rapid and less uniform, and are induced by a greater number of extrastimuli than the arrhythmias in VT-S patients (36). These findings suggest that both groups have an electrophysiologic substrate that will support arrhythmias and also that a different substrate is present in each group.

b. Anatomy of the Substrate

Myocardial hypertrophy, increased interstitional collagen, and the presence and ultrastructure of macroscopic myocardial scar may promote unidirectional block and slow conduction. Macroscopic scar may act as a central electrical obstacle around which a reentrant wave front may circulate. This form of macroscopic reentry is suspected as the etiology of about 10% of scar-related VT-S (40). In the majority, however, the reentrant circuit is believed to be smaller and to occur within the scar tissue. In a canine infarct model, fractionated electrograms have been recorded from tissue showing islands of electrically normal but abnormally oriented myocardial fibers that are widely separated from each

other by fibrous tissue (41). The slow conduction in this setting is theorized to occur because of poor cell-to-cell electrical coupling created by the interspersion of scar tissue (42). Thus, the electrical inhomogeneity of scar tissue, particularly at border zones where normal and abnormal tissue interdigitate, is fertile ground for reentry. The origin of clinical VT-S due to previous myocardial infarction has usually been localized to this region (43,44).

Infarct size, the incidence of an LV aneurysm, and the percentage of solid scar that forms a barrier between the endocardium and the epicardium are all greater in hearts manifesting VT-S (Table 2) (45). In addition, there is a greater circumferential extent of a uniform thickness-spared endocardium (ribbon-spared subendocardium) in patients with VT-S which is consistent with the localization of human VT-S to this region. As mentioned above, the electrophysiologic substrate for VT-S and VF may not be the same. The difference between them may be partly explained by different anatomic substrates. In a study by Stevenson et al. (46), two separate areas of myocardial scar were more frequent in patients resuscitated from sudden death than in patients with stable VT-S.

TABLE 2

PATHOLOGY OF VENTRICULAR TACHYCARDIA

Characteristics	Means		p values
	No VT	VT	
weight (g)	459	531	.04
radius of the LV (cm)	1.9	2.3	.004
% of hearts with LV aneurysm	14	73	.0001
area of ribbon-spared endocardium (cm^2)	0.04	0.15	.006
coronary artery score	11.7	12.0	.75

Adapted from Bolick et al., Circulation 74:1266, 1986.

c. Variability of the Substrate

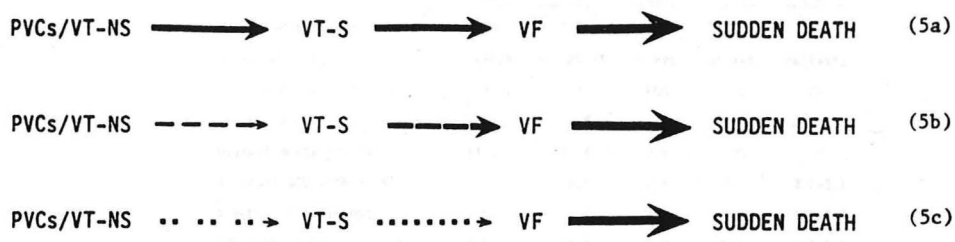
Despite evidence that a fixed substrate is present in patients with VT-S or VF, not all patients with these arrhythmias have demonstrable heart disease or are inducible at EPS. This suggests that the Substrate Hypothesis is incomplete. It is possible and probable that transient and variable factors play an important role in some patients. To illustrate the contribution of these factors to the substrate, the substrate arrows will be converted from solid to dashed (Eq. 4).

PVCs/VT-NS ⇢ VT-S ⇢ VF ⟹ SUDDEN DEATH (4)

Among the variable factors of potential importance are myocardial ischemia, variations in autonomic tone or circulating catecholamine levels (47), changes in serum electrolytes (especially potassium) (48), or the effect of antiarrhythmic drugs (49). Other mechanisms of arrhythmogenesis, which are not amenable to provocation by EPS (i.e., abnormal automaticity), may also play a role. These transient factors probably contribute to some episodes of sudden death and cannot be overlooked. However, the assumption that a life-threatening arrhythmia, especially uniform and electrically stable VT-S, is due solely to them is

potentially dangerous if a fixed substrate exists and is not recognized. For example, hypokalemia is a frequent occurrence after CPR and is usually the result of the arrest rather than the cause (50). Therefore, evaluation and therapy must be based on a clear understanding of the potential role of both fixed and transient electrophysiologic abnormalities.

To conclude, the combination of an abnormal electrophysiologic substrate and "triggering" arrhythmias most completely defines the potential risk of sudden death. In some patients, a fixed substrate is present and very little ambient arrhythmias are required to trigger lethal arrhythmias (Eq. 5a). In others, the fixed abnormalities alone are insufficient to support a sustained arrhythmia, and a contribution from some of the transient factors is required before lethal arrhythmias can occur (Eq. 5b). In a structurally normal heart, only profound abnormalities of the transient factors will provide the substrate for lethal arrhythmias (Eq. 5c). The importance of PVCs and VT-NS is best understood in the context of the underlying electrophysiologic substrate.



III. THE PROMISE AND THE PERILS

A. Risk Assessment

The promise of arrhythmia management is that patients at risk for sudden death can be detected, and preventive therapy instituted, prior to the occurrence of a lethal arrhythmia. Using the history, physical exam, and routine lab alone, patients can be categorized into groups with substantially different risks of sudden death. Unfortunately, the historical risk factors for sudden death are the same as the risk factors for coronary artery disease in general. In the Framingham study, a multivariate risk analysis identified a subpopulation of patients that represented 10% of the group but sustained almost 50% of the sudden deaths (51). In this high risk group, the annual sudden death incidence rate was 6.5% for men and 2.6% for women. Therefore, the specificity of this approach is limited. Ambulatory monitoring (AM), SAECG, EPS, and measures of LV function have therefore all been utilized in an attempt to improve predictive accuracy. Using the framework of the "Tachyarrhythmia Equation" derived above, we can address the promise and perils of using these techniques.

The discussion that follows will focus primarily on the role of these tests in predicting initial arrhythmic events in patients recovering from an acute myocardial infarction and in predicting arrhythmia recurrences in patients who have suffered from previous VT-S or sudden death. The value of limiting the focus to these 2 patient populations is the high prevalence of the desired endpoints, the relative uniformity of the underlying disease process, the large body of available literature, and the clinical relevance. It is hoped that the insights gained from this approach will promote an organized and rational approach to arrhythmia management and outweigh the potential difficulties of extrapolating this data to other patient populations.

1. Post-Myocardial Infarction

a. Ambulatory Monitoring (AM)

In patients recovering from an acute myocardial infarction, the risk of sudden death in the first post-infarct year is 5-6%. This is greater than the risk in subsequent years and in most other patient populations. In these patients, the detection of ventricular arrhythmias on AM identifies a population at increased risk of dying from ventricular tachyarrhythmias (Table 3).

TABLE 3 PROGNOSTIC VALUE OF ARRHYTHMIAS POST-MYOCARDIAL INFARCTION

	MPIP	MILIS	COP	HIPNY	BHAT
Number of patients	819	533	2035	1739	1640
Arrhythmia (A)	>3 PVC/h	>10 PVC/h	>1 PVC	Gr 3-5	multiple
Recording duration (hrs)	24	24	ECG	1	24
Follow-up duration (yr)	2	1.5	3	5	2.1
Overall mortality (%)	11.2	11.4	12.6	~20	10
% annual SCD with A (%)	6	8.5	2.8	~4	3.8-5.1
% annual SCD without A	2.6	2.8	1.6	~1.6	1.2-2.0
SCD with A/SCD without A	2.5	3.0	1.8	2.4	2.3-2.7

MPIP, Multicenter Postinfarction Program (52); MILIS, Multicenter Limitation of Infarct Size (53); COP, Coronary Drug Project (54); HIPNY, Health Insurance Plan of New York (55); BHAT, Beta Blocker Heart Attack Trial (56)

The convenience, safety, availability, cost, and ease of interpretation have made this technique the gold standard for arrhythmia assessment. However, there are several pitfalls in the utilization of this technique.

1. Arrhythmia detection depends on the duration of the recording period and on the time from the preceding infarction (57).
2. The arrhythmia(s) that is the best dichotomous discriminator of risk is not well defined (56).
3. Arrhythmias imply little about the presence of the substrate.
4. The prognostic significance of arrhythmias may vary with time from infarction (53,57).
5. Arrhythmias are only a moderate marker of risk and do not predict sudden death, per se (59).

The incidence of arrhythmias post-myocardial infarction varies with the time from the acute event. They are frequent in the acute phase, decline to a nadir at 3-5 days, and then increase again to a plateau at 6-12 weeks after infarction. Unfortunately, the correlation between acute phase arrhythmias and either subsequent outcome or chronic phase arrhythmias is poor (59). Arrhythmia detection also depends on the duration of the recording and varies from ~13%, using a standard 12-lead ECG, to ~80%, using multiple 12-24 hour duration recordings. The standard practice of obtaining a single 24-hour recording at 10-14 days after infarction will therefore not identify some patients who have arrhythmias.

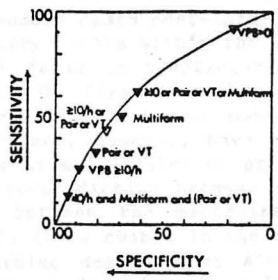
AM is usually performed to detect an arrhythmia (or arrhythmias) that is used to dichotomize patients into "treatment" and "no treatment" groups. However, the best arrhythmia to use in this regard is unsettled. Bigger et al. (52) found that 3 PVCs/h was the best discriminator between patients at low and high

risk in the Multi-Center Post-Infarction Program (MPIP). This arrhythmia was present in 30% of patients and detected 50% of the sudden deaths over 2 years. However, Mukharji et al. (53) in the Multi-Center Investigation of the Limitation of Infarct Size (MILIS) found that 10 PVCs/h had the strongest statistical association with sudden death ($p<0.001$). This arrhythmia was detected in 15% and detected 10 of the 29 sudden deaths (34%).

The occurrence of VT-NS is also an independent predictor of lethal arrhythmias. However, neither the number of beats per run nor the rate of the VT-NS adds further prognostic significance (17). In the MPIP study, the odds ratio of sudden death was 6.6 with VT-NS compared to patients with no arrhythmias. However, the hazards ratio (risk of sudden death in patients with VT-NS vs. patients without VT-NS) was only 2. In MILIS, repetitive forms (couplets, VT-NS) had an odds ratio of 2.4 but were only marginally statistically associated with sudden death ($p = 0.08$). The incidence of VT-NS post-MI varies from 1-12% and averages about 10% (17,52,60). In the majority of patients, these arrhythmias are asymptomatic and brief (3-4 beats) and in up to 75% they occur only once (60). Because patients may have VT-NS with otherwise low frequency arrhythmias, the optimum arrhythmia to use as a cut-off for therapy is uncertain.

Kostis et al. (56) recently reviewed this problem using data on 1640 placebo-treated patients from the BHAT trial. Very low frequency arrhythmias (>0/24h) were found to be a sensitive (92%) but nonspecific (16%) marker of sudden death mortality. The analysis of repetitive forms showed an increase in specificity (81%) but a loss in sensitivity (34%) (Fig. 4). PVC >10/h alone had a sensitivity of 25% and a specificity of 88%. The potential for reducing the incidence of sudden cardiac death, the number of patients treated, and the number of patients exposed to the risk of therapy without the potential for benefit will therefore be dramatically affected by the arrhythmia chosen as the basis for therapy.

FIGURE 4



Kostis, et al., JACC
10:231, 1987

In this study, regardless of the arrhythmia utilized, the relative risk of dying was ∿2.5 times higher in the population with the arrhythmia than in the population without the arrhythmia. Similar odds ratios have been noted in other large studies (Table 3). Therefore, while several arrhythmias have a strong statistical association with sudden death, they are only modest markers of that risk.

The increase in relative risk imparted by arrhythmias should not obscure the fact that it is the absolute risk and the risk-to-benefit ratio that should be important in therapeutic decision-making. The absolute risk of sudden death in

patients with arrhythmias post-MI was 6% with MPIP, 8.5% in MILIS, and ∿5% in BHAT. In the BHAT trial, arrhythmias were useful in further stratifying risk in 4 clinical subgroups, and in fact, had the greatest power in the lowest risk subgroup. In the low risk subgroup, the presence of arrhythmias increased the risk 4-fold, but only to 3.3%. In the high risk subgroup, the presence of arrhythmias doubled the risk of sudden death. However, patients without these arrhythmias had a sudden death rate of 14%. From this study, it is obvious that antiarrhythmic drug (AAD) treatment based on arrhythmias alone would result in treatment of a low risk subgroup, while a high risk subgroup would be untreated. This limitation of arrhythmias in predicting sudden death can be understood in the context of the Tachyarrhythmia Equation.

↑ PVCs/VT-NS ----→ VT-S ——→ VF ⟹ SUDDEN DEATH (6a)

↓ PVCs/VT-NS ——→ VT-S ——→ VF ⟹ SUDDEN DEATH (6b)

Equation 6a represents the low risk population. The first substrate arrow is narrow, indicating a low risk of PVCs precipitating VT-S because of the low incidence of the substrate. This risk increases with an increased frequency of arrhythmia, but the overall risk remains small. For the high risk subgroup, illustrated in Eq. 6b, the first substrate arrow is much wider, indicating a greater chance of developing VT-S. The risk is greater in Eq. 6b than in 6a, despite the presence of higher frequency arrhythmias in Eq. 6a than 6b.

The occurrence of sudden death post-infarction is highly skewed (61). About 50% to 75% of the mortality occurs within the first 6 months, and after this, the total sudden death risk falls to ∿2-3%/year. In the MILIS study, 79% of all sudden deaths occurred in the first 7 months. When AM was repeated at 6 months, the findings were no longer predictive of sudden death. Moss et al. (57) reported similar findings. Others, however, have reported that arrhythmias detected early and late after myocardial infarction predict sudden death risk for up to 4 years (52,54,55). The contradiction between these studies may be due to (a) a fundamental difference between the mechanisms of arrhythmias detected early compared to late post-MI, (b) a change in the substrate with time, or (c) the low incidence of sudden cardiac death >6 mo after infarction (1.4% in the MILIS study). These data make one question the value and significance of arrhythmias detected >6 mos after an infarct. Finally, while arrhythmias are independent predictors of sudden death, no study has shown that any arrhythmia predicts sudden death, per se. Rather, cardiac mortality from all causes is predicted.

In summary, arrhythmias detected by AM can be used to select patients after infarction at increased risk of dying suddenly. The best arrhythmia to be used in this regard is unclear. Arrhythmias are, at best, only modest predictors of mortality and are not specific for sudden death. Because arrhythmias provide little insight into the presence of the substrate, their use as the sole marker of arrhythmic risk is limited.

b. Markers of Left Ventricular Dysfunction (LVEF)

Myocardial function is the single best predictor of total mortality and sudden cardiac death post-infarction (20-23). LV dysfunction and arrhythmias are are closely associated, but are independent risk factors for sudden death (52,53). In the MPIP study (52), LVEF <30% was associated with a 3.5 fold increase of dying. In the MILIS study (53), an LVEF <40% had a sensitivity of 68% and a specificity of 69% for detecting sudden death and detected more sudden deaths than did arrhythmias. The presence of a discrete left ventricular aneurysm has a particularly strong association with VT-S and VF as discussed in the section on electrophysiology and anatomy of the substrate. In addition, it has recently been appreciated that LV dilatation plays an additional role in increasing the risk of sudden death (62).

Unfortunately, medical therapy to improve LV performance is limited, and the traditional approaches may, in fact, be detrimental (63). In contrast to AM, the results of these tests are not additionally useful in managing risk (see below).

c. Signal-Averaged ECG (SAECG)

As described above, SAECGs can detect low amplitude late potentials in patients with VT-S. Several investigators have found similar abnormalities in 26 to 44% of post-infarct survivors and have found the results to be useful in predicting arrhythmic events (Table 4). The results appear to be independent of arrhythmias and LV function (64,68-70).

TABLE 4 (+) SAECG POST-MYOCARDIAL INFARCTION

	# patients	Incidence	Arrhythmic Events (+) SAECG	Arrhythmic Events (-) SAECG	p value
Kuchar (64)	200	39%	17%	1%	<0.001
Denniss (65)	306	26%	21%	4%	<0.001
Gomes (66)	102	44%	29%	4%	0.003
Breithardt (67)	160	30%	15%	5%	---

In Kuchar's study (64), an abnormal SAECG had a sensitivity of 93% and a specificity of 65%. The sensitivity was 68% and specificity 75% for predicting instantaneous death and non-fatal VT/VF in the study by Denniss et al. (65). The positive predictive accuracy was 19%. Gomes et al. (66) found that the SAECG had a sensitivity of 87% and a specificity of 63% for predicting arrhythmic events. Patients with a positive SAECG had a 29% event rate, compared to a 3.5% event rate in patients with a normal result.

These studies underscore the importance of markers of the substrate in risk assessment. Because signal averaging is non-invasive, it is potentially widely applicable. However, the QRS widening produced by bundle branch block may mask late potentials. Infarct location and the time from infarction may also be important (71,72). While sensitivity and specificity are good, the predictive accuracy of a positive test is low. For the moment, the major drawback is the lack of widespread availability of this technique. The SAECG cannot be utilized to gauge efficacy of antiarrhythmic drugs but has been useful postoperatively in gauging the effectiveness of arrhythmia surgery (30,73,74).

d. Electrophysiologic Studies (EPS)

Electrophysiologic study is a technique that has gained wide acceptance in the management of cardiac arrhythmias (34-39). Utilizing programmed extrastimulation (the organized introduction of multiple premature depolarizations), this test attempts to ascertain whether an arrhythmic substrate exists. In contrast to AM or SAECG, this technique is invasive and requires hospitalization. However, it can be performed safely even in patients with VT-S and VF and has an overall risk profile virtually identical to routine cardiac catheterization (75). It is not widely available and requires special expertise and equipment. Stimulation protocols are not yet standardized and interpretation of the results are somewhat subjective. Nonetheless, its utility in other settings has led to the investigation of its potential role in the post-myocardial infarction population (Table 5).

TABLE 5

EPS POST-MYOCARDIAL INFARCTION

	# patients	# ES	(+) criterion	% +	useful
Greene (76)	48	1	≥2 IVR	40	yes
Hamer (77)	70	1-2*	≥6 IVR	17	yes
Richards (78)	165	2*	> 10 s VT	23	yes
Denniss (65)	403	2*	> 10 s VT	34	yes
Waspe (79)	50	3	≥7 IVR	34	yes
Santarelli (80)	50	2	≥10 IVR	46	no
Roy (81)	150	2	≥6 IVR	23	no
Marchlinski (82)	46	2	≥4 IVR	22	no

* high stimulation current; ES - extrastimuli; IVR - intraventricular reentrant beat

Multiple authors have found EPS to be predictive of long term outcome after MI (76-83). Green et al. (76) found 15 of 19 patients with positive EPS had events compared to 4 of 29 with negative results. Hamer et al. (77) found a 33% incidence of sudden death in patients with a positive EPS, compared to a 4% incidence in patients with a negative response. In the study by Richards et al. (78), the incidence of instantaneous death and spontaneous VT was significantly higher in the "electrically unstable" group than in the "stable" group.

Waspe et al. (79) found a 41% incidence of late sudden death with the induction of >7 beats of VT-NS compared to 0% in patients without inducible VT-NS. However, the inducible patients had a lower mean ejection fraction and a higher incidence of anterior infarction than the non-inducible group. Denniss et al. (65) found the induction of uniform VT-S, but not VF, was associated with a two-year survival of 73%, compared to 93% for patients without inducible VT-S. However, the results of EPS were not useful in the studies by Santarelli (80), Roy (81), or Marchlinski (82).

The differences between these studies may be due to differing patient populations, differing stimulation protocols, and differing criteria for a positive study. The largest and most recent studies from Australia (65,78) suggest that EPS can successfully predict outcome. However, the stimulation protocol (high output) and endpoints are not typical of EPS performed in the U.S. In addition, the independence of this data from other markers of risk has not been confirmed. Therefore, the role of EPS post-MI still remains unclear.

e. Combinations and Comparisons

In a few studies, these tests have been directly compared or combined in the same population. In a study by Schulze et al. (84), all 8 sudden deaths that occurred were detected by both an LVEF <40% and complex arrhythmias (Lown 3-5). However, the specificity of AM was 75%, compared to 49% for an LVEF <40%. The positive predictive accuracy of AM was 40%, compared to 18% for an LVEF <40%. In the MILIS study (53), >10 PVCs/h on AM had a sensitivity of 34% and a specificity of 86%. LVEF <40% was more sensitive (75%), but less specific (68%). Only 3 sudden deaths occurred in patients with LVEF >40%, compared to 19 in patients with <10 PVCs/h. The combination of an LVEF <40% and >10 PVCs/h had a sensitivity of 25%, a specificity of 93%, a positive predictive accuracy of 18%, and a negative predictive accuracy of 96%.

In a study by Marchlinski et al. (82), neither inducibility at EPS or the presence of Lown Grade 3-5 arrhythmias predicted sudden death over a mean follow-up of 18 months. An LVEF <40% was useful and had a sensitivity of 84% and a specificity of 70%. Kuchar et al. (72) compared AM, SAECG, and LVEF and found that each test had independent prognostic value in predicting VT-S or sudden death. LVEF had the best sensitivity (92%), specificity, and positive predictive accuracy. Lown Grade 3-5 arrhythmias had the lowest sensitivity and positive predictive accuracy, while the SAECG had excellent sensitivity (92%) but only modest specificity and positive predictive accuracy. A combination of these tests appears particularly useful. In another study by Kuchar et al. (64), arrhythmic events occurred in 31% of patients with a positive SAECG and Grade 3-5 arrhythmias. However, the combination of an abnormal SAECG and an LVEF <40% had better sensitivity (80%), the same specificity (89%), and a higher incidence rate (34%). In the study by Gomes et al. (66), SAECG had a sensitivity of 87%, compared to 80% for the AM and LVEF <40%. The specificity of the SAECG (63%) was greater than either the LVEF (54%) or the AM (42%). Patients with 2 abnormal tests had event rates of ∿35%. The combination of an abnormal SAECG and an LVEF <40% had the highest odds ratio and provided excellent sensitivity (91%) and moderate specificity (59%).

In summary, AM, LVEF, SAECG, and EPS can all be used to prognosticate risk of arrhythmic events in a post-myocardial infarction patient population. The markers of the substrate (EPS, LVEF, SAECG) appear to be more powerful than markers of the triggering arrhythmias (AM), but no single test is ideal. The limitations may be partially related to the multiple variables that contribute to this process and therefore a combination of tests appears to improve accuracy.

2. Post-Sustained Ventricular Tachycardia or Sudden Death

Once a patient has survived an episode of VT-S or sudden death, an aggressive approach to risk assessment and management is mandated. The risk of recurrence depends upon whether the arrhythmia occurred in the setting of an acute myocardial infarction (4). In fact, only a minority of resuscitated patients actually suffer myocardial necrosis. In these, the occurrence of the acute arrhythmia does not necessarily imply increased risk for future events. Rather, these patients should be evaluated in the context of the above discussion. In patients without infarction, empiric treatment is associated with high mortality (30% in the 1st year, 41% over 2 years) (4). The recurrences tend to occur early (mean 17 weeks) and, therefore, prompt and aggressive management is required. Surprisingly, little data on the prognostic value of baseline AM, SAECG, LVEF, or EPS are available.

a. Ambulatory Monitoring (AM)

Weaver et al. (85), in Seattle, recorded "complex" ventricular arrhythmias (bigeminy, trigeminy, repetitive, or multifocal) in 66% of 144 sudden death survivors. These "complex" arrhythmias were associated with an increased risk for recurrent sudden death. Sensitivity was 84% but specificity was only 40%. Unfortunately, patients with sudden death in the setting of acute myocardial infarction were included in this study. In addition, the mean time to recording of the Holter was 11 months after the event. In patients in whom AM was performed >1 year after the event, arrhythmias were of no prognostic significance. Therefore, these data are not a true reflection of the significance of ambient arrhythmias in patients with primary VT-S and VF.

b. LV Function

The Seattle group (3) also reported on catheterization data in 64 patients after sudden death. Patients who had recurrences had lower LVEFs and more severe contraction abnormalities than patients who did not. Ritchie et al. (20) found LVEF to be the best predictor of mortality in 154 survivors of sudden death. Arrhythmias did not add significantly to risk. In this study, 29% of patients had a normal LVEF and an excellent prognosis. Myerburg et al. (13) reported a similar incidence of preserved LV function in this population. Swerdlow et al. (86) found that the severity of heart failure was the strongest independent predictor of mortality in 239 patients with VT-S or VF.

c. Electrophysiologic Study (EPS)

EPS has been widely used in patients with VT-S and sudden death (37-39,87-91). Initial studies by Ruskin (87), Morady (39), Kehoe (88), and others (37-38) suggested that non-inducibility was a good prognostic finding (Table 6).

TABLE 6 EPS IN SURVIVORS OF CARDIAC ARREST: Outcome in Non-Inducible Patients

Author	Patients (n)	Diagnosis (% IHD)	Mean follow-up (mo)	Recurrent CA (%)
Ruskin (87)	8	74	15	0
Morady (39)	19	74	26	5
Kehoe (88)	44	80	14	0
Zheutlin (89)	32	50	24	3
Skale (90)	15	33	22	13
Wilber (91)	32	66	34	19
Roy (37)	47	72	20	32
Eldar (38)	33	33	27	9

CA - cardiac arrest; IHD - ischemic heart disease

Many of these non-inducible patients who had events during exercise or had positive exercise tests were successfully managed with anti-ischemic therapy. However, results from two large studies do not support the benignity of non-inducibility. Roy et al. (37) studied 119 survivors of sudden death, 61% of whom were inducible into VT-S or VF. After a mean follow-up of 18 months, 15% of patients with inducible arrhythmias died suddenly, compared to 32% without inducible arrhythmias. Eldar et al. (38) studied 108 patients after aborted sudden death, 69% of whom were inducible. The actuarial survival, sudden death rates, and recurrences of VT-S were not different between the patients with or

without induced arrhythmias. However, the ability to suppress inducibility is a good finding and will be discussed under risk management.

In summary, the data available on baseline AM, SAECG, EPS, or LVEF in predicting future events in patients with VT-S or sudden death is limited. Depressed LVEF has the best prognostic value but the data include patients with sudden death in the setting of infarction. "Complex" arrhythmias (Grades 3-5) may also be useful. Patients with VT-S or VF in the setting of coronary artery disease who have their episode during exertion and have negative EPS may have a favorable prognosis. EPS may provide useful data relative to the nature of the substrate [i.e., fixed (Eq. 3) or variable (Eq. 4)], and the stability and hemodynamic tolerance of an arrhythmia. However, non-inducibility does not necessarily preclude arrhythmia recurrence probably because of the contribution of the variable factors to the substrate. These patients constitute a select subpopulation in which a high frequency of abnormalities on these tests is to be expected. This phenomenon may, therefore, limit the ability of baseline tests to further separate the population into groups of different risk. The real value of these tests in this patient population is in providing the framework for risk management. This will be the next topic of discussion.

B. Risk Management

Interventions to prevent sudden death must take many forms to have a significant impact on this catastrophe. Since sudden death and coronary artery disease are intimately linked, measures that attempt to prevent coronary artery disease (primary prevention) have the greatest potential for meaningfully reducing its toll. These efforts, however, are clearly beyond the scope of this presentation. Secondary prevention, or prevention of sudden death in patients in whom overt heart disease is already manifest, is an important, but as yet, elusive goal. The post-infarct population will again serve as the example for this discussion. Tertiary prevention, or the prevention of recurrent sudden death, will also be discussed. This is an increasingly important problem and is the basis for the development of important new techniques and therapies that may significantly improve the prognosis for these patients and further our knowledge of this complicated problem.

1. Post-Myocardial Infarction

a. Antiarrhythmic Drug Therapy (AAD)

1) Therapeutic Trials

Despite evidence that arrhythmias post-infarct are associated with an increased risk of sudden death, no chronic antiarrhythmia prophylaxis trial has convincingly demonstrated a beneficial event on survival. Some of the limitations of these trials include small size, failure to document the presence of arrhythmias before therapy, use of a fixed-dosage regimen, and failure to assess arrhythmia control. The studies that have addressed some of these issues will be discussed below.

Kosowsky et al. (93) randomized 78 patients to a standard procainamide dose or no therapy. There was no difference in PVC frequency, but the incidence of VT-NS and couplets was less in the procainamide group. Fewer treated patients died suddenly but this did not achieve statistical significance. Side effects required 23 of 39 patients to stop procainamide.

In a 3-month double-blind study of mexiletine in 344 high risk survivors of infarction, Chamberlain et al. (94) found that mortality was not affected by therapy despite a lower incidence of PVCs. Side effects requiring withdrawal occurred 5 times more frequently in the mexiletine group. Ryden et al. (95) performed a double-blind, randomized trial of tocainide versus placebo in 112 patients. Despite a significant reduction in PVC frequency and VT-NS over a 6-month follow-up, the incidence of VF or symptomatic VT was not different. Therapy was withdrawn in 39% of the tocainide patients because of side effects or inefficacy. Hugenholz (96) gave aprindine or placebo to 310 patients manifesting "malignant" arrhythmias after infarction. Dosage was adjusted to achieve arrhythmia control on follow-up AM. There was a significant reduction in "malignant" arrhythmias in the treatment group at 1 year (49% vs. 20%), but the incidence of VF or sudden death was not different.

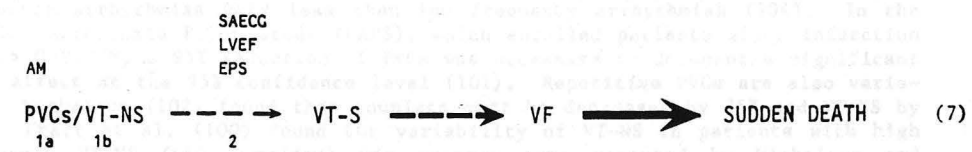
In a recent study, Gottleib et al. (97) treated 143 patients with aprindine or placebo in a double-blind, dose-adjusted trial. Patients had an LVEF <40%, Grade 3 or higher arrhythmias, or both. Arrhythmias, but not sudden death mortality was reduced by treatment. However, aprindine increased mean survival duration from 22 to 86 days.

The methodologic flaws noted preclude drawing any firm conclusions about the efficacy of AAD in preventing sudden death. The failure of these trials and others to show any benefit of antiarrhythmic therapy on survival may indicate an actual lack of efficacy of these drugs, an inability to detect real differences because of small study size, or a combination of harmful and beneficial effects of the drugs (98). This last possibility must be considered in light of the potential for proarrhythmia of these agents and will be discussed subsequently. A new multicenter dose-adjusted trial of the efficacy of arrhythmia suppression in preventing sudden death after infarction, the Cardiac Arrhythmia Suppression Trial (CAST), will provide important data on this issue.

2) Limitations of Antiarrhythmic Therapy

a) Endpoints of Therapy

To successfully and rationally use antiarrhythmic drugs (AAD), we must address several fundamental questions. The first and most fundamental is, What is the optimal endpoint of therapy? (Eq. 7).



(7)

AAD therapy at sites 1a or 1b (suppression of ambient arrhythmias) is the most frequently utilized endpoint of therapy, but has several perils. The first is the uncertainty about the degree of arrhythmia suppression necessary to reduce sudden death risk. Since complete arrhythmia suppression is unlikely and probably unnecessary, we must decide what level of arrhythmia control (if any) optimally decreases the incidence of sudden death without excessive cost,

inconvenience, side effects, and risk. For example, the MILIS study (53) proposed that >10 PVCs/h was useful for identifying patients at increased risk of sudden death after infarction. It would be logical to attempt to reduce arrhythmias below this level, but in some cases this might be impossible. We must then ask whether we should reduce PVCs by a certain percentage, to a specified level, or whether we should abolish repetitive forms alone, without substantially reducing PVC frequency. Since sudden death risk after infarction appears to be non-linear with respect to PVC frequency, even substantial reductions of PVC frequency might not decrease risk. In the case of a patient with 300 PVCs/h, a 90% reduction in PVC frequency to 30 PVCs/h would still potentially leave the patient in a high risk group. At the present, we do not know if the patient's risk has been substantially reduced by the statistically significant reduction in ventricular ectopy or if it has been changed at all.

Another potential endpoint of AAD therapy is the prevention of the development of VT-S and VF (site 2). Since PVCs and VT-NS themselves are not life-threatening and rarely symptomatic, their suppression might not be necessary if the potential to develop VT-S could be dramatically altered. That is, the risk of sudden death with 10 PVCs/h "off drug" might not be the same as the risk of 10 PVCs/hr "on drug". Perhaps only "therapeutic" plasma AAD levels are required and not arrhythmia suppression, per se. There is some data to support this concept in patients with VT-S. Unfortunately, in patients without VT-S, there is no sure way to assess this endpoint of therapy. Clearly, until we know what constitutes an acceptable therapeutic endpoint, it will be difficult to answer the question of AAD efficacy in preventing sudden death.

b) Assessing Drug Effect

Assuming resolution of the above problems and an acceptable therapeutic endpoint of therapy, the next peril to be overcome is how to gauge AAD effect in the face of the tremendous spontaneous variability of arrhythmias (99-103). Morganroth et al. (99) looked at spontaneous variability of arrhythmias in patients with at least 30 PVCs/hr and found that when comparing one 24-hour AM to another, PVCs must be decreased by 83% to exclude spontaneous variability. Pratt et al. (100) found similar results in 110 patients with high frequency PVCs and VT-NS. In this study, a reduction of 78% of PVCs was necessary to establish drug effect when comparing two 24-hour AM. Arrhythmia variability was greater in patients with coronary disease than in patients without coronary disease and therefore required greater suppression (84% vs. 64%). While these studies were not conducted in an acute post-infarct population, data from patients after an infarction are similar (101).

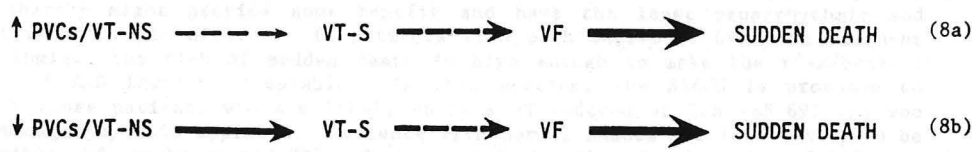
Arrhythmia variability is also a function of arrhythmia frequency. High frequency arrhythmias vary less than low frequency arrhythmias (104). In the Cardiac Arrhythmia Pilot Study (CAPS), which enrolled patients after infarction with >10 PVC/h, a 95% reduction of PVCs was necessary to document a significant drug effect at the 95% confidence level (101). Repetitive PVCs are also variable. Michelson (102) found that couplets must be decreased by 75% and VT-NS by 65%. Pratt et al. (100) found the variability of VT-NS in patients with high frequency VT-NS ($\geq$10 runs/day) was greater than reported by Michelson and required an 85% reduction of episodes to be confident of drug effect at a 95% level. When VT-NS occurred infrequently ($\leq$5/day), even complete suppression could occur spontaneously.

The potential for finding discordant effects of therapy on these arrhythmias is self evident. A 50% reduction in PVC frequency might occur while VT-NS might be completely suppressed. It would be difficult to know if this was a result of drug effect or spontaneous variability. One potential solution to this problem is to increase the duration of the control and therapeutic recordings. With 48- and 72-hour recordings, lesser degrees of PVC suppression are required to be certain of drug effect. However, cost and inconvenience are increased by this approach.

c) Proarrhythmia (Site 1, 2)

The final hurdle to overcome in the use of AAD for preventing sudden death is proarrhythmia. Proarrhythmia can occur with virtually any antiarrhythmic drug and may cause an increase in the frequency of a previously evident arrhythmia (Eq. 8a) or the development of a new and previously unseen arrhythmia (Eq. 8b). The overall incidence of proarrhythmia averages 5-10%. Arrhythmia variability, as discussed above, is also central to this discussion. A spontaneous 85-95 percent decrease in arrhythmia frequency is a 6-19 fold reduction in frequency. Therefore it is theoretically possible that 6-19 fold increases in arrhythmia frequency can occur spontaneously. Pratt et al. (101) have confirmed that an 18-fold increase in PVC frequency is required to establish a proarrhythmic effect in a post-MI patient population with ≥10 PVCs/hr. A lesser increase in PVC frequency, however, is required to diagnose proarrhythmia when high frequency PVCs exist (104).

Independent of effects on the frequency and repetitiveness of ambient arrhythmias, AAD may also be proarrhythmic by altering the substrate (site 2). The classic example of this form of proarrhythmia is torsade de pointes. This is believed to be due to an increase in the inhomogeneity of recovery, but despite an association with QT prolongation, there is unfortunately no definite QT duration that clearly defines this risk (105). The other proarrhythmic effect of AAD is inherent in their ability to slow conduction and create conduction block. Patients with insufficient electrophysiologic abnormalities to sustain reentrant arrhythmias in the absence of drug, may therefore develop VT-S on drugs (105). Unfortunately, this phenomenon occurs most frequently in patients with a history of VT-S and poor LV function (i.e., those patients who warrant therapy the most) (106), and in an occasional patient causes incessant VT-S and VF. These different forms of proarrhythmia are represented in the Tachyarrhythmia Equations below.

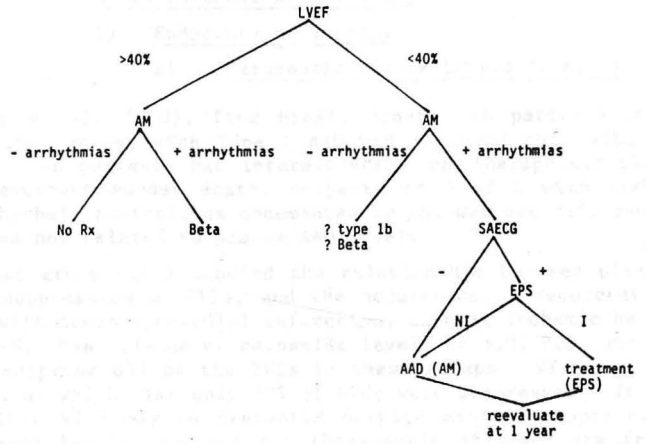


In view of the uncertain benefits of therapy and the recognized risks, it seems reasonable to confine AAD therapy to patients at significant risk. Unfortunately, it is unlikely even with firm endpoints and clear indicators of drug effect that AAD would be 100% effective in preventing sudden death. If one liberally assumes that antiarrhythmic therapy can reduce arrhythmic deaths by 50% but conservatively estimates a 5% proarrhythmic effect, then the population to be treated must have a ≥10% chance of having VT-S or VF to have a favorable benefit/risk ratio (treatment of 100 patients with a 10% risk of dying will save 5 and cause proarrhythmia in 5).

We see, from the discussion on risk assessment (Table 1), that an unselected patient population after infarction has approximately a 6% incidence of sudden death in the first year. In subsequent years, the risk is approximately 2-3%. Therefore, only a select sub-population of patients is likely to benefit from AAD therapy, mostly within the first year after infarction. Clearly, secondary prevention is a noble and important goal but the present approach to risk assessment and risk management with AAD has several important limitations. Other treatment modalities [CABG (107), beta blockers (108)] have been shown to decrease sudden death and should play a role, but an indepth discussion of these approaches is beyond the scope of this discussion. Based on the preceding discussion, the following algorithm is suggested as an approach to the prevention of sudden death after infarction.

ALGORITHM 1

PREVENTION OF SUDDEN DEATH AFTER MYOCARDIAL INFARCTION

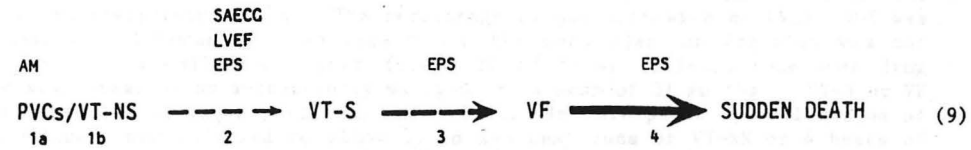


The use of beta blockers in patients with arrhythmias but good LV function is supported by subgroup analysis of the BHAT trial (109) and is an attempt to maximize potential benefit while minimizing risk. Therapy for patients with depressed LVEF but infrequent arrhythmias is justified by their increased risk for arrhythmic death. Unfortunately, however, therapy must be empiric. If beta blockers are tolerated they should be considered. Alternatively, empiric Type 1b AAD therapy might provide some benefit and have the least proarrhythmic and negative inotropic effects. In patients with both depressed LVEF and frequent arrhythmias, the risk of sudden death is high enough to make the risk/benefit ratio of AAD therapy acceptable. In this setting, the SAECG is proposed to detect those patients who are likely to have VT induced at EPS (65,69) and who may managed by this approach. Patients with normal SAECGs are less likely to be inducible and can be spared EPS and be managed with AM. Continuation of AAD past 6-12 months should be reevaluated in each patient.

2. Post-Sustained Ventricular Tachycardia and Sudden Death

In patients with previous VT-S or VF, the use of AM to guide therapy suffers from the same potential limitations addressed previously. The high risk of recurrence justifies invasive EPS and the utilization of surgery or implantable

devices if medical therapy fails or is associated with a high recurrence risk. The routine use of EPS and the spontaneous occurrence of VT-S and VF provide several additional endpoints to establish therapeutic efficacy in these patients. These endpoints are illustrated with the Tachyarrhythmia Equation (Eq. 9) and will be discussed in detail below.



(9)

a. Antiarrhythmic Drug Therapy

1) Endpoints of Therapy

a) Therapeutic Plasma Levels (Site 2)

Myerburg et al. (110), from Miami, treated 16 patients who had suffered previous cardiac arrest with Type 1 AAD and followed them with monthly AM and drug levels. Ten patients had intermittently sub-therapeutic plasma AAD levels and 8 had recurrent sudden death, compared to 0 of 6 with stable therapeutic levels. Arrhythmia control, as documented by AM, was not different between the 2 groups and was not related to plasma AAD levels.

This same group (111) studied the relationship between plasma procainamide levels, the suppression of PVCs, and the occurrence of recurrent VT-S in groups of patients with acute myocardial infarction, chronic ischemic heart disease, and recurrent VT-S. Mean plasma procainamide levels of 5.0, 9.3, and 14.9 μg/ml were required to suppress 85% of the PVCs in these groups. VT-S was suppressed at a level of 9.1, at which time only 30% of PVCs were suppressed. It is evident from this study that VT-S may be prevented despite minimal suppression of PVCs and that the plasma levels required for therapeutic efficacy are frequently higher than those generally considered "therapeutic". Greenspan et al. (112) have reported similar findings. Part of the discrepancy between therapeutic drug levels and therapeutic drug effect may be due to the fact that therapeutic levels are usually those required to suppress PVCs in stable patients and may have little relevance to the level required to prevent VT-S or VF in unstable patients.

These studies suggest that the achievement of critical plasma AAD levels may be a satisfactory and beneficial endpoint in some patients with VT-S and that dramatic suppression of ambient PVCs might not be necessary. The lack of a clear relationship between blood levels, ambient arrhythmia suppression, and efficacy further suggests that the mechanism of action of drugs in this setting is an alteration of the substrate (site 2).

b) Suppression of Ambient Arrhythmias (Sites 1a,1b)

In addition to the limitations discussed, up to 50% of patients with VT-S or VF have insufficient arrhythmias to guide therapy by AM (113). In addition, arrhythmia control may not be independent of LVEF (114). Nonetheless, Vlay et al. (115) treated 59 survivors of VT-S and VF with investigational AAD to suppress symptomatic VT-S. All patients had VT-NS on baseline AM. The suppression of VT-NS was accomplished in 26 patients, and after a 1-year follow-up, none had syncope or death compared to a 34% incidence in 18 patients with persistent VT-NS. The mean time to achievement of the "therapeutic" AM was 30 days. Evaluation of other arrhythmia characteristics as a means to guide therapy were not addressed.

Graboys et al. (116) treated 123 patients with previous VT-S or VF with a variety of AAD to suppress 100% of VT-NS and R-on-T arrhythmias, 90% of couplets, and 50% of PVCs on AM and maximal exercise testing. AAD were pre-selected (an average of 6 acute drug trials) with "trendscription". The average hospital stay was 17 days. After a mean follow-up of 30 mos, the annual sudden death rate was 2.3% in the 98 patients in whom this degree of arrhythmia control was achieved, compared to 43.6% in those patients in whom arrhythmias were not controlled. The difference between these groups was independent of age or prevalence of coronary artery disease, but 16 of the 17 patients without structural heart disease were in the drug-responding group. The percentage of patients with an LVEF <50% was not different between the two groups but the mean ejection fraction was not reported. In a follow-up report (117), 24 of these patients underwent drug withdrawal after being successfully managed for a mean of 31 months. VT-S or VF recurred in 50% of these patients, and 4 died. In this paper the definition of drug efficacy was modified to allow up to 2-3 beat runs of VT-NS or 4 beats of VT-NS on exercise testing. These papers suggest that recurrent VT-S or VF can be prevented by suppression of VT-NS and PVCs. However, it is evident that the approach used by these authors is time consuming, expensive, and significantly different from that usually practiced.

Several studies have evaluated AM as a means of guiding amiodarone therapy in patients with VT-S (118-120). Kim et al. (118) looked at 4 different criteria of therapeutic efficacy and found that arrhythmia-free survival was better in each effectively treated group regardless of the criterion used. However, the ability to detect a poor outcome varied from 31 to 47% and specificity varied from 75 to 94% depending on the criterion utilized. Suppression of VT-NS alone (site 1b) had the best specificity (i.e., fewest false positives) but the poorest sensitivity. Sensitivity in general was poor, meaning that many patients judged to be effectively treated by AM nonetheless had a poor outcome.

Veltri et al. (119) studied the value of serial 24-, 48-, and 72-hour AMs in these patients. Persistent VT-NS after 1 week of amiodarone therapy had an overall predictive accuracy of approximately 85%. Only 9% of 34 patients without VT-NS on any AM had recurrent arrhythmic events, compared to 12 of 18 (66%) with persistent VT-NS. However, persistent VT-NS on 24-hour AM only detected 8 of 15 patients with recurrent arrhythmic events. When duration of AM was increased to 72 hours, sensitivity was increased from 53% to 80% but at the expense of specificity (97% to 84%). In a study by Marchlinski (120), the suppression of 85% of PVCs and all complex forms was considered effective therapy in 55 patients. Failure to achieve this control was associated with an ∿50% recurrence rate of sudden death or VT-S. However, 18% of patients with a good response still had a recurrence.

In summary, despite a previous episode of VT-S or VF, a significant percentage of patients will not have sufficient arrhythmias on AM to use this technique to guide therapy. In patients with arrhythmias treated with amiodarone, AM has been a reasonably sensitive means of detecting a poor prognosis. Unfortunately, suppression of ambient arrhythmias, especially VT-NS, does not assure a good outcome.

c) Non-Inducibility at EPS (Site 2)

Patients with VT-S or sudden death frequently have arrhythmias induced at EPS. The incidence varies with the form of underlying heart disease, the clinically documented arrhythmia, the clinical presentation, and the EPS protocol

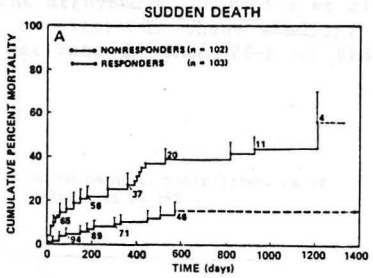
(33). In patients with uniform VT-S and previous myocardial infarction, inducibility is virtually 100%. Patients with other forms of heart disease have lower inducibility. Patients presenting with VF or sudden death are inducible ∿70% of the time.

The arrhythmia induced must be assessed in the context of the stimulation protocol and the clinical setting. Uniform VT-S is never induced in normal patients. While it can be induced in patients after myocardial infarction who have never manifested this arrhythmia, it is usually rapid and induced with an aggressive protocol (121). In patients with clinically occurring VT-S, a tachycardia of similar morphology and rate is usually reproduced. However, several previously unseen arrhythmias of different morphologies are frequently induced as well (122). Polymorphic VT or VF can be induced in up to 40% of patients without these arrhythmias and therefore must be interpreted with caution. Their suppression as an endpoint of therapy may not be meaningful.

However, the ability to reproducibly induce a uniform arrhythmia provides a useful endpoint to guide therapy (37,38,86,123,124). Numerous studies have documented the value of this approach in managing these patients. Those patients in whom therapy prevents the induction of a previously inducible arrhythmia have a better prognosis than patients in whom inducibility cannot be suppressed (Fig. 5; Table 7). By multivariate analysis, Swerdlow et al. (86) found that after the severity of heart failure, lack of effective therapy by EPS was the strongest independent predictor of mortality in VT-S and VF patients.

FIGURE 5

Actuarial survival curve based on EPS



Swerdlow et al., New Eng. J. Med. 308:1436, 1983

TABLE 7

EPS IN PATIENTS WITH VT-S or VF: Outcome with Inducible Ventricular Arrhythmias and Conventional Medical or Surgical Therapy

Author	Patients (n)	% I	% S	Follow-up (mo)	% CA-S	%CA-NS
Kehoe (88)	44	64	64	14	0	78
Benditt (92)	34	80	80	18	6	40
Roy (37)	119	70	68	18	15	21
Skale (90)	62	74	34	22	0	22
Wilber (91)	166	79	75	28	12	27
Eldar (38)	108	69	20	24	15	75
Swerdlow (86)	239	86	50	24	16	39*
Ruskin (87)	31	81	76	15	0	50

I - inducible; S - suppressed; CA - cardiac arrest; NS - nonsuppressed
* includes 27 patients treated with amiodarone

The response to therapy judged by EPS is a function of the stimulation protocol (doubles, triples, bursts) (33) and the endpoint chosen (<6 beats, <15 beats, <VT-S) (125) and therefore may vary somewhat from lab to lab. The underlined values are used in our electrical lab. If VT-S or VF can be reproducibly induced, we routinely perform serial drug testing.

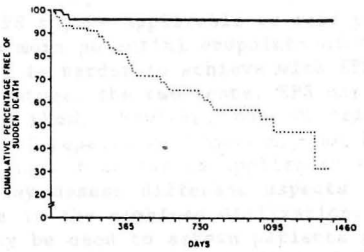
The major limitations of this technique are its invasive nature and its limited availability. Moreover, unlike AM which frequently overpredicts good outcomes, EPS may underpredict good outcomes (126-129). Thus, while non-inducibility is a marker of a good prognosis, persistent inducibility is not necessarily a specific marker of a poor prognosis. This is well recognized when testing amiodarone by EPS (130-131). Finally, as with AM, it is not clear that EPS is responsible for the good outcome. It may be that EPS and AM simply detect patients who will do well anyway.

d) Hemodynamic Stability of VT-S (Site 3)

Arrhythmia prevention is clearly the optimal endpoint of treatment, but in many patients tested by EPS this cannot be achieved (126). In these patients, alternative endpoints or approaches must be considered. Since an important determinant of the hemodynamic tolerance of an arrhythmia is the rate (132), a potential endpoint of therapy is to slow VT-S sufficiently to prevent hemodynamic collapse (site 3, Eq. 9). Waller et al. (133) recently reported that patients in whom induced VT-S had an increase in cycle length of at least 100 msec and who did not have severe hemodynamic symptoms had excellent survival in comparison to patients who did not tolerate their induced arrhythmias (Fig. 6). However, the incidence of arrhythmia recurrence was no different between the groups (39% vs 50%). This confirms the role of EPS in predicting both arrhythmia recurrence and the hemodynamic tolerance of the arrhythmia. Horowitz et al. (134) and Kadish et al. (135) have found similar results. In these studies, the recurrence of an arrhythmia was non-fatal in patients in whom VT-S at EPS was hemodynamically tolerable.

FIGURE 6

Sudden death based on hemodynamic tolerance of arrhythmias at EPS



Adapted from
Waller et al., J Am Col Cardiol 10:83-89, 1987.

e) Combination and Comparison of AM and EPS

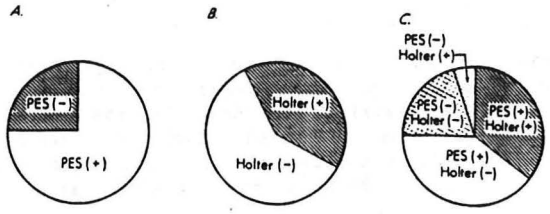
The evidence presented thus far suggests that there are advantages and disadvantages to each of these techniques. However, some patients cannot be managed by both approaches. While the majority of patients can undergo EPS, not all patients have enough ambient arrhythmias to guide therapy. Marchlinski et al. (120) found that 26% of patients with VT-S/VF had <10 PVCs/h and no complex forms. Swerdlow and Peterson (113) found that more patients could be managed with EPS (82%) than AM (50%).

In patients managed by both techniques, EPS has generally been better than AM. Chua et al. (136) compared the value of 24-hour AM (suppression of Grade 4 and 5 arrhythmias) to EPS (<6 beats inducible) in predicting outcome in 89 patients with symptomatic VT. The sensitivity, specificity, and positive and negative predictive values were all better for EPS compared to AM. Skale et al. (90) from Indiana evaluated 62 patients resuscitated from sudden cardiac death. None of the 14 patients without inducible VT after serial EPS had an arrhythmic event. Of 20 patients managed with AM, 4 of 9, in whom all Grade 4 and 5 arrhythmias were suppressed, died suddenly. Platia and Reid (137) compared EPS to AM in 44 patients with VT-S or VF. The positive and negative predictive values at EPS were excellent (88% and 94%). The presence of VT-S on AM had a positive predictive value of 70%, but the negative predictive value was only 50%. Outcome was not significantly different between patients with or without VT-NS on AM. Ezri et al. (138) used non-inducibility of EPS to define efficacy of drug or surgical treatment of VT-S. Only 4 of 13 non-inducible, non-amiodarone treated patients had a significant decrease of ambient ectopy. Herling et al. (139) found similar results in 11 non-inducible patients after successful surgery.

Kim et al. (127) found that efficacy of mexiletine was similar if either inducible sustained arrhythmias or spontaneous ambient arrhythmias were suppressed. They also evaluated (126) the concordance of these 2 techniques in predicting drug efficacy in 54 patients with VT-S treated with Type 1a agents. Therapy was judged to be effective in only 25% of patients by EPS but in up to 75% of patients by AM. AM and EPS gave discordant results 50% of the time, usually because AM predicted a good outcome and EPS did not.

In summary, EPS may be applicable to more patients with VT-S and VF than AM and one can assess more potential endpoints of therapy with EPS than with AM. A successful endpoint is harder to achieve with EPS than with AM, and there is frequent discordance between the two tests. EPS may underpredict good outcomes while AM may overpredict them. However, the AM criteria evaluated in most studies (i.e., suppression of repetitive forms) may not have been an adequate endpoint of therapy. Since neither test can be applied to all patients, there is a role for each, and since they assess different aspects of the tachyarrhythmia equation, there may be value in the combined utilization. It has been suggested that arrhythmias on AM may be used to screen patients prior to performing EPS (129,140-141) (Fig. 7). However, Pratt et al. (142) found that AM in the baseline state does not predict arrhythmia inducibility. Regardless, the poor negative predictive value (high false negative rate) of AM argues against relying solely on it to guide therapy in high risk patients. EPS appears to compare favorably to AM from an economic perspective (143).

FIGURE 7



S.G. Kim, Circulation 76:1, 1987

b. Non-Medical Therapy

1) Surgery/Catheter Ablation (Site 2); Pacing (Site 1,2,3)

Despite the importance of coronary artery disease in sudden death, coronary artery bypass grafting (CABG) alone is usually insufficient therapy for these patients (144). Ambient arrhythmias are usually unaffected (145) and a fixed substrate is not modified. Likewise, in patients with VT-S and left ventricular aneurysms, simple aneurysmectomy is usually not curative of the arrhythmia (146). In recognition of this, several surgical approaches have been developed to address the presence of a fixed anatomic electrophysiologic substrate (144).

In patients with inducible VT-S and confluent myocardial scar, endocardial mapping at the time of EPS can often be used to localize the origin of the tachyarrhythmia. The area (or areas) can then be focally ablated in the operating room by resection (subendocardial resection, SER) or cryoblation. Using this technique, Miller et al. (146,147) reported an ∿90% survival rate and an ∿80% cure rate in patients with medically refractory VT-S. This approach should be strongly considered in patients with medically refractory arrhythmias and left ventricular aneurysms who have relatively preserved left ventricular function, especially if other surgery (i.e., CABG) is considered. In our limited experience, we have operated on 4 such patients and have obtained a 100% survival and a 100% cure rate. Other surgical approaches including blind SER (148) and encircling endocardial ventriculotomy (149) have been successfully utilized. However, their non-focal nature carries the risk of injuring more tissue than is necessary and further impairing LV performance.

Catheter ablation is a new technique which has met with only limited success (150). More precise endocardial mapping techniques and new energy forms (i.e., radiofrequency and laser) will likely make this approach more viable in the future. Pacing may rarely be used to diminish ambient arrhythmias (site 1) or prevent VT-S (site 2). Antitachycardia pacing may be used to terminate VT-S (site 3) but is limited by the risk of acceleration to VF (151). With the advent of implantable defibrillators, the role of this modality will increase.

2) CPR and Defibrillation (Site 4)

All family members of these patients should be trained in CPR and should be knowledgeable about community emergency services. Patients who remain at high risk for sudden death and who are not candidates for curative therapy (i.e., nonmapable VT-S or VF, primary cardiomyopathies), or in whom there are insufficient means to guide therapy (non-inducible and infrequent arrhythmias), are candidates

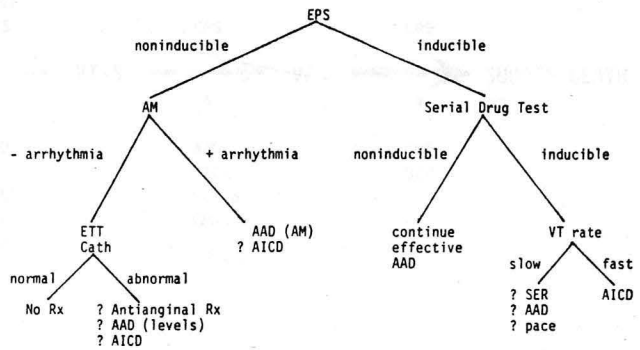
for automatic defibrillators. External (152) and implantable (153) devices are available. The portable external device can be applied by a family member and will automatically detect VF and will deliver up to 3-180 joule shocks in an attempt to terminate it. While the device can potentially save lives (152), the requirement for application in an extremely stressful situation by a family member is a potential limitation to its usefulness.

An implantable fully automatic device, the automatic implantable cardioverter defibrillator (AICD), is now commercially available and can sense VT-S and VF and deliver up to 4 shocks of 25-32 joules in an attempt to revert these arrhythmias (site 4). Survival from arrhythmias with this device is excellent but morbidity is significant because implantation requires exposure of the heart. The device is large and disfiguring, has a short battery life, is non-programmable, and does not have back-up bradycardia pacing (153). Future refinements in this device will enhance its role in these patients.

Our present approach to the management of patients with VT-S or VF is shown in the following algorithm.

ALGORITHM 2

PREVENTION OF RECURRENT VT-S/VF

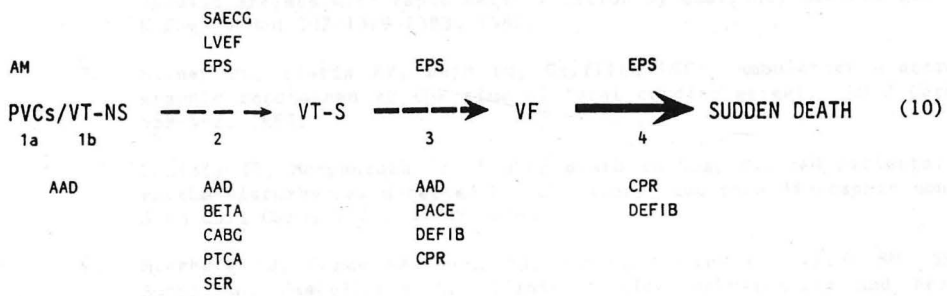


I believe all patients with VT-S or sudden cardiac death in the absence of acute infarction should undergo EPS and AM off antiarrhythmic drugs if possible. In patients who are inducible at EPS, I favor management with serial EPS-guided drug testing. Those patients in whom VT-S cannot be suppressed may be treated with a drug that slows VT-S and renders it hemodynamically tolerable or can be considered for surgery or the AICD. Patients who are non-inducible and who have frequent ambient ectopy are candidates for therapy guided by AM recognizing its substantial limitations. The AICD should be considered in these patients. In patients who are non-inducible and who have infrequent ventricular ectopy, exercise testing and coronary arteriography should be performed to look for reversible myocardial ischemia. Further therapy in these patients may include antianginal drugs, antiarrhythmic drugs, the AICD, or CABG. However, CABG and blind aneurysm resection are not recommended unless the patient has undergone EPS, since the potential for arrhythmia recurrence post-surgery is substantial if a fixed substrate exists and is not addressed.

V. SUMMARY AND CONCLUSIONS

Sudden cardiac death is usually the result of ventricular tachyarrhythmias that occur in the setting of coronary artery disease. The presence of an abnormal electrophysiologic substrate is the most important determinant of risk and is a multifactorial process. Multiple noninvasive techniques may be employed to detect a subset of individuals at elevated risk, but they are limited by poor sensitivity and specificity. Those techniques that evaluate the substrate appear to be more useful than those that assess ambient arrhythmias. Antiarrhythmic drug therapy guided by ambulatory monitoring is limited by poorly defined endpoints, arrhythmia variability, and proarrhythmia. The premise that lethal ventricular tachyarrhythmias can be prevented by the suppression of asymptomatic arrhythmias with antiarrhythmic drugs is unproven.

In patients with sustained ventricular tachycardia or ventricular fibrillation, the high risk of recurrence warrants aggressive management. Suppression of nonsustained arrhythmias on ambulatory monitoring is not an assurance that lethal arrhythmias will not recur and provides no insight into the hemodynamics of a recurrence. Electrophysiologic testing is valuable in predicting outcome and assessing multiple potential endpoints of therapy, including the role of arrhythmia surgery and implantable devices. A multi-modality approach holds the greatest promise for significantly reducing sudden death and can be readily understood in the context of the tachyarrhythmia equation.



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