The PVC Hypothesis

Craig R. Malloy, M.D.

Medical Grand Rounds

University of Texas Southwestern Medical Center

February 21, 1991

The Hypothesis

Interpretation of drug effects: cellular and clinical electrophysiology

- Ionic basis of membrane potential
- The cardiac action potential
- Mechanisms of ventricular arrhythmias
- Classification of antiarrhytmic agents
- The modulated receptor theory applied to sodium channel blockers

Study Design: Treatment, Suppression and Correlation

Effects of Antiarrhythmic Therapy on Ventricular Ectopy and Mortality

- Class I: IMPACT and other trials of IA and IB agents
- Class II: Secondary prevention with ß adrenergic blockers
- Class III: Low dose amiodarone
- Class IV: Calcium channel blockers
- Class IC: NHLBI-supported studies, the CAPS and CAST
- Effects of Class I agents on mortality after myocardial infarction

Conclusion

Ventricular arrhythmias are a significant cause of sudden death in patients with heart disease. Since these arrhythmias can be suppressed by drug therapy, it seems logical that the risk of sudden death should be reduced by drugs (3,6). In spite of the appealing simplicity of this argument, the management of ventricular arrhythmias is in flux, for three reasons. First, several new antiarrhythmic agents have been introduced recently. Second, newer methods of evaluation - signal averaged ECG and electrophysiological testing - are now widely available. Finally, randomized clinical trials have been unsupportive of what has been termed "the PVC hypothesis (51)." In fact, results of the landmark Cardiac Arrhythmia Suppression Trial challenge fundamental concepts of arrhythmia therapy (8). This brief review will summarize the background for these traditional concepts and outline current antiarrhythmic drug classification before commenting on the CAST and its clinical implications.

THE HYPOTHESIS

The premises of the PVC hypothesis are: 1) PVCs may induce ventricular fibrillation and sudden death, 2) the risk of death is related to the frequency of PVCs, and 3) drug therapy reduces the frequency of PVCs. The inference is simple enough: *suppression of PVCs by drug therapy is beneficial*. The extent to which these epidemiologic and drug effect trials can be extended to decisions regarding an individual patient is uncertain. Evidence for the PVC hypothesis will be summarized to clarify when it should be applicable.

The first premise is that PVCs may induce ventricular tachycardia, ventricular fibrillation and sudden cardiac death. Numerous animal studies, clinical observations in the coronary care unit, and results of ambulatory monitoring (34, 49) all support the conclusion that PVCs may initiate fatal ventricular fibrillation under the appropriate conditions. It has also been suggested that the rate and complexity of ventricular ectopy is predictive of sudden death (41), and some authorities concluded more than 15 years ago that simple premature ventricular contractions are of no particular significance as "warning arrhythmias (36, 40)." Thus, it is important to determine if simple PVCs, complex ectopy or both are somehow related to sudden death.

Table 1. Mortality among 1739 men with prior myocardial infarction according to type and number of PVCs. These patients were monitored for 1 hour, and were followed for 3 years (New Engl. J. Med. 297:750-757, 1977, reference 53).

	Number of patients		Sudden coronary Deaths	(number)
No PVCs	844		4.3%	(36)
Simple PVCs	433		4.2%	(18)
1-9/hour		332	4.4%	
>10/hour		101	3.3%	
Complex PVCs	462		15.5%	
1-9/hour		109	6.4%	(7)
>10/hour		353	18.7%	(66)

Complex ventricular ectopy refers to one or more of the following: multiform PVCs, couplets, bigeminy, R-on-T (PVCs which interrupt the preceding T wave), or ventricular tachycardia (VT). The latter is typically divided into sustained and nonsustained VT (NSVT). A reasonable definition of NSVT is: at least three and no more than 15 consecutive premature ventricular contractions at a rate > 120 beats/min. This definition is arbitrary and conservative, in the sense that many investigators would accept longer periods (typically 30 seconds) of VT as "nonsustained." However, longer periods of VT (16 or more beats) would exclude patients from the population of important studies (8).

An association between increased mortality and frequent PVCs has been reported in numerous epidemiological studies. Fewer studies have separated the complexity of ventricular ectopy from the frequency of PVCs. Ruberman et al. (53) analyzed both factors in a prospective study of men with suspected coronary disease (prior MI or angina). Over the 3 year follow-up period, the risk of death (all cause) or sudden cardiac death was no different among patients with simple PVCs compared to patients without PVCs (Table 1). Patients with complex ectopy as defined above had substantially increased mortality from all causes of sudden cardiac death. In a later report with 5 year follow-up, the importance of complex ectopy in predicting sudden cardiac death was preserved, and there was a smaller excess risk of sudden cardiac death even in patients with simple PVCs (54). Bigger and colleagues also reported a substantial correlation between complex ventricular ectopy (VT) and survival in patients recovering from myocardial infarction (Table 2); similar conclusions have been reported by Moss et al. (5, 42).

Table 2. Relation between ventricular tachycardia and survival in patients with recent myocardial infarction. Continuous 24 hour ECGs were recorded prior to hospital discharge; all diffferences between the groups shown below were highly significant (from Am. J. Cardiol., 48: 815, 1981, reference 5).

	Ventricular tachycardia	
	yes	no
PVCs/hour (± s.d.)	161 ± 226	18 ± 88
% pts. with > 10 PVCs/hour	64	21
% pts. with		
bigeminy	74	26
multiforms	86	48
pairs	82	23
R on T	60	26
Probability of 3 year survival	46%	81%

Together, these and numerous other reports indicate that the risk of death or sudden cardiac death among patients with coronary disease is increased by PVCs, and that complex forms have a particularly strong association. In contrast to these observations, other studies have also shown that relatively healthy individuals may have significant ventricular ectopy without an obvious increase in mortality (see 35 and references). For example, Kennedy et al. followed patients with significant ectopy for an average of 6.5 years (35). The initial clinical evaluation lead them to believe that these patients were at low risk for sudden death. About 25% had coronary disease documented by catheterization; these patients were treated with propranolol. Patients were otherwise not treated for arrhythmias, and at at an average followup of 6.5 years there was less than 2% cardiac mortality.

Table 3. Clinical characteristics of patients with ventricular ectopy followed for 6.5 years (from New Engl. J. Med. 312: 193, 1985, reference 35).

Age	46
Male sex	80%
PVCs/hour (group mean)	566
multiform	63%
couplets	60%
ventricular tachycardia	26%
R on T	4%

This and other reports do not support the notion that PVCs are uniformly deleterious, in marked contrast to the studies of patients after myocardial infarction or with angina. Collectively, these studies suggest that concommitant ischemic or other structural heart disease is a necessary component of the PVC hypothesis.

Table 4. Positive and negative predictive accuracy of PVCs (recorded during 1 hour of ECG monitoring) for sudden cardiac death. These data were originally presented in the New Engl. J. Med. 297:750-757, 1977. TP, true positive, FN, false negative, FP, false positive, TN, true negative, PPV, positive predictive value, NPV, negative predictive value.

complex PVCs and $\geq$ 10 PVCs/hour

	yes	no	
dead	66 (TP)	61 (FN)	TP/(TP+FP) = PPV = 19%
alive at 3 years	287 (FP)	1325 (TN)	TN/(TN+FN) = NPV = 96%
total	353	1386	

As an aside, the format of presentation of this type of data influences the clinical perception of the risk of PVCs. Another way of presenting the information reported by Ruberman et al. is the sensitivity and specificity of complex ventricular arrhythmias for predicting sudden cardiac death. The presence of complex and frequent ventricular ectopy is not a highly sensitive predictor of sudden death: sensitivity is 52%. The specificity is better, 82%, and the positive and negative predictive accuracy are calculated in Table 4. Thus, although PVCs confer excess risk, the presence of even complex ventricular alone does not have good predictive value for sudden death in some ambulatory patients.

The second premise is that the risk of death is independently related to the frequency and complexity of PVCs. After a myocardial infarction the risk of death clearly is related to left ventricular function and recurrent ischemia, and studies over the last decade demonstrate that a third factor, the frequency and complexity of PVCs, is also independently predictive of death. The interaction between PVCs and LV function was analyzed in the MILIS trial; results are shown in Table 2. Similarly, Bigger et al. also found that ventricular arrhythmias are an independent risk factor for mortality, independent of ventricular function (4). Gomes, et al., used a combination of signal-averaged ECGs, ejection fraction and 24 hour ECGs to predict sudden cardiac death in the first year after myocardial infarction (17). These studies all support the conclusion that, among patients in the first year after myocardial infarction, PVCs confer risk independent of ventricular function.

Table 5. Relations among ventricular arrhythmias, ejection fraction and sudden death after acute myocardial infarction (data from the Am. J. Cardiol. 54:31, 1984, reference 43)

Ejection Fraction	Repetitive PVCs	n	Mortality
> 40	no	314	2%
	yes	30	8%
≤ 40	no	141	10%
	yes	40	18%

The third premise is that drug therapy reduces the rate and complexity of PVCs sufficiently to confer beneficial effects. There is no doubt that drug therapy can suppress ventricular ectopy, but three questions must be considered when assessing the use of these drugs for an individual patient: 1) Are the observed changes spontaneous? 2) What is the appropriate target level of reduction in PVCs? and 3) What is the risk of fatal proarrhythmia which could outweigh a beneficial effect?

There is spontaneous variability in the frequency of both simple PVCs and the more complex forms as well (21). We cannot rely on symptoms because few patients have a good correlation between symptoms and rhythm. This issue was extensively investigated in the 1970s, and by 1983 it was generally felt that 2 24 hour ECGs before therapy and 2 24 hour ECGs during therapy showing 75% suppression were required to document drug effect. More recent clinical trials such as the CAST and

CAPS (see below) required 70 or 80% PVC reduction plus 90 to 100% reduction in VT on single 24 hour ECGs. The importance of spontaneous variability was recently illustrated in the CAPS in which 37% of patients achieved suppression (defined as > 70% reduction in PVCs and > 90% reduction in NSVT) on placebo (10). It is important to appreciate that these targets do not represent a well-established threshold below which cardiac mortality is reduced; these criteria were established simply to confirm that drug therapy has an effect on ventricular ectopy. (It is conceivable that a drug could have a beneficial effect on mortality if it abolished NSVT but had no effect on the frequency of simple PVCs; studies addressing this issue have not been performed.)

The risk of aggravating ventricular arrhythmias by antiarrhythmic therapy (proarrhythmia) was emphasized by Velebit et al. in 1982 (61). It is generally thought that about 5-20% of patients will show a significant increase in ventricular ectopy when treated with Class I agents (defined below; see Table 6). It is also generally thought that proarrhythmia is an acute consequence of drug therapy.

In sum, there is convincing evidence from large studies that PVCs are independently related to sudden death among patients with a previous MI (3, 6), but the predictive value of ventricular ectopy is not necessarily high. Further, these conclusions may not apply to patients without structural heart disease. Indeed, most trials which address the PVC hypothesis enrolled patients with previous myocardial infarctions, and some required a minimal level of ventricular ectopy. With this in mind, and having briefly reviewed the premises, the specific clinical implications of the hypothesis can be stated:

Patients with a previous myocardial infarction and a significant frequency of PVCs should be treated with antiarrhythmic agents which suppress all complex ventricular ectopy and >80% of all PVCs on a 24 hour ECG; the benefit of this treatment will be improved survival.

The subsequent discussion of this hypothesis will exclude data from studies of hypertrophic cardiomyopathies, dilated cardiomyopathies, mitral valve prolapse syndrome, long QT syndromes, and other conditions associated with ventricular ectopy and sudden death. No attempt will be made to assess the role of electrophysiologic studies in refining or testing this hypothesis (67).

INTERPRETATION OF DRUG EFFECTS: CELLULAR AND CLINICAL ELECTROPHYSIOLOGY

The widely-used classification scheme for antiarrhythmic drug mechanisms introduced by Vaughn Williams has proven surprisingly functional when interpreting clinical studies (60). In particular, some of the clinical consequences of Class I agents can be understood in terms of the cellular basis of the drug effects. Therefore, normal and abnormal cellular electrophysiology will be summarized briefly before considering the relevance of cellular electrophysiology to drug effects.

Ionic basis of membrane potential and the resting cell membrane

The electrical potential across a myocardial cell membrane is determined by two factors: 1) the concentration gradient for three ions: sodium, potassium and calcium; and 2) the permeability of the membrane to each ion. In the heart, it is generally accepted that the *ion gradients* are generated and maintained primarily by the Na-K ATPase. This sodium gradient, in turn, drives exchange mechanisms (Na-Ca and Na-H), and other energy-dependent ion pumps also modulate the concentration of intracellular cations. *Membrane permeability* is controlled by ion channels. These are protein molecules that span the lipid bilayer; each type of molecule is relatively specific for potassium, sodium or calcium. The flux of ions through each channel is thought to be controlled by gates within the channel which are opened or closed by changes in membrane voltage. Flux of ions through these channels is independent of direct exchange with other ions.

At rest, the membrane potential is described by the Nernst equation. This relation for monovalent cations is:

$$E_m = \frac{RT}{F} \log \frac{g_K[K]_o + g_{Na}[Na]_o}{g_K[K]_i + g_{Na}[Na]_i}$$

where RT/nF = 61 millivolts at 37°. R is the gas constant, T is temperature, F is the Faraday constant, and g is the membrane conductance of a particular cation. At rest, the membrane of nonpacemaker cells is much more permeable to potassium than other ions (i.e., g_{Na} is small). Normally, $[K^+]_{out}$ is $\approx$ 4.5 mM, and $[K^+]_{in}$ is $\approx$ 130 mM. Thus, the normal resting potential is about -90 mV.

Membrane activation and the cardiac action potential

Normal cardiac electrical activity is divided into 5 phases which are best resolved in Purkinje fibers: phase 0, rapid depolarization; phase 1, fast repolarization; phase 2, plateau; phase 3, repolarization to diastolic potential; phase 4, resting, or diastolic potential. Pacemaker cells such as those in the sinoatrial or atrioventricular nodes show characteristic behavior during diastole: sodium permeability increases gradually. Thus, these cells or other cells which acquire automaticity show gradual depolarization during diastole.

The interplay between the resting potential of a cell and the subsequent action potential is strongly influenced by the Class I agents, and this interaction has important clinical consequences. The action potential is initiated by depolarization of the cell membrane to the *threshold voltage* which initiates phase 0. This rapid depolarization is due to opening or activation of the fast sodium channels. To a first approximation, the maximal rate of depolarization (dV/dT, V_{max}) is proportional to the number of available sodium channels. Thus, if a cell depolarizes before full recovery (for example, depolarization occurs at -60 mV rather than -90 mV), dV/dT will be depressed because not all sodium channels have recovered. If a drug blocks a sodium channel, then V_{max} will also be reduced. One additional consequence of a reduced number of sodium channels is a reduced conduction velocity, which plays a key role in the antiarrhythmic and toxic effects of these drugs.

Normally, the fast sodium channels are rapidly activated and are rapidly inactivated. Calcium channel and a slow sodium channel activation produce the plateau phase of the action potential. Phase 3, repolarization, is a consequence of complete calcium and slow sodium channel inactivation, and the slow reappearance of a high level of permeability to potassium. Because of the current importance of Class I agents for treating ventricular arrhythmias and their known interaction with the sodium channel, the calcium and potassium channels will not be considered further.

Mechanisms of ventricular arrhythmias

Traditionally, ventricular arrhythmias are considered as a disorder of impulse formation or impulse conduction, or a combination of both mechanisms. At a clinical level, it is difficult to satisfactorily analyze the spectrum of ventricular ectopy within this framework. For example, the precise interaction between a reentrant mechanism and altered automaticity in NSVT is unclear. It is likely that some arrhythmias are genetrated by one mechanism (automaticity) and maintained by another (reentry). The conditions precipitating a particular arrhythmia are also important. For example, VT due to intoxication with cardiac glycosides appears to be enhanced automaticity. Since antiarrhythmic agents can influence both conduction as well as impulse formation, analyzing the mechanisms of action of antiarrhythmics under clinical conditions is to some degree speculative (58,59). Nevertheless, basic cellular studies have shaped our concepts of Class I action. These studies show that ventricular arrhythmias are associated with ischemia, cellular depolarization is caused by ischemia (11,28, 29,33,38,39,45,57,64,65), and ischemia has implications for automaticity, conduction velocity, and drug interactions with the sodium channel.

Automaticity in ventricular myocytes and Purkinje is controlled largely by factors which shorten electrical diastole. These factors are: 1) maximal diastolic potential, 2) slope of diastolic depolarization, and 3) the threshold potential. Autonomic influences may alter the maximum diastolic potential, but the most important factor in determining automaticity is slope of depolarization. All cardiac cells have the potential for phase 4 depolarization which can be induced by fiber stretch, ß adrenergic stimulation, acidosis, other consequences of ischemia, and hypokalemia. (Digitalis intoxication appears to cause a very rapid phase 4 depolarization known as oscillatory afterpotentials.)

Altered conduction velocity plays a central role in reentry, the mechanism thought to sustain most ventricular tachycardia. Specifically, conduction around an obstacle in an electrical circuit must be slow enough so that the impulse can reenter the refractory tissue when an action potential can be evoked. Thus, drugs which depress conduction velocity could have a beneficial effect on reentrant ventricular tachycardia induced by a single premature beat.

Classification of antiarrhythmic agents

Vaughn Williams suggested that there are four mechanisms of antiarrhythmic effects: blockade of the sodium channel, calcium channel, potassium channel, or ß adrenergic receptors (Table 6 and reference 60). In 1980 Harrison suggested subclassification based on effects on the surface ECG at clinical doses in patients (20). Although this combined classification scheme has become a clinical shorthand, it is not based on chemical structure or physical properties of the drugs, nor is it based purely on the mechanisms of drug action. In fact, there are

at least four fundamental weaknesses of this classification scheme, particularly with regard to clinical utility. *First*, a drug may have more than one effect. For example, propafenone has both class I and class II effects, and quinidine and disopyramide are anticholinergic agents. *Second*, a parent drug may fall into one class, but its metabolites fall into another. For example, procainamide (class I) is metabolized to N-acetylprocaineamide (NAPA, Class III). *Third*, Some drugs such as quinidine delay action potential duration which is unrelated to its class I features. Thus, the antiarrhythmic effect may be due to a property of a drug other than its Class I effects. *Fourth*, numerous clinically relevant features (half life, CNS penetration, side effect profile, etc.) may be different.

In spite of these liabilities, this classification scheme has come into widespread use, and it provides a remarkably useful guide for the analysis of the PVC hypothesis. The factors which define each class are summarized in Table 6. The subdivision of Class I is based on differences in the rate at which drugs become attached to and are released from the sodium channel (20). Note that the order of listing classes IA and IB is reversed to reflect that the kinetics of Class IA agents are intermediate between IB and IC.

Table 6. Antiarrhythmia mechanisms. "PVC suppression" is the fraction of patients showing a reduction in frequency of PVCs by 80% or more.

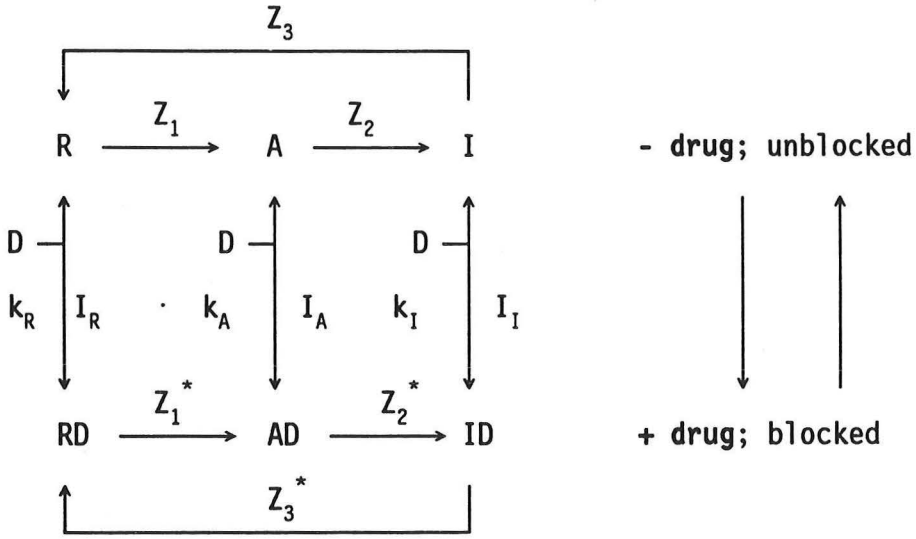
CLASS AND MECHANISM	ELECTROPHYSIOLOGIC EFFECTS	ECG EFFECTS	DRUGS	PVC SUPPRESSION
I - Na channel blocker (rate of release from Na channel)				
IB rapid	little effect on V_{max}; ↓APD	none	lidocaine	
			tocainide	≈40%
			mexiletine	≈40%
IA intermediate	Reduced V_{max} and prolong repolarization	↑QT, ↑JT (toxic: ↑QRS)	disopyramide	≈50%
			procainamide	≈50%
			quinidine	≈50%
			moricizine	≈65%
IC slow	Reduced V_{max} and delay conduction	↑PR, ↑QRS	encainide	≈80%
			flecainide	≈80%
			propafenone	≈70%
			indecainide	
			lorcainide	≈70%
II - β adrenergic blocker	block sinus and AV nodes	↓HR, ↑PR	propranolol	≈40%
			timolol	
			metoprolol	
			sotalol	
III - K channel blocker	prolong repolarization		amiodarone	≈90%
			sotalol	
			bretylium	
IV - Ca channel blocker	block sinus and AV nodes	↓HR, ↑PR	verapamil	
			diltiazem	

The Modulated Receptor Model Applied to Sodium Channel Blockers

The empirical Harrison subdivision can be interpreted as the clinical expression of differing rates of attachment and detachment of a drug from the sodium channel, and consequent effects on the rate of phase 0 depolarization. Although the molecular basis for these differences are not known, the modulated receptor hypothesis provides a framework for understanding these differences.

Three observations indicate that *the interactions of Class I agents with the sodium channel are time and voltage dependent*: 1) these agents cause the voltage dependence of sodium channel inactivation to shift to more negative potentials, 2) effects of class I agents on V_{max} progressively increase in a train of depolarizations (use dependence), and 3) use-dependent depression of V_{max} recovers more rapidly at more negative potentials (reviewed in reference 25).

The modulated receptor hypothesis assumes that sodium channel blockers associate with the transmembrane channel on a relatively specific receptor, and that channels associated with drugs do not conduct. Further, there are thought to be three states of the receptor for antiarrhythmic drugs on the sodium channel: rested, activated, and inactivated, and each state of the receptor has different kinetics of interaction with drugs (Table 7). As shown in the following scheme, the rested (R) channel is converted to an active (A) channel with a rate constant Z_1 during rapid depolarization. The active channel is inactivated with rate constant Z_2 to create a channel in the inactive (I) state. This channel is eventually converted to a rested channel to complete the cardiac cycle for that channel.



Each state has a different affinity (dissociation and association rate constants, k and I) for a sodium channel blocker, and the kinetics of cycling of the channel associated with a drug is altered (deonoted by *). All of the Class I agents have a low affinity for the rested channel. However, the rate at which these drugs dissociate from the inactive channel differs substantially among the subgroups. This is shown experimentally by use dependent block: V_{max} is depressed with early depolarization. According to this hypothesis, this reduction is an index of the number of channels which have recovered from block.

Table 7. States of sodium channels and their relation to ion conductance and drug binding.

State	Phase	Ion passage?	Available to be opened by depolarization?	Available for binding by drug?
closed (rested, R)	4	no	yes	no (low affinity)
open (active, A)	0	yes	n.a.	yes (high affinity)
inactive (I)	1-3	no	no	yes (high affinity)

Class IB agents dissociate very rapidly from the sodium channel during diastole, and use dependence reaches its maximal effect quickly. Therefore, there is little effect on dV/dT in sinus rhythm because the drug has been removed from the sodium channel. Thus, the very fast onset-offset kinetics mean that intraventricular conduction is not affected (QRS is normal). However, dV/dT is strongly effected by very rapid premature beats. Thus, there is little effect on the ECG by IB agents in sinus rhythm, but they can be expected to suppress very fast rhythms such as ventricular fibrillation.

Class IA agents dissociate more slowly from the sodium channel than IB. Consequently, at high (toxic) concentrations, all of these agents cause widening of the QRS. Quinidine and probably the other IA agents also delay repolarization, but this effect on lengthening the action potential is unrelated to its class I effects. Thus, the IA agents also show lengthening of the QT interval which is not a cardinal effect with regard to this classification scheme.

Finally, IC agents dissociate very slowly from the sodium channel, and show very slowly developing use-dependent block. Consequently, even in sinus rhythm, fewer channels are available to carry the inward sodium current, conduction velocity is decreased, and intraventricular conduction (HV and QRS) is prolonged. Like the IB agents, there is little effect on the action potential duration or the effective refractory period.

Thus, the overall effect of a drug on cellular electrophysiology depends on the interaction between drug association-dissociation kinetics, heart rate, and the factors which control resting membrane potential. Depolarized cells have more sodium channels in the inactive state. Therefore, all class I agents will bind sodium channels in ischemic tissues preferentially over normal tissues. For this reason, ischemia probably amplifies the typical effects of each drug on the sodium channel.

STUDY DESIGN: TREATMENT, SUPPRESSION AND CORRELATION

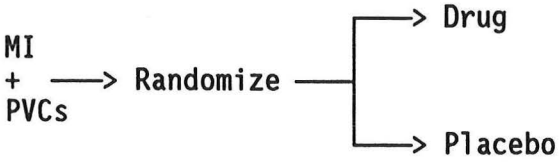
The hypothesis required the following: previous MI, significant ventricular ectopy on a baseline 24 hour ECG, and significant suppression of ventricular ectopy. A study addressing this hypothesis should have several features:

1) large enrollment to prevent type II error,
2) randomized drug assignment to prevent treatment allocation error,
3) double blind design,
4) reporting of all-cause and sudden death mortality to prevent bias in cause-specific mortality and difficulties in defining arrhythmic death,
5) a requirement of significant PVCs for enrollment,
6) assessment of PVC suppression to document antiarrhythmic efficacy.
7) selection of drugs which have minimal side effects to preserve the double blind design.

Ideally, drugs which are generally available should be studied, and standard clinical practice should be reproduced. Mimicking clinical practice in a standardized fashion may be a contradiction in terms, but drug and dose titration to a clinical endpoint could be features of a randomized study.

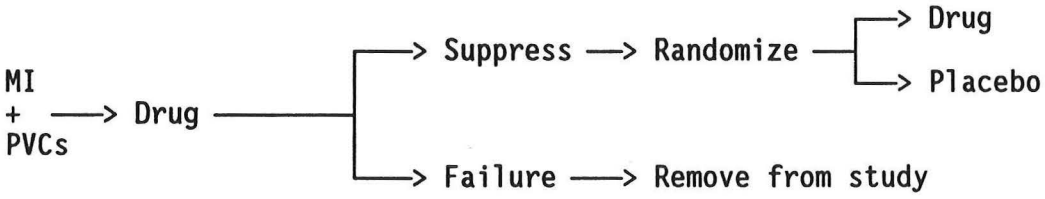
Three possible trial designs are illustrated in the following figures.

Treatment hypothesis: Does treatment reduce mortality?



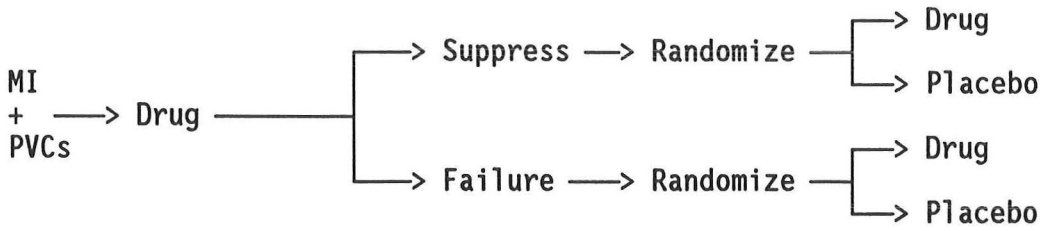
This design was used in the ß blocker secondary prevention trials. The limitation is that the treated group includes both responders (PVC suppression) and nonresponders. Although monitoring could be performed, some patients will die after the drug is initiated but before suppression is assessed, thus obscuring the relation between PVC suppression and mortality.

Suppression hypothesis: Does drug therapy and PVC suppression reduce mortality?



This trial design tests the hypothesis that suppression of PVCs (not just treatment) reduces mortality. The "drug" step refers to an open-label titration period with different agents and doses until suppression criteria are met. Notice, however, that this trial design permits analysis of one selected group: those patients who respond to antiarrhythmic therapy. This group of patients, regardless of therapy, may have a different prognosis compared to those who fail to respond.

Correlation hypothesis: Does mortality correlate with treatment or suppression?



The advantage of this design is that the consequences of selecting patients by suppression criteria will be evaluated. Recall that PVC suppression criteria are used only to confirm a drug effect. Thus, benefit from minimal suppression (e.g., eliminate NSVT but not PVCs) could be identified by this protocol.

EFFECTS OF ANTIARRHYTHMIC THERAPY ON VENTRICULAR ECTOPY AND MORTALITY

Most studies designed to test the PVC hypothesis involve patients with recent MI and PVCs. At least 10 randomized, prospective, double blind studies with parallel placebo groups have been reported for the IA and IB agents, and one study (CAPS/CAST) reports on the IC agents. There is an enormous literature describing the class II and class IV agents; these will be summarized very briefly as they bear on the relations among drug therapy, ventricular ectopy, and sudden death.

Class I

Studies of the class I agents fall into two catagories: short term studies which were limited to the first few weeks after an infarction, and longer term studies which assessed mortality at 4 to 12 months after enrollment. Unfortunately, all of the studies of the IA agents which meet the criteria identified above were short-term studies, and their results are summarized in Table 8. The studies of IB agents were longer-term, between 3 and 12 months (Table 9). In no study was there a significant effect on mortality.

Table 8. Six short-term trials of IA agents: date of publication, design and mortality results. All-cause mortality was not significantly different between treated and control groups in any study (data from references 24,30,31,36,46,63).

Date	Author	#pts	drug	entry window (hours)	follow-up (days)	deaths/randomized control	deaths/randomized treated	% mortality control	% mortality treated
1967	Holmberg	104	quin.	<24	14	4/55	9/49	7.3	18.4
1974	Jones	103	quin.	<24	3	2/58	1/45	3.4	2.2
1969	Koch-Weser	70	proc.	<72	8	3/33	3/37	9.1	8.1
1976	Jennings	95	diso.	<48	h.s.	5/49	2/46	10.2	4.3
1980	Nicholls	199	diso.	<24	h.s.	12/99	10/100	12.1	10.0
1980	Wilcox	316	diso.	<24	42	10/158	14/158	6.3	8.9

Table 9. Four long-term trials of IB agents: date of publication, design and mortality results. All-cause mortality was not significantly different between treated and control groups in any study. Mortality in the study by Bastien et al. was reported by Furberg (data from references 1,12,15,26,56.)

Date	Author	#pts	drug	entry window (days)	follow-up (months)	deaths/randomized control	deaths/randomized treated	% mortality control	% mortality treated
1980	Ryden	112	toc.	2	6	5/56	5/56	8.9	8.9
1980	Bastian	146	toc.	7-10	6	3/74	4/72	4.1	5.6
1980	Chamberlain	344	mex.	6-14	3-4	19/163	24/181	11.7	13.3
1985	IMPACT	630	mex.	3-25	12	15/313	24/317	4.8	7.6

The International Mexiletine and Placebo Antiarrhythmic Coronary Trial (IMPACT) was designed to "ascertain whether the sustained release form of mexiletine ... would be effective in reducing the occurence of ventricular arrhythmias in patients with recent documented myocardial infarction (26)." Thus, this study was not designed to test the PVC hypothesis, and not all (but most) patients had PVCs. The clinical characteristics and all-cause mortality at 1 year are summarized in Table 9. There was no significant effect of mexiletine on mortality.

Table 10. IMPACT: characteristics of patients randomly assigned to receive mexiletine or placebo (summary; data from J. Am. Coll. Cardiol. 1984; 4: 1148-63). There were no statistically significant differences between groups in baseline features or mortality.

Variable	Mexiletine	Placebo
n	317	313
Male sex (%)	85.2	81.8
Age (years)	56.5	57.1
CHF (%)	20.2	16.6
Angina (%)	17	15
PVCs (% of patients)	92.0	90.6
Ventricular tachycardia (%)	8.7	12.8
Mortality (all cause)	7.6%	4.8%

Numerous variables confound direct comparison of these studies. Variable definitions of complex ventricular ectopy, lack of quantitative ejection fraction measurements, mixed patient populations (time between MI and enrollment, symptomatic vs. asymptomatic PVCs, duration of arrhythmias, etc.), variable durations of ECG recordings, variable definitions of suppression, etc. all limit comparison. Further, dose titration and selection of alternative drugs was not studied. Thus, although no study showed a beneficial effect, the low statistical power and restrictive design could obscure a benefit of Class IA or IB agents.

Class II: ß adrenergic blockers

The beneficial effects on all-cause mortality of ß adrenergic blockers in secondary prevention after myocardial infarction are well-established (2,14, 47,48,66). It should be noted that the ß blocker trials were treatment trials (not suppression trials), so the design is fundamentally different from CAST. Nevertheless, the interaction of ß-adrenergic blockers with arrhythmias and death does bear on the PVC hypothesis. Pooled data indicate a 20% reduction in all-cause mortality with ß blockers, but a *greater* effect, about 30% reduction, in sudden death. Thus, ß blockers are the *only* antiarrhythmic agents shown to reduce the incidence of sudden death in randomized trials (aspirin is not considered here as an antiarrhythmic agent). There are at least two possible interpretations. First, ß blockers reduce ischemia and thereby modify the anatomic/electrical substrate for the induction of arrhythmias, particularly by catecholamines. Second, ß blockers reduce PVCs. Unfortunately for the PVC hypothesis, two studies (Beta Blocker Heart Attact Trial, and a trial of metoprolol in acute myocardial infarction) found that ß blockers had little effect on PVCs, but reduced the risk of ventricular fibrillation significantly (2, 55). Thus, it appears that the weak PVC suppression effects of ß blockers can be dissociated from their antifibrillatory effects.

Class III

Amiodarone has been studied in one trial which has been reported as an abstract (7). In that study, approximately 300 post-MI patients with complex PVCs were randomized to placebo, standard antiarrhythmic agents, and low dose amiodarone. At one year, mortality was significantly reduced in the amiodarone group only. These observations from a small study cannot be extrapolated to patients with a previous MI and complex ventricular ectopy until considerably more information is available from this and other trials. Amiodarone has numerous and frequent side effects. Nonetheless, this trial provides a hint that PVC suppression using other than Class I (sodium channel blocking) agents could be beneficial (50).

Class IV: Calcium channel blockers

Secondary prevention trials with calcium channel blockers do not appear to reduce sudden death, and there is some evidence for deleterious effects (22). These observations of a lack of effect of anti ischemia agents suggests that the beneficial effects of ß blockers are not due solely to reducing ischemia.

Class IC: Cardiac Arrhythmia Pilot Study and Suppression Trial (CAPS and CAST)

Several factors stimulated the Cardiac Arrhythmia Suppression Trial (CAST). Previous studies enrolled relatively small numbers of patients, so a beneficial effect of arrhythmia suppression could have been missed, and in some cases the studies were not designed as mortality trials. These studies generally used a single dose of a single agent without adjustment of either according to PVCs during treatment. Thus, clinical practice was not really tested. A third factor was that physicians were practicing as if the PVC hypothesis was correct, and a significant fraction of the middle-aged or elderly population was taking a Class I agent (23, 62). Finally, new agents with good efficacy in PVC suppression and apparently

reduced toxicity were becoming available in the United States.

The objective of CAST was to "test the hypothesis that the suppression ov ventrticular arrhythmias by antiarrhythmic agents reduces the rate of death from arrhythmia (8)." To determine if this study would be practical, the Cardiac Arrhythmia Pilot Study (CAPS) was performed (9,10). CAPS screened over 30,000 patients in 10 centers. Approximately 10,000 patients had a qualifying MI, and a satisfactory 24 hour ECG was obtained in 3957 patients. Of these, 502 met arrhythmia and other criteria, and were randomized.

The primary issue addressed in CAPS was to determine whether sufficiently safe and effective drugs were availabel which could be used in a parallel, double blind, placebo controlled trial. Secondary objective were the methods for screening patines, determining mortalit in the placebo group, and methods to meaure psychosocial vairables. CAPS was not designed to test the PVC hypothesis, i.e., it was not a mortality trial.

CAPS demonstrated that enough patients could be enrolled in a mortality study designed to test the suppression hypothesis. The drugs ultimately selected for CAST - encainide, flecanide and moricizine - were chosen because earlier studies and the CAPS found that they are among the most effective for suppressing PVCs, and that these agents were relatively well tolerated. The agents which are less effective in suppressing PVCs (the widely-used IA and IB agents) or which had substantial toxicity (amiodarone) were not tested. Three additional findings in CAPS also influenced the design of CAST: 1) flecainide was found to induce CHF in patients with impaired LV function (19), 2) the overall incidence of arrhythmic deaths was 4.5% in all groups in one year, and 3) 37% of patients met suppression criteria when treated with placebo.

There were two major differences between CAST its predecessor. First, the CAST tested the suppression hypothesis, i.e., it included only patients who demonstrated PVC suppression. Second, an open label titration phase without a placebo group was included. In response to observations in CAPS there were also several relatively minor modifications in CAST. Patients with ejection fractions less that 30% were not treated with flecainide in the CAST; patients with an ejection fraction greater than 30% were randomized to all three agents. The defininition of NSVT and suppression were made more stringent, and a depressed ejection fraction ($\leq$40%) was required if patients were randomized more than 90 days after an infarction.

Table 11. Comparison of selected design features of CAPS and CAST (after Pratt and Moye, Am. J. Cardiol. 65: 20B, 1990.)

Feature	CAPS	CAST
Overall design	treatment	suppression
Parallel placebo group	yes	yes
Double blind	yes	yes
Open label titration	no	yes
PVCs/hour for enrollment	≥10	≥6
LVEF limits	≥ 20%	≤ 55% (6-90 days post MI) ≤ 40% (91 days -2 years)
ß-adrenergic blockers	encouraged	encouraged
Definition of NSVT	3-9 beats @ > 100 bpm	3-15 beats @ ≥ 120 bpm
PVC suppression goal on 24 hour ECG	70% reduction	80% reduction
NSVT suppression goal	90% if > 10 runs 100% if ≤ 10 runs	90% if > 5 runs 100% if ≤ 5 runs

CAST enrolled patients between 6 days and 2 years after a myocardial infarction. All patients had a minimum of 6 PVCs/hour on an 18 hour recording, and patients with syncope or presyncope were excluded. Patients were also excluded if they had ventricular tachycardia at a rate >120 bpm for more than 15 beats. Some of the baseline characteristics of patients treated in the flecainide-encainide-placebo arms of the CAST are summarized in Table 12.

Table 12. CAST: characteristics of patients randomly assigned to receive encainide, flecainide or placebo (summary; data from New Engl. J. Med. 1989; 321:406-412.) Results are presented as mean ± standard deviation. Ventricular tachycardia means 3 to 14 beats of VT at > 120 beats/min.

Variable	Therapy	Placebo
n	730	725
Male sex (%)	81.1	83.1
Age (years)	61±10	61±10
Ejection fraction	0.40±0.10	0.39±0.09
Angina (%)	18.6	19.3
24 hour ECG PVCs/hour	127±254	128±249
≤10 PVCs/hr	15.1%	16.2%
10.1-50	39.8%	40.7%
50.1-100	19.6%	15.8%
> 100	27.5%	27.3%
Ventricular tachycardia/24 hrs		
none	78.8%	79.9%
1	10.7%	11.4%
2-5	6.2%	5.2%
>6	4.3%	3.5%

All NHLBI clinical trials require an outside Data and Safety Monitoring Board. During routine analysis a marked excess in mortality was noted, and discontinuation of the encainide/flecainide arms was recommended in April, 1989. There was a *3.6-fold excess in cardiac death among patients randomized to encainide or flecainide*. This difference was highly significant (nominal p = 0.0006) and was remarkably consistent across all subgroups (Table 13). Specifically, baseline ECG characteristics, age, ejection fraction, or use of digitalis, diuretics, ß blockers or calcium channel blockers did not account for the marked difference in mortality.

Table 13. Mortality in CAST: Events in patients randomly assigned to receive encainide, flecainide or placebo (data from New Engl. J. Med. 1989; 321:406).

Variable	Treatment group (n = 730)	Placebo group (n=725)
Average exposure (days)	293	300
Death from arrhythmia or cardiac arrest	33	9
Other cardiac death	14	6
Noncardiac or unclassified death	9	7
Total deaths or cardiac arrest	56	22

These astonishing results from an average of only 10 months of therapy have profound implications for treatment of arrhythmias. Furthermore, two very important and unexpected observations raise questions about traditional concepts of the interactions among PVCs, sudden death and drug therapy.

The first startling observation is the very low mortality in the placebo group (Table 14). In spite of the fact that the placebo group had an average ejection fraction of 39%, 38% of the placebo group had at least 2 previous infarctions, and 42% of the placebo group had more than 50 PVCs/hour, the mortality was more like a very low-risk population. Direct comparison to older studies is not valid because even the CAPS was performed prior to the widespread use and availability of angioplasty and thrombolytic therapy. It is conceivable that the low mortality rate in the placebo group is attributable to the open label titration period during which high risk patients died during dosage adjustments and drug changes. It is difficult to understand, however, how only these patients could be at high risk only if untreated. (If the patients who died during drug titration were randomly assigned to placebo or drug therapy, it seems unlikely that they would die at a higher rate in the placebo group.)

Table 14. Post MI patients without ventricular ectopy: comparison to sudden death and total mortality in the CAPS/CAST population. All mortality rates were adjusted to estimate mortality in the first year after MI.

	Sudden death mortality	Total mortality
Post MI patients with 0 PVCs		
BHAT placebo	1.2	2.5
Bigger et al.	1.5	3.0
Ruberman et al.	1.4	4.1
CAST and CAPS (all patients have PVCs)		
CAPS all pts.	4.6	9.0
CAST enc/flec	5.4	9.2
CAST placebo	1.5	3.6

The second surprising observation was the continuously increasing difference in survival between treated and untreated patients. The traditional concept of proarrhythmia is that it occurs soon after drug initiation in sicker patients. In fact, a reasonable rule of thumb is that the risk of PVCs and sudden death is high in the same population at risk for proarrhythmia. In this population at moderate risk, an excess mortality due to proarrhythmia should have occurred early, within the first month. Although this observation is unprecedented, a satisfactory explanation has not been provided.

Effects of Class I agents on mortality after myocardial infarction

To date, all trials of Class I agents have found either no efffect or an adverse effect on mortality. The Class II agents do not suppress PVCs well, yet they have a clear beneficial effect on sudden death, presumably by an antifibrillatory effect which is independent of PVC suppression. The anti-ischemic benefit of beta blockers is likely play an important role, but there is an additional effect because Class IV agents are not beneficial with respect to sudden death. The trials of class II agents do not test the PVC hypothesis because of the influence of ß-adrenergic blockers on neurohumoral state. Nevertheless, taken together, these studies indicate that the hypothesis stated in the introduction is incorrect. Three *speculative* interpretations can be offered.

PVCs may be mechanistically unrelated to sudden death in the ambulatory patient. The events leading to fatal ventricular tachycardia and fibrillation may be modification of the substrate (myocardium) by ischemia, acidosis, catecholamies, autonomic innervation, extracellular cations, etc. The development of ventricular fibrillation is unrelated to ambient ventricular ectopy, although PVCs and VT may occur just prior to VF. According to this formulation, PVCs identify patients at risk for these events, but suppression of ventricular ectopy is simply irrelevant to long-term survival. To prevent sudden death, then the target of therapy should be the myocardial substrate for fatal ventricular arrhythmias, and reducing the

risk of events such as ischemia, alteration of ion concentrations, etc.

Currently available agents are valuable for some patients, but fatal proarrhythmia effects obscure this benefit. If this is the case, then perhaps patients at high risk of proarrhythmia should not be treated. The continuously increasing mortality among patients in the treatment arm of CAST could be interpreted as a new type of proarrhythmia which is due to the interaction of IC agents with reversibly ischemic tissues. Patients in CAST clearly had suppressing plasma concentrations of IC agents, and painful or silent ischemia may have occured in a significant fraction of these patients (16, 18, 37, 44, 52). The CAST may be demonstrating that IC agents may have a particularly deleterious interaction with ischemic tissue, and the continuing excess mortality in the treatment arm may be a consequence of continuing ischemia.

The appropriate group of patients to be treated has not been identified. Most trials performed subgroup analysis, and did not detect special effects in any one group. The typical risk stratification criteria (coronary anatomy, ejection fraction, rate and complexity of PVCs, etc.) do not appear to satisfactorily identify those patients who could benefit from therapy. Better methods or an expanded role of current methods for evaluation of the electrical substrate may be necessary to identify those patients who will benefit from PVC suppression (13, 67). Some practioners take the position that electrophysiologic testing should be perfomed in patients at increased risk of sudden death even if patients are asymptomatic. Inducible sustained VT may indicate that these patients are at increased risk, and drug suppression may be beneficial only in this catagory of patients. This approach has not been subject to study by randomization of patients with inducible arrhythmias to therapy or placebo.

Another possibility, even less likely but more intriguing, is that patients who do not show suppression of PVCs with IC agents are exactly the group which will benefit. Conceivably, the fact that a patient shows excellent suppression of ectopy may itself indicate that the patient is in a low risk group.

CONCLUSION

Although randomized trials do not support the PVC hypothesis, ventricular arrhythmias do provide important information in a patient with ischemic heart disease (prognosis), or they may provide the first evidence of important structural heart disease. CAST has increased the sensitivity of physicians to the toxic effects of antiarrhythmics, and the need for balancing the potential benefits of antiarrhythmic therapy against clear risks. To make this judgement, the arrhythmia, the anatomic substrate, and the electrophysiologic substrate must be thoroughly evaluated. The indications for treatment as well as the endpoint of treatment should be clearly established before embarking on aggressive evaluation and treatment strategies.

One objective of therapy may be to relieve palpitations which are very bothersome but not prognostically important, and the patient is not satisfied by reassurance. This may involve treating supraventricular as well as ventricular arrhythmias, especially among patients with depressed left ventricular function or valvular heart disease. Class I and class III agents are valuable, although each of these agents have the potential for significant noncardiac toxicity, proarrhythmia and depression of left ventricular function. A prudent course would

be to use ß adrenergic blockers where appropriate, and IA or IB agents if the symptomatic response is not adequate. The therapeutic endpoint is symptom relief only.

If the objective is to prolong survival among patients with minimal symptoms (palpitations) but prognostically significant arrhythmias, then the only antiarrhythmic therapy of demonstrated benefit is ß blockers. CAST clearly indicates that IC agents should be avoided among patients with ischemic heart disease and minimally symptomatic ventricular arrhythmias. The use of Class I or class III agents with the sole objective of preventing sudden death has not been demonstrated, although there may be a role for these agents if therapy is guided by electrophysiologic testing.

Finally, CAST raises other questions. For example, since studies with the scope of CAST have not been performed for the standard IA and IB agents, do *any* Class I agents have a role in treatment of bothersome palpitations which are prognostically benign? What is the role of IC agents in patients with obviously malignant arrhythmias such as primary ventricular fibrillation or severe symptoms such as syncope? Do IC agents have any role in supraventricular arrhythmias? These questions have not been addressed in controlled trials.

Acknowledgement

I appreciate secretarial assistance by Wendy Geary.

References

1. Bastian BC, Macfarlane PW, McLauchlan JH, Ballantyne D, Clark R, Hillis WS, Rae AP, Hutton I. A prospective randomized trial of tocainide in patients following myocardial infarction. *Am Heart J* 100:1017-1022, 1980.
2. Beta Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA* 247:1707, 1982.
3. Bigger JT. Definition of benign versus malignant ventricular arrhythmias: target for treatment. *Am J Cardiol* 52:47-C, 1983.
4. Bigger, JT Jr et al. The Multicenter Post-Infarction Research Group. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation* 69:250,1984.
5. Bigger JT, Jr et al. Prevalence, characteristics and significance of ventricular tachycardia (three or more complexes) detected with ambulatory electrocardiographic recording in the late hospital phase of acute myocardial infarction. *Am J Cardiol* 48:815, 1981.
6. Bigger JT. Antiarrhythmic Treatment: An overview. *Am J Cardiol* 53:8B, 1984.
7. Burkhart F et al. Improved survival of patients with asymptomatic ventricular arrhythmias after myocardial infarction with amiodarone: A randomized, controlled trial. *Circulation* 80 (Suppl II):II-119, 1989. (abstract)
8. Cardiac (The) Arrhythmia Suppression Trial (CAST) Investigators Preliminary Report. Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *New Eng J Med* 321:406, 1989.
9. Cardiac (The) Arrhythmia Pilot Study (CAPS) Investigators. Recruitment and baseline description of patients in the Cardiac Arrhythmia Pilot Study. *Am J Cardiol* 61:704-713, 1988.
10. Cardiac (The) Arrhythmia Pilot Study (CAPS) Investigators. Effects of encainide, flecainide, imipramine and moricizine on ventricular arrhythmias during the year after acute myocardial infarction: The CAPS. *Am J Cardiol* 61:501-9, 1988.
11. Carmeliet, E. Cardiac transmembrane potentials and metabolism. *Circ Res* 42:577-87,1978.
12. Chamberlain DA, Jewitt DE, Julian DG, Campbell lRWF, Boyle DMcC, Shanks RG. Oral mexiletine in high-risk patients after myocardial infarction. *Lancet* 2:1324-1327, 1980.
13. ESVEM (The) Investigators. The ESVEM trial: Electrophysiologic study versus electrocardiographic monitoring for the selection of anti-arrhythmic therapy of ventricular tachyarrhythmias. *Circulation* 79:1354, 1989.
14. Frishman WH et al. Beta-adrenergic blockade for survivors of acute myocardial infarction. *New Engl J Med* 310:830, 1984.
15. Furberg CD. Effects of antiarrhythmic drugs on mortality after myocardial infarction. *Am J Cardiol* 53:32-C, 1983.
16. Gibson RS et al. Prevalence and clinical significance of painless ST-segment depression during early post-infarction exercise testing. *Circulation* 75:1136, 1987.

17. Gomes JA et al. A new noninvasive index to predict sustained ventricular tachycardia and sudden death in the first year after myocardial infarction: based on signal averaged electrocardiogram, radionuclide ejection fraction and Holter monitoring. *J Am Coll Cardiol* 10:349, 1987.
18. Gottlieb SO et al. Silent Ischemia on Holter monitoring predicts mortality in high-risk post-infarction patients. *JAMA* 259:1030,1988.
19. Greene HL et al. Congestive heart failure after acute myocardial infarction in patients receiving antiarrhythmic agents for ventricular premature complexes (Cardiac Arrhythmia Pilot Study). *Am J Cardiol* 63:393, 1989.
20. Harrison DC. Antiarrhythmic drug classification: New science and practical applications. *Am J Cardiol* 56:185,1985.
21. Harrison DC. Methods for documenting antiarrhythmic efficacy. *Am J Cardiol* 52:37C, 1983.
22. Held PH et al. Calcium channel blockers in acute myocardial infarction and unstable angina: an overview. *Brit Med J* 299:187, 1989.
23. Hine L, Gross JP, Kennedy DL, Outpatient anti arrhythmic drug use from 1970 - 1986. *Arch Int Med* 199:1524, 1989.
24. Holmberg S, Bergman H. Prophylactic quinidine treatment in myocardial infarction: a double blind study. *Acta Med Scand* 181:297-304, 1967.
25. Hondeghem L, Katkung BG. Antiarrhythmic agents: the modulated receptor mechanism of action of sodium and calcium channel-blocking drugs. *Ann Rev Pharmacol Toxicol* 24:387-423, 1984.
26. IMPACT Research Group. International mexilitine and placebo anti-arrhythmic coronary trial. 1. Report on arrhythmias and other findings. *J Am Coll Cardiol* 4:1148, 1984.
27. ISIS - 1 Collaborative Group. Randomized trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction. *Lancet* ii:57, 1986.
28. Janse MJ, van Capelle, FJL, Morosink H, Kleber, AG, Wilms-Schopman,F, et al. Flow of "injury" current and patterns of excitation during early ventricular arrhythmias in acute regional myocardial ischemia in isolated porcine and canine hearts. Evidence for two different arrhythomogenic mechanisms. *Circ Res* 47:151-65,1980.
29. Janse MJ, Cinca J, Morena H, Fiolet JWT, Kleber AG, et al. The "border zone" in myocardial ischemia. An electrophysiologic, metabolic, and histochemical correlation in the pig heart. *Circ Res* 44:576-88.
30. Jennings G, Model DG, Jones MBS, Turner PP, Besterman EMM, Kidner PH. Oral disopyramide in prophylaxis of arrhythmias following myocardial infarction. *Lancet* 1:51-54, 1976.
31. Jones DT, Kostuk WJ, Gunton RW. Prophylactic quinidine for the prevention of arrhythmias after acute myocardial infarction. *Am J Cardiol* 33:655-660, 1974.
32. Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction. *N Eng J Med* 311:1144, 1984.
33. Karagueuzian HS, Fenoglio JJ, Weiss MB, Wit AL, Coronary occlusion and reperfusion: Effects on subendocardial cardiac fibers. *Am J Physiol* 238:H581-93,1980.
34. Kempf FC, Josephson ME, Cardiac arrest recorded on electrocardiograms. *Am J Cardiol* 53:1577-1582, 1984.
35. Kennedy HL et al. Long-term follow-up of asymptomatic healthy subjects with frequent and complex ventricular ectopy. *New Engl J Med* 312:193, 1985.

36. Koch-Weser J, Klein SW, Foo-Canto LL, Kastor, JA, DeSanctis RW. Antiarrhythmic prophylaxis with procainamide in acute myocardial infarction. *N Engl J Med* 281:1253-1260, 1969.
37. Kou, WH et al. Effects of flecainide acetate on production of electrical induction of ventricular tachycardia and occurrence of ischemic ventricular fibrillation during the early post-myocardial infarction period: evaluation in conscious canine model of sudden death. *J Am Coll Cardiol* 9:359,1987.
38. Lazzara R, Hope RR, El-Sherif N, Scherlag BJ, Effects of lidocaine on hypoxic and ischemic cardiac cells. *Am J Cardiol.* 41:872-78, 1969.
39. Lazzara R, El-Sherif N, Scherlag BJ. Disorders of cellular electrophysiology produced by ischemia of the canine His bundle. *Circ Res* 42:577-87, 1975.
40. Lie KI, Wellers HJJ, Downar F, Darrer D, Observations on patients with primary ventricular fibrillation complicating acute myocardial infarction. *Circulation* 52:755-9, 1975.
41. Lown B. Sudden cardiac death: The major challenge confronting contemporary cardiology. *Am J Cardiol* 43:313, 1979.
42. Moss AJ et al. Ventricular ectopic beats and their relation to sudden and nonsudden cardiac death after myocardial infarction. *Circulation* 60:998. 1979.
43. Mukharji, et al. Risk factors for sudden death following acute myocardial infarction. *Am J Cardiol* 54:31-36, 1984.
44. Nademanee K et al. Prognostic significance of silent myocardial ischemia in patients with unstable angina. *J Am Coll Cardiol* 10:1, 1987.
45. Nguyen-Thi A, Ruiz-Ceretti E, Schanne OF. Electrophysiologic effects and electrolyte changes in total myocardial ischemia. *Can J Physiol Pharmacol* 59:876-83,1980.
46. Nicholls DP, Haybyrne T, Barnes PC. Intravenous and oral disopyramide after myocardial infarction. *Lancet* 2:936-938, 1980.
47. Norris RM et al. A double-blind trial of metoprolol in acute myocardial infarction by intravenous propranolol. *Lancet* ii:883, 1984.
48. Norwegian Multicenter Study Group: Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *New Eng J Med* 304:801, 1981.
49. Panidis IP, Morgenroth, J. Analysis of ambulatory electrocardiograms in 15 patients during spontaneous ventricular fibrillation with special reference to preceding arrhythmic events. *J Am Coll Cardiol* 2:798, 1983.
50. Patterson E et al. Ventricular fibrillation in a conscious canine model of sudden coronary death: Prevention by acute and chronic amiodarone administration. *Circulation* 68:857, 1983.
51. Pratt CM (ed). A symposium: The Cardiac Arrhythmia Suppression Trial - Does it alter our concepts of and approaches to ventricular arrhythmias? *Am J Cardiol* 65:1B, 1990.
52. Rappaport E, Remedios P. The high risk patient after recovery from myocardial infarction: recognition and management. *J Am Coll Cardiol* 1:391, 1983.
53. Ruberman W et al. Ventricular premature beats and mortality after myocardial infarction. *New Engl J Med* 297:750, 1977.
54. Ruberman W et al. Ventricular premature complexes and sudden death after myocardial infarction *Circulation* 64:297,1981.
55. Ryden L et al. A double-blind trial of metoprolol in acute myocardial infarction: effects on ventricular tachyarrhythmias. *N Eng J Med* 308:614, 1983.

56. Ryden L, Amman K, Conradson TB, Hofvendahl S, Mortensen O, Smedgard P. Prophylaxis of ventricular tacharrhythmias with intravenous and oral tacainide in patients with and recovering from acute myocardial infarction. *Am Heart J* 100:1006-1012,1980.
57. Singh BN, Vaughan Williams EM. Effect of altering potassium concentration on the action of lidocaine and diphenylhydantoin on rabbit atrial and ventricular muscle. *Circ Res* 29:286, 1971.
58. Singh BN, Nademanee K. Control of arrhythmias by selective lengthening of cardiac repolarization: Theoretical consideration and clinical observations. *Am Heart J* 109:421, 1985.
59. Singh BN, Editorial: When is QT prolongation anti-arrhythmic and when is it pro-arrhythmic? *Am J Cardiol* 63:867, 1989.
60. Vaughan William EM. A classification of antiarrhythmic actions reassessed after a decade of new drugs. *J Clin Pharmacol* 24: 129-147,1984.
61. Velebit, et al. Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. *Circulation* 65: 886, 1982.
62. Vlay SC. How the university cardiologists treats ventricular premature beats: A nationwide survey of 65 university medical centers. *Am Heart J* 110:904, 1985.
63. Wilcox RG, Rowley JM, Hampton JR, Mitchell JRA, Roland JM, Banks DC. Randomized placebo-controlled trial comparing oxprenolol with disopyramide phosphate in immediate treatment of suspected myocardial infarction. *Lancet* 2:764-769,1980.
64. Wit AL, Friedman PL. Basis for ventricular arrhythmias accompanying myocardial infarction. Alterations in electrical activity of ventricular muscle and Purkinje fibers after coronary artery occlusion. *Arch Int Med* 135:459-72,1975.
65. Weiss J, Shine KI. Extracellular potassium accumulation during myocardial ischemia: Implications for arrhythmogenesis. *J Mol Cell Cardiol* 113:699-704,1980.
66. Yusuf S et al. Beta-blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* 27:235, 1985.
67. Zipes, et al. Guidelines for clinical intracardiac EPS. *Am J Coll Cardiol* 14:1827, 1989.

The PVC Hypothesis in Practice

A 61 year old man was referred for evaluation of ventricular ectopy. He had a 20 pack-year history of smoking which he discontinued 10 years ago, a history of hypertension which was not being treated, a positive family history for coronary disease, and no other risk factors.

Six months ago he developed chest pain with extreme exertion, and 5 weeks ago he developed prolonged chest pain which lasted 2 hours. He sought medical attention 7 hours after the onset of pain. His ECG was consistent with an acute anteroseptal MI. CK increased to 1000 with 10% MB fraction, thrombolytic therapy was not used, and he did well without evidence of heart failure or complaints of chest pain.

Late in his hospitalization a submaximal ETT was negative. An echocardiogram showed anteroapical akinesis, and the left ventricular ejection fraction measured by MUGA was 41%. The PR interval and QRS duration were normal. He was discharged after 10 days in the hospital on ASA and a ß-adrenergic blocker. A 24 hour ECG obtained 2 weeks later showed 10 PVCs/hour, 2 couplets, a 4-beat run of VT and a 10 beat run of VT, both at 120 beats/min. He complained only of palpitations which he has had for many years.

Should he be treated with additional drugs?