VENTRICULAR ECTOPIC ACTIVITY IN THE AMBULANT PATIENT: ITS PREVALENCE, ASSESSMENT AND MANAGEMENT

J.V. Nixon, M.D.

Thursday, 5 July 1984

Medical Grand Rounds
Souwestern Medical School
University of Texas Health Science Center
Dallas, Texas

"EVER SINCE DYING CAME INTO FASHION,
LIFE HAS NOT BEEN SAFE."

Old Yiddish Proverb (1)

CONTENTS

INTRODUCTION

Of the one million individuals who died of cardiovascular disease last year in the United States, 35 per cent may be described as experiencing sudden cardiac death. Because it is well accepted that the documentation of ventricular arrhythmias is statistically associated with subsequent sudden death, it is widely hypothesized that the suppression of such asymptomatic arrhythmias with drugs can prevent these deaths (2). Furthermore, for several reasons, the numbers of patients with ventricular arrhythmias seen by cardiologists is increasing. These reasons include (a) more readily-available and more sophisticated monitoring equipment, (b) more survivors of myocardial infarction due to coronary care units, (c) more survivors of out-of-hospital cardiac arrest due to proficient ambulance survices and community training programmes, and (d) increased physician awareness of ventricular ectopic activity and of antiarrhythmic therapy.

More recent examination of the issues has uncovered several interesting and confounding findings. It has been suggested that not all ventricular ectopic activity is a harbinger of subsequent sudden death, and therefore does not require therapy. There has been great difficulty in finding a universally acceptable system of classification for management purposes. Recent reports have shown that, should therapy be commenced, the currently available techniques for assessing drug efficacy are not ideal. Thus, the management of ventricular ectopic activity remains an issue that continues to be vigorously debated in the cardiology community.

It is my intention in this review to summarize what is currently known, what criticisms have been raised regarding diagnosis and management, and to suggest a scheme of which patients should be considered for antiarrhythmic therapy

CHARACTERISTICS OF VENTRICULAR ECTOPIC ACTIVITY

Table 1 lists the clinical, physiological and pathological circumstances associated with ventricular ectopic activity (VEA)(3). VEA is common at any age, even in younger subjects free of cardiac disease (4-14), and its prevalence increases with age (15-17). It is well accepted that the prevalence of VEA is higher in patients with cardiac disease, particularly coronary artery disease (36-54). VEA may be precipitated by exercise (60-63). Finally, while VEA always appears similar in any given electrocardiographic recording, its etiology and significance may both differ, factors that confound the issue of management (3). The classical example of this latter characteristic is the documentation of asymptomatic ventricular tachycardia in differing clinical circumstances such as predischarge studies after myocardiac infarction or routine studies in an ambulatory setting (43, 48,57). Further details of these characteristics are given below.

Table 1. Characteristics of ventricular ectopic activity

They are common
- increase with age
- increase with ventricular scarring
- infarction
- hypertrophy
- infection

do not increase with coronary arteriosclerosis per se

can be precipitated/aggravated by exercise
- ischemia
- increased sympathetic activity
- increased heart rate

Electrocardiographically similar arrhythmias may have different causes and significance

From Bigger (reference 3).

PREVALENCE OF VENTRICULAR ECTOPIC ACTIVITY

Normal population

Table 2 lists the studies reporting the prevalence of ventricular ectopic activity in an apparently normal and healthy population. It is important to note that the study subjects in the majority of these reports are described as apparently normal because little beyond a physical examination, chest x-ray and routine electrocardiogram was performed to rule out cardiac disease. The exception to this is the report by Flegg et all (17) who included a thallium-201 perfusion study at rest and during exercise in their elderly subjects.

As can be seen from the table, irrespective of the duration of the period of monitoring, VEA is relatively common. Nevertheless, the more frequent and complex forms of VEA remain very infrequent. Since Clarke et al (7) noted in 1976 that the prevalence of VEA appears to increase with age, several studies have demonstrated that to be so (15-17). The studies of Glasser et al (15), Camm et al (16), and Flegg and Kennedy (18) are confined to subjects over the age of 60 years, and show a prevalence of any VEA ranging from 69 to 100 per cent, with a prevalence of frequent and/or repetitive VEA ranging from 9 to 20 per cent. These data may be contrasted with studies confined to subjects under the age of 35 years 9,12 - 14). In these latter reports, the prevalence of any VEA ranges from 10 to 54 per cent and the prevalence of frequent and/or repetitive VEA from 0 to 4 per cent.

The only study reporting the coronary arterty anatomy of similarly selected apparently healthy normal individuals with VEA was by kennedy et all (18). From an original cohert of 62 subjects aged 21 to 65 years, 25 underwent cardiac catherization. Fourteen subjects had normal coronary arteries, 5 had nonsignificant and 6 had significant (> 50 per cent luminal narrowing) coronary artery disease. Because all the subjects were selected for study due to their VEA, the investigators were obviously able to conclude that in this subset of individuals, VEA is not consistantly associated with cardiac disease. They also reported that the characteristics of the VEA such as frequency and complexity did not distinguish either the presence or the severity of coronary artery disease. This latter conclusion is in contrast to other reported findings in patients with known coronary artery disease as will be seen below.

TABLE 2. PREVALENCE OF VENTRICULAR ECTOPIC ACTIVITY IN A POPULATION DESCRIBED AS CLASSICALLY NORMAL

	Year	N	Age Range (yrs)	Duration of monitoring (hrs)	any VEA (%)	Frequent VEA (%)*	Repetitive VEA (%)*
Hinkle et al (4)	1969	301	54-60	6	62	9	13
Rodstein et al (5)	1971	712	17-65	Routine ECG	68	-	-
Raffery and Cashman (6)	1976	53	20-70	24	28	4	0
Clarke et al (7)	1976	86	16-25	48	73	10	2
Kennedy and Underhill(8)	1976	25	37-69	24	100	(70)	(57)
Brodsky (9)	1977	50	23-27	24	50	0	4
Verbaan et al (10)	1977	74	20-80	24	76	9	1
Goulding (11)	1977	100	25-74	24	16	0	0
Scott et al (12)	1980	131	10-13	48	26	0	0
Rabkin et al (13)	1981	3983	25-34	Routine ECG	10	-	-
Sobotka et al (14)	1981	50	22-28	24	54	2	2
Glasser et al (15)	1979	15	60-84	24	100	13	20
Camm et al (16)	1980	106	75-96	24	69	14	9
Flegg and Kennedy (17)	1982	98	60-85	24	80	17	15

*Frequent VEA is > 10 VPBs/hours; repetitive VEA is more than 2 VPBs consecutively.

There are certain environmental factors that are thought to be associated with the development of VEA. Such factors include smoking, caffeine, antomobile driving and public speaking. Sparse anecdotal reports in the literature fail to support these clinical dicta Clarke et at (7) in this study of normal subjects noted no difference in prevalence of VEA between nonsmokers and smokers. DeBacker and colleagues (19) attempted to control life style by dividing 81 apparently healthy men with persistent VEA into three groups. The first or control group were instructed to continue their current life style. The second group were told to abstain from caffeine and cigarettes, and reduce their alcohol intake to less than 4 drinks per week. The third group were identical to the second in abstinence, with the addition of a supervised physical conditioning programme. The investigators reported no significant alterations in the frequency of VEA.

Automobile driving appears to result in an increased occurrence of VEA in subjects with coronary artery disease. In 65 normal healthy subjects, Bellet et al (20) showed no VEA while driving, in contrast to several instances of both frequent and complex VEA in 66 patients with coronary artery disease. In England, Taggert and associates (21) reported similar findings.

Observations on public speakers are less consistent. Taggart et al (22) reported an incidence of VEA in both normal individuals and coronary artery disease patients. Moss and Wynar (23) monitored 10 house officers presenting Grand Rounds and found no VEA, although heart rates increased to 187 beats per minute in two persons. In a study of football and basketball coaches during games, the occasional occurrence of VEA could not be related to particular incidents such as scores, dropped passes, interceptions, missed lay-ups, and so on (24). A small study of the cardiac response to a sauna bath has shown an increased prevalence of VEA in both normal subjects and patients with coronary disease (25).

Lown and his colleagues have drawn attention to the fact that VEA may subside during sleep (26). These observations have been confirmed by other investigators studing apparently healthy individuals (27, 28). Conversely, Savage et al (33) has reported that sleep has no effect on the prevalence of VEA in patients with ideopathic hypertrophic subaortic stenosis (IHSS) (29). Both Lown (30) and Winkle (31) suggest that the reduction in resting heart rate and circulating catecholamines are responsible for the suppresson of VEA.

Several diagnostic procedures are thought to provoke VEA. Troup and colleagues (32) observed no increase in VEA after electroconvulsive therapy. Two studies of patients undergoing gastroscopy report development of VEA in 20 per cent and 4 per cent of patients respectively (33, 34). Roeske et al (35) have reported a significant incidence of VEA in patients over 60 years undergoing barium enema examination.

In summary, it is evident that VEA is a normal finding and its prevalence increases with advancing age. While it is difficult to individualize, it is also clear that a number of daily stresses and certain stressful medical diagnostic circumstances may provoke the occurrence of VEA, particularly in older individuals and those with coronary artery disease.

Cardiac Disease.

Coronary Artery Disease.

Table 3 lists the studies of patients who underwent electrocardiographic monitoring following documentation of an acute myocardial infarction, with follow-up of these individuals for a period of 6 months to 5 years (36-54). The end-point in most of these reports was sudden cardiac death. The importance of these studies is that they have been consistently utilized to project the prevalence of VEA in the overall adult patient population and to justify the widespread use of antiarrhythmic therapy.

The studies in Table 3 have been selected because their conclusions are based on pre-discharge evaluations of patients with a myocardial infarction. Information regarding the prevalence and management of VEA in the pre-hospital and coronary care unit phase of myocardial infaction may be found elsewhere (55).

Several interesting points emerge from these 19 studies. The age range of the patients was from 24 to 90 years, although most studies were carried out for patients under 75 years. The period or follow up ranged from 6 months to 5 years. The frequency of any VEA rang from 12 to 88 per cent, with the occurrence of frequent and/or complex VEA ranging from 1 to 45 per cent. While the numbers reflecting the documentation of any VEA are comparable to those in apparently normal subjects (range 10 to 100 per cent) shown in Table 2, the per cent range for incidence of frequent and/or complex VEA is substantially higher than in normals (range 0 to 20 per cent).

TABLE 3. PREVALENCE OF VENTRICULAR ECTOPIC ACTIVITY IN PATIENTS WITH CORONARY ARTERY DISEASE

	YEAR	N	AGE RANGE (YRS	DURATION OF MONITORING (HRS)	ANY VEA (%)	FREQUENT VEA (%)	REPETITIVE VEA (%)	PRIOR MI	DURATION OF FOLLOW UP (YRS)	INCREASED RISK OF SD
Coronary Drug Project (36)	1973	2035	30-65	Routine ECG	12	.	1	Yes	3	Yes
Kotler et al (37)	1973	160	30-64	12	80	.	.	Yes	4	Yes
Vismara et al (38)	1975	64	39-85	10	77	.	.	Yes	2	Yes
Luria et al (39)	1976	143	60	8	.	.	.	Yes	2	No
Moss et al (40)	1977	272	65	6	50	14	4	Yes	1	Yes
Schulze et al (41)	1977	81	56	24	65	.	17	Yes	1	Yes
Ruberman et al (42)	1977	1739	35-74	1	52	.	.	Yes	4	Yes
Anderson et al (43)	1978	915	<66	6	.	.	7	Yes	2	No
Bigger et al (44)	1978	100	25-90	24	88	.	13	Yes	0.5	Yes
DeSoyzaet al (45)	1978	56	24-73	24	71	29	31	Yes	1.5	No
Moss et al (46)	1979	940	<66	6	50	.	.	Yes	5	Yes
DeBusk et al (47)	1980	90	<70	24	79	.	12	Yes	1	-
Moller et al (48)	1980	100	<70	24	.	.	19	Yes	0.5	No
Taylor et al (49)	1980	106	27-66	24	.	.	45	Yes	2.5	Yes
Ruberman et al (50)	1980	1739	35-74	1	.	.	.	Yes	5	Yes
Bigger et al (51)	1981	430	.	24	.	.	12	Yes	3	Yes
Rapaport et al (52)	1983	139	.	24	.	.	.	Yes	3	Yes
MPMIRG (53)	1983	886	<70	24	86	20	.	Yes	1	Yes
Mukharji et al (54)	1984	553	60	24	.	15	.	Yes	2	Yes

Although the Coronary Drug Project (36) and the study by Luria and associates (39) both showed an association between cardiac death and any VEA on predischarge ambulatory monitoring, the majority of subsequent studies have shown an increased incidence of subsequent sudden death in those patients with documented frequent and/or complex VEA (37, 38, 40 - 42, 43, 44, 46, 49 - 54). For many years, complex VEA was the descriptive term for Lown Class III through V of VEA which included multifocal ventricular premature beats (VPBs), pairs or more consecutive VPBs (ventricular tachycardia) and the R-on-T phenomenon (56). As will be discussed below, this classification of VEA has provoked considerable debate and a revised classification is now recommended.

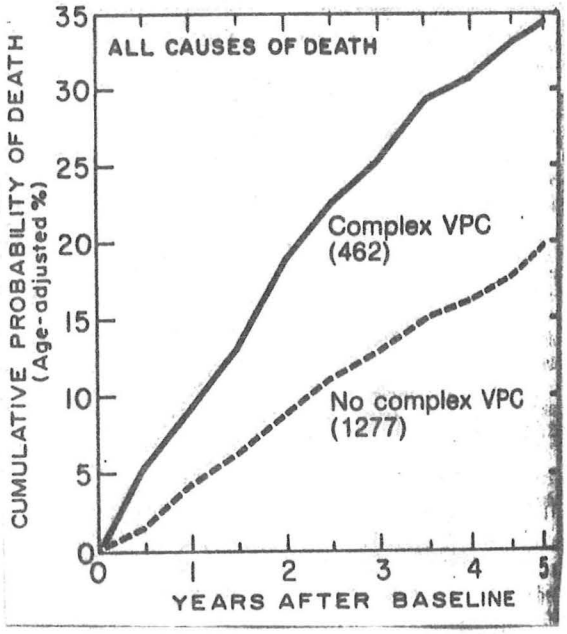

Figure 1. Mortality over 5 years in male survivors of myocardial infarction in relation to prevalence of complex VEA (ref. 50).

Figure 1 is taken from the work of Ruberman et al in their study of 1739 men with a previous myocardial infarction (42,50). All underwent ambulatory monitoring predischarge for one hour only and were followed for up to 5 years. The association between complex VEA and sudden death is clearly seen. Bigger et al (51), who compared the occurrence of ventricular tachycardia on predischarge recordings with subsequent survival over 3 years, showed a significant association compared to a group of patients without documented ventricular tachycardia.

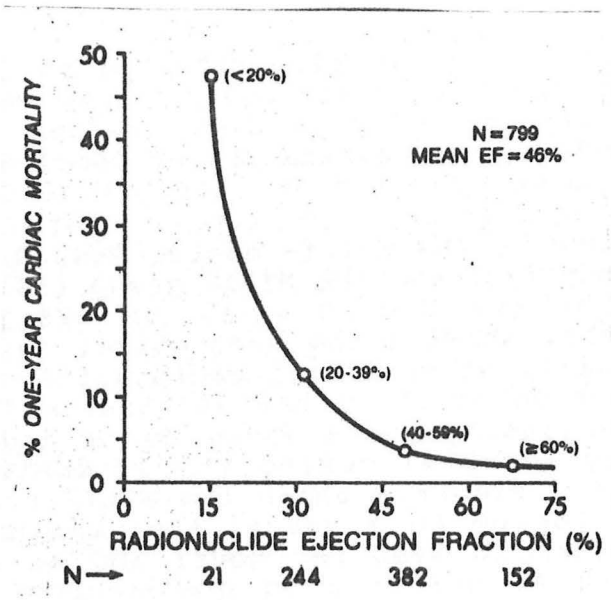

Figure 2. Cardiac mortality in four categories of radionuclide ejection fraction. Determined predischarge (ref 53).

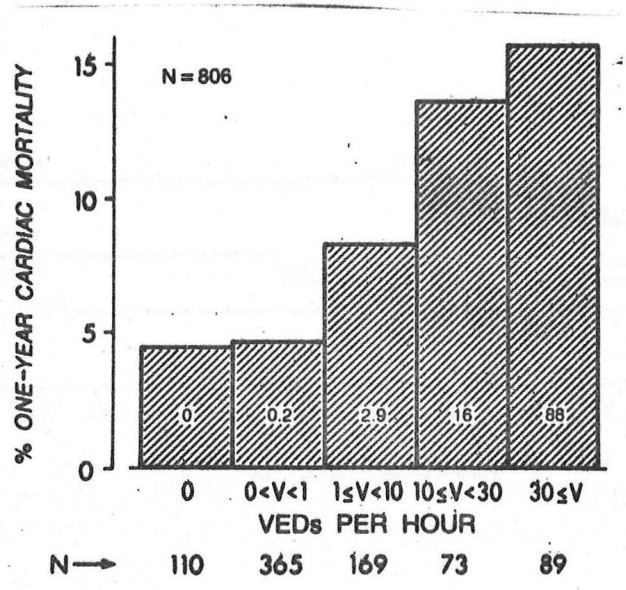

Figure 3. Cardiac Mortality rate in five categories for frequency of VEA (ventricular ectopic depolarizations, VEDs) determinined predischarge (Ref. 53).

Schulze and his colleagues (41) reported in 1977 that while complex VEA recorded predischarge in post myocardial infarction patients statistically predicts sudden death in the subsequent 12 months, the combination of complex VEA and a radionuclide assessment of ejection fraction of less than 40% per cent is an even stronge predictor. This work has recently been confirmed by the Multi- center Post Myocardial Infarction Study Group (53) and the MILIS group (54) Figures 2 & 3 are taken from the MPMISG study of 886 patients followed for 12 months, showing the statistical association with increasing mortality of declining radionuclide assessed left ventricular ejection fraction and increasing frequency of VEA. Both these findings were shown to be independent variables predicting survival during the 12 months after myocardial infarction. Figure 4 shows the MILIS roup data. From data collected for up to 2 years, the combination of frequent VEA (more than 10 VPBs per hour) and an ejection fraction of less than 40 per cent on predischarge studies showed an incidence of sudden death of 18 per cent during the period of follow-up.

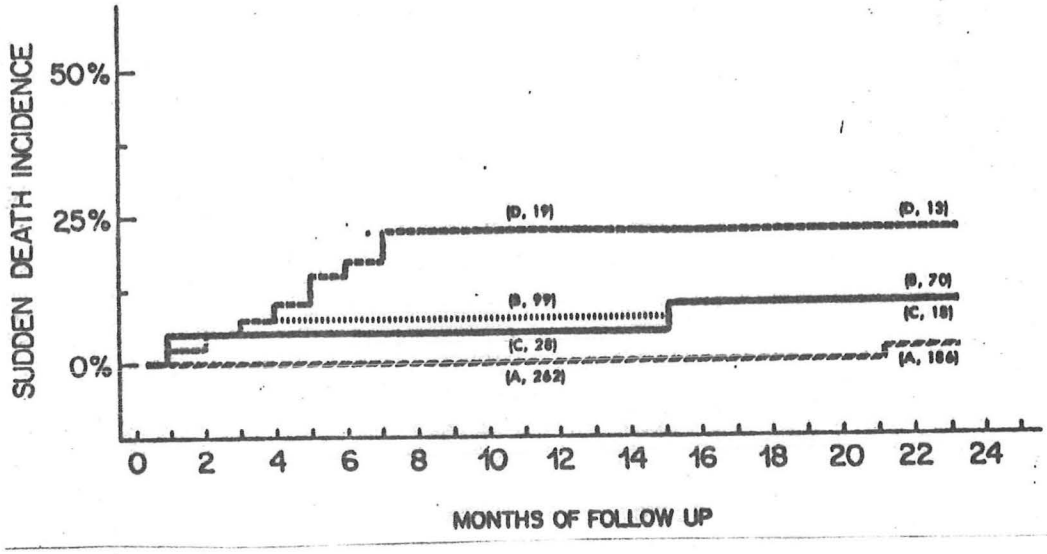

Figure 4. Incidence of sudden death in four risk groups: A, EF>40%, VEA<10 1 hour; B, EF<40%, VEA<10/hours; C, EF>40%, VEA>10/hour; D, EF<40%, VEA>10/hour (ref. 54)

Of the four studies that failed to demonstrate an association between VEA and an increased risk of cardiac death, two were confined to an analysis of the documentation of ventricular tachycardia on serial ambulatory recording following discharge from hospital after myocardial infarction (43, 48). While Anderson et al (43) showed a higher survival rate in patients without ventricular tachycardia, the difference was not statistically significant. Moller and colleagues (48) showed no association whatsoever. Winkle et al (57) have reported the documentation of ventricular tachycardia by ambulatory monitoring in 23 patients with stable cardiac disease. Because only 1 resulted in ventricular fibrillation and 83 per cent were asymptomatic, they suggested that this rhythm may not be as malignant as is generally assumed. These findings are in contrast to the reports of Bigger and his colleagues (44, 51) who showed a clear statistical association between ventricular tachycardia recorded predischarge post myocardial infarction an increased risk of both sudden and cardiac death in the subsequent 3 years (Figure 5). Apart from the fact that Bigger's studies contain more patients who are followed for a longer period of time, it is difficult to explain the disparity of these reports. Clearly more investigation is necessary regarding the significance of ventricular tachycardia detected by ambulatory monitoring.

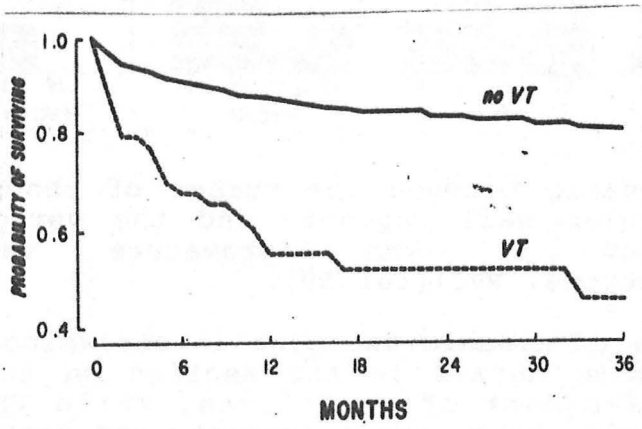

Figure 5. Survival curves of patients with (VT) and without (no VT) ventricular tachycardia over a follow up duration of 3 years (ref. 51)

In 1977, Calvert and associates (58) reported a general concept that the more complex grades of VEA are associated with more severe degrees of both coronary artery disease and segmental left ventricular dysfunction in patients undergoing cardiac catheterization for evaluation of ischemic heart disease. These observations were promptly confirmed by Califf et al (59). Figure 6 shows the association between frequency of VEA and degree of left ventricular dysfunction. In Taylor and associates study from Baltimore (49), there was a significant increase in triple vessel disease and proximal left arteries descending coronary artery disease in patients with complex VEA.

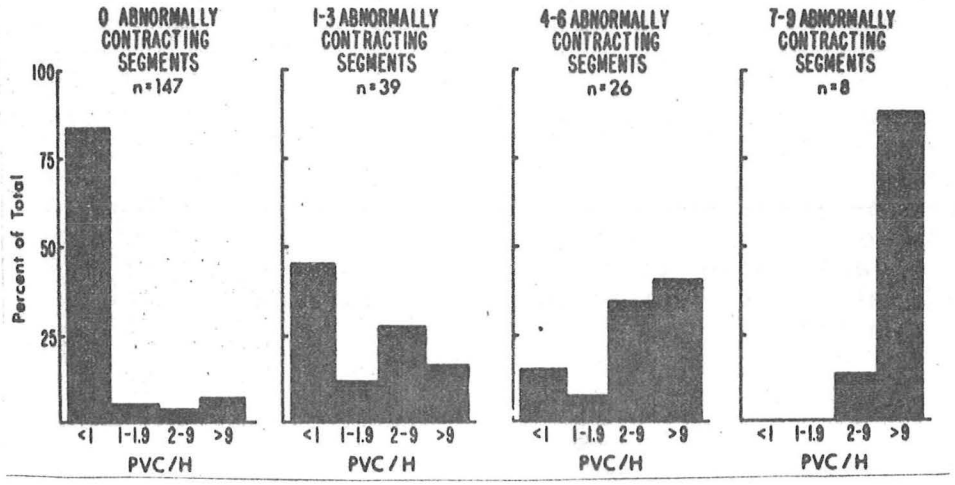

Figure 6. Relationship between the number of abnormal left ventricular wall segments and the verage hourly frequency of VEA (premature ventricular contractions, PVC)(ref 59).

The value of dynamic exercise in assessing VEA will be discussed in more detail in the section on techniques. Regarding the assessment of prevalence, while VEA may be induced by exercise in both normal subjects and patients with coronary artery disease, ambulatory monitoring is a far more sensitive monitor (60 - 63).

In summary, the prevalences of both VEA per se and the complex forms of VEA are increased in the presence of coronary artery disease. Furthermore, the frequency with which VEA occurs appears to correlate with the distribution of the coronary pathoanatomy and the degree of left ventricular dysfunction. The recording of frequent or complex VEA on predischarge ambulatory monitoring after a myocardial infarction appears to carry an increased risk of sudden death during the following 6 to 12 months at least.

Cardiomyopathy

The frequency of VEA and the high incidence of sudden death in IHSS are both well documented, and as might be anticipated, they have been causally related. In a preliminary report in 1975, Ingham et al observed VEA in 24 of 27 patients (89) per cent) including ventricular tachycardia in 2 patients, all of which correlated poorly with symptoms (64). In a comprehensive study from the NIH, Savage and associates (29) reported that 83 of 100 patients had some VEA. Twenty three patients had frequent VEA (more than 10 VPBs per hour) and 27 had repetitive VEA (two or more VPBs consecutively), of whom 19 had ventricular tachycardia. They observed that more than 50 per cent of VEA was asymptomatic and both sleep and beta-blockers had little effect on its occurrence. Because of limited follow up information, they were unable to confirm the suspicion that the detection of VEA on IHSS may be of prognostic value. similar findings have subsequently been reported by McKenna and colleagues (65)(Figure 7). In a subsequent report of follow up data on 254 patients with IHSS, 32 of whom died suddenly, McKenna et al (66) suggest that the cause of death in these patients is a ventricular arrhythmia. Using programmed electrical stimulation prior to surgery for the obstructive form of IHSS, Anderson et al (67) have demonstrated the marked vulnerability of these patients to ventricular arrhythmia induction.

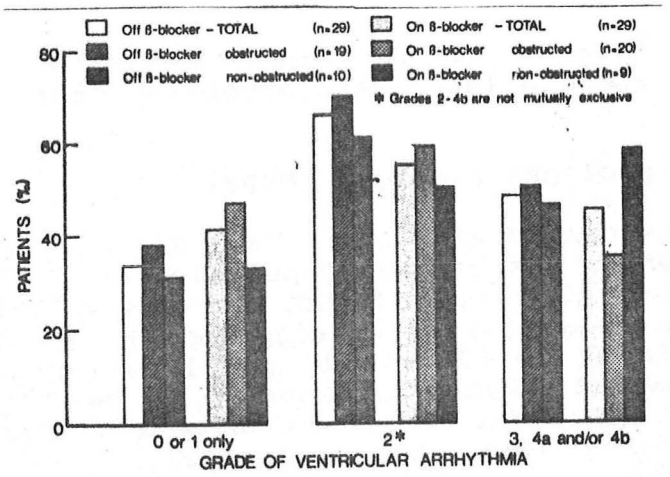

Figure 7. Prevalence of grades of VEA in patients with obstructive and nonobstructive hypertrophic cardiomyopathy, both on and off beta-blocking agents (Ref 65)

Congestive or dilated cardiomyopathy is associated with a high prevalence of VEA (55). Recently, Huang et al (68) have reported that in a series of 35 patients, 81 per cent had frequent VEA and 60 per cent had asymptomatic, nonsustained ventricular tachycardia (Figure 8). Because of small numbers and no follow up, the authors were unable to conclude as to whether documented ventricular tachycardia was of prognostic importance.

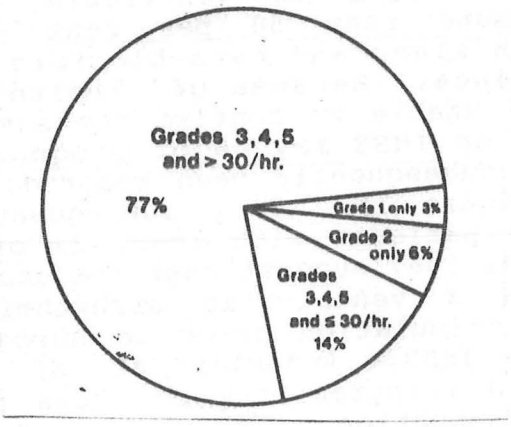

Figure 8. Prevalence of VEA by Lown's classification in patients with ideopathic dilated cardiomyopathy (ref. 68).

Mitral valve prolapse syndrome (MVPS)

VEA is associated with the MVPS. With a prevalence of some form of MVPS in the general population of 6 to 21 per cent (69,70), the occurrence of VEA becomes of clinical importance. Winkle et al (71) have reported VEA in 18 of 24 patients and Demaria et al (72) in 18 of 31 patients. Both studies also reported high incidences (50 per cent) of frequent or complex VEA. Wei et al (73) have also reported a significant incidence of drug-refractory ventricular tachycardia with MVPS.

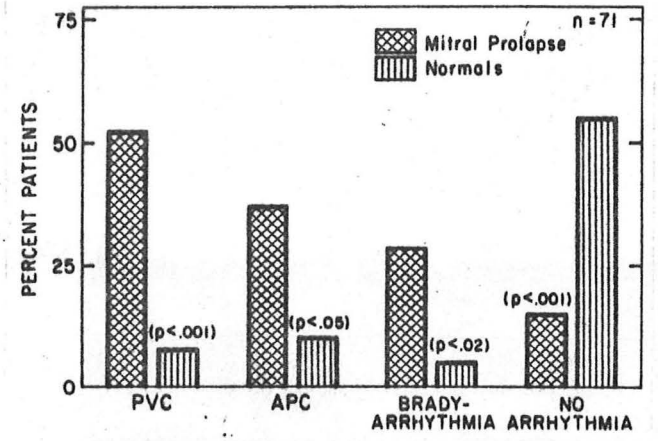

Figure 9. Prevalence of cardiac arrhythmias in patients with mitral valve prolapse and in normal subjects. (PVC, premature ventricular contractions; APC, atrial premature contractions). (Ref 72).

There are numerous anecdotes in the literature of sudden death in patients with MVPS(74) however, considering the frequency with which the syndrome occurs, the incidence of sudden death is quite rare. Furthermore, any association between VEA and sudden death in the MVPS remains uncertain and may be coincidental.

Chronic Obstructive Pulmonary Disease (COPD)

Patients with COPD are known to have a variety of cardiac arrhythmias including VEA. In one survey by Kleiger and Senior (75), VEA occurred in 18 of 25 patients, including 3 with ventricular tachycardia. While the precise etiology of the VEA in such patients is uncertain, confounding factors include hypoxemia, acidosis, pulmonary hypertension, cor/pulmonale and a variety of medications known to be cardiac stimulants (31).

The Long Q-T Syndrome

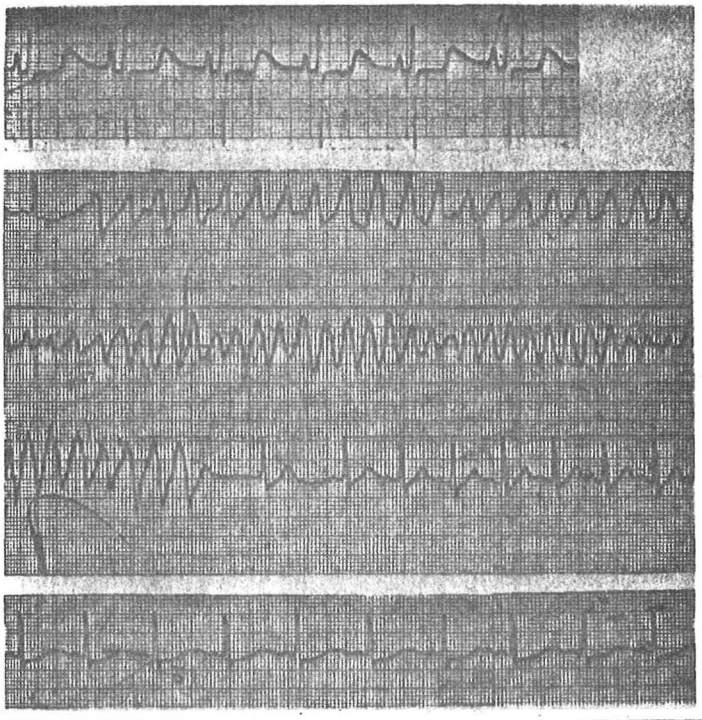

Figure 10. The long Q-T intervalis shown in the upper ECG preceding les torsade-de-pointes seen below (ref 92).

Prolongation of the electrocardiographic Q-T interval may be associated with ventricular arrhythmias and sudden death, particularly when associated with torsade-de-pointes (76, 77). Details of les torsade-de-pointes were discussed by Dr. Rude in his Grand Rounds on ventricular tachycardia (78).

The congenital form of the long Q-T syndome may occur with (79) or without deafness (80,81). The acquired form of the syndrome may be caused by a variety of disorders listed in Table 4. An example of a long Q-T syndrome and its subsequent ventricular arrhythmia are shown in Figure 10 (92). Because of the circumstantial association between VEA and the long Q-T syndrome, and between sudden death and les torsade-de-pointes, patients with the long Q-T syndrome should be considered at high risk for sudden death, and thus managed appropriately.

Table 4. Causes of the Long Q-T Syndrome

Primary

- Jervell and Lange-Neilson syndrome (79)
- Romano-Ward syndrome (80,81)

Secondary

- Autonomic Dysfunction (82)
- Coronary artery Disease (83)
  - Acute myocardial infarction
  - Myocarditis
- Cardiac ganglionitis (84)
- Mitral valve prolapse syndrome (85)
- Central nervous system disorders (86)
- Liquid protein diet (87)
- Electrolyte disturbances (88)
- Drugs - Quinidines (89)
  - Disopyramide (90)
  - Phenothiazines (91)
  - Tricyclic antidepressants

Drug-induced VEA

The issue of drug-induced or iatrogenic VEA is an important one because it affects initiation of therapy, selection and continuation of drug and unfortunately when not considered, the prognosis of the patient.

Table 5. Categories of Drug Initiating or Exacerbating VEA

Cardiac glycosides
Type I and II Antiarrhythmic of Drugs
Psychotropic agents
Anththracyclines
Bronchodilators
Potassium-losing Diuretics

The incidence of ventricular arrhythmias associated with cardiac glycosides varies between 8 and 35 per cent, with an associated mortality rate of 3 to 12 per cent (93). In a report of 114 patients who presented with digitalis intoxication, Shapiro (94) observed VEA in 70 per cent. He also observed that while serum glycoside levels tend to be higher in patients with electrocardiographic evidence of toxicity, they are not uniformly so. Furthermore, the concept of drug interaction is important with cardiac glycosides (95). Serum digoxin levels, for example, increase approximately twofold when quinidine is concurrently administered.

The Type I antiarrhythmic drugs are all known to produce VEA at toxic levels. At therapeutic dose levels, they have also been shown to produce life-threatening ventricular arrhythmias. The association between the long Q-T syndrome with its potential for the development of les torsade-de-pointes and drugs such as quinidine and disopyramide has already been discussed (89,90). Between 30 and 60 per cent of patients who are resuscitated after out-of-hospital cardiac arrest are found to be taking antiarrhythmic drugs (38,96). Recently, in 6 patients resuscitated after out-of-hospital cardiac arrest, Ruskin et al (97) have shown electrophysiologically provokable ventricular arrhythmias present on therapy and absent when the antiarrhythmic regimen was withdrawn.

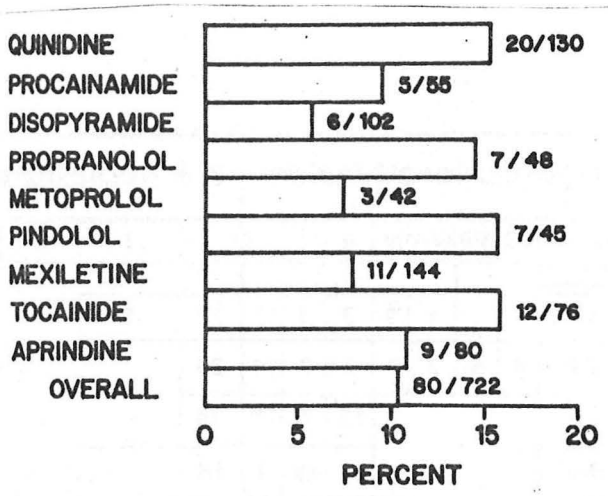

Figure 11. Frequency of aggravation of VEA by nine antiarrhythmic agents (ref. 98)

Figure 11 is taken from the paper by velebit and colleagues (97) showing that Type II antiarhythmic drugs, the beta-blockers, may also cause aggrevation of VEA at therapeutic levels of the drug.

The association between psychotropic agents and the long Q-T syndrome has already been discussed (91). Fowler and associates (99) have documented that complex VEA may occur with both phenothiazines and tricylic antidepressants at therapeutic levels of the drug and in the absence of cardiac disease.

The association of VEA with anthracycline therapy, and in particular adriamycin therapy, may be due in the initial stages of therapy to hypersensitive irritability, or in the later stages of therapy to the development of a cardiomyopathy (100).

Several classifications of bronchodilator drugs are well known to have cardiac stimulating properties, including the classic adrenergic agents, the xanthine deviative and the newer beta-2 agonists. However, Banner et al (100) have shown that these properties may not be of clinical relevance. When comparing the arrhythmogenic effects of orally administered ephedrine, aminophylline and terbutylline, only terbutylline produced a sinificant increase in VEA. In studies of the effects of intraveneous aminophlline in patients undergoing cardiac catheterization, Croft (102) has recorded similar fundings.

	Baseline		Hydrochlorothiazide								K+ Repletion		
VEA	O	I	PLASMA K+	BG	IVB	IVA	III	II	I	O	I	II	
Pt. #1	24*		3.0			1	9	3	9	12	23	1	
#2	24		2.8	5	6	7	0	3	7	14	24		
#3	24		3.4					13	0	11	24		
#4	23	1	3.3					3	18	3	18	6	
#5	23	1	2.4				1	0	20	3	23	1	
#6	21	3	2.8	6	0	1	0	24	0	0	10	7	7
#7	23	1	3.1					5	19	0	0	23	1

VEA GRADE I ■ ≤30 Unifocal VPB/hr. II ■ >30 Unifocal VPB/hr. or >1 VPB/min. III ■ Multifocal IVA ■ Couplets IVB ■ Ventricular Tachycardia BG ■ Bigeminy *Hr./24 hr. OF VEA OF THAT GRADE

Figure 12. Development of VEA in 7 of 21 patients with hypertension before and during hydrochlorothiazide therapy, and after potassium repletion (ref 99).

The issue of drug-induced VEA produced by potassium-losing dieuretics administered to patients with hypertension is one that continues to be debated vigorously. Its existence has been known for several years (103). Since we (104) reported that the lower then serum potassium level, the more complex the docmented VEA, been the various rationales for correction of the hypokalemia and/or the VEA have challenged (105, 106). Correction of the hypokalemia and treatment of frequent and/or complex VEA in the presence of hypertensive heart disease would appear to be a logicalmanagement approach.

MONITORING TECHNIQUES

Ambulatory Monitoring

Although the routine ECG has been used to detect VEA, and has been advocated as sufficient to identify patients at an increased risk of sudden death (5, 36, 107), ambulatory monitoring is considered the technique of choice for the detection of VEA. Since Holter originally described his technique (108), different periods of duration of ambulatory monitoring have been used for the detection of VEA, the assessment of efficacy of antiarrhythmic therapy and the determination of prognosis in certain subsets of patients. After comparing 12 to 24 hours of monitoring, Lopes and colleagues (28) recommended 24 hours in order to better characterize the VEA. Kennedy and associates (109) compared 1,6,12, 24, 36 and 48 hours of ambulatory monitoring, and their results are shown in Figure 13. They showed that for the detection of the more frequent and complex VEA, at least 36 hours of monitoring is recommended. As will be seen, however, the frequency with which ambulatory monitoring is carried out is more important than the duration of a single study.

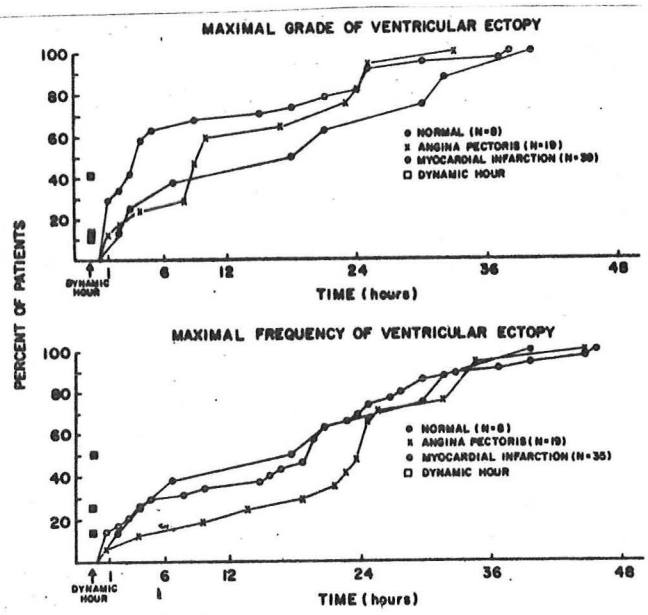

Figure 13. Cumulative data on the maximal grade and maximal frequency of VEA during up to 48 hrs of ambulatory monitoring (Ref 109).

Normal variability

The tabulation of prevalence studies in normal subjects or in patients with cardiac disease demonstrates the inconstant relationship between VEA and many physiological and pathological variables. The use of ambulatory monitoring in the assessment of the efficacy of antiarrhythmic therapy has further identified the limitations of the ambulatory monitoring technique. Both Winkle (110) and Morganroth et al (111) have addressed the issue of normal spontaneous variability, demonstrating that it is quited marked and during any given period of time may mimic drug efficacy or the aggravation of arrhythmias Figure 14 and 15). Winkle (110) showed a variability of occurrence of VEA from-99 per cent to +1100 per cent of a period of continuous monitoring of 5 1/2 hours, and concluded that variability was such that a suppression of greater than 90 per cent sustained for one hour was necessary to confirm a therapeutic antiarrhythmic effect. Under similar circumstances, Morganroth et al (111) advocated a suppresion of VEA of greater than 83 per cent between two 24-hour recordings or greater than 65 per cent between two 72-hour recordings. Subsequently, Michelson and Morganroth (112) have shown that spontaneous variability of complex VEA such as complets and ventricular tachycardia is similar, and requires a reduction of greater than 75 per cent in frequency of repetitive VEA to documenttherapeutic antiarrhythmic efficacy.

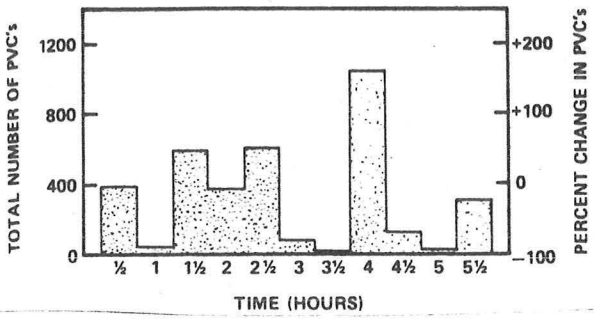

Figure 14. Frequency of VEA during each half hour of monitoring showing spontaneous variability (Ref 110)

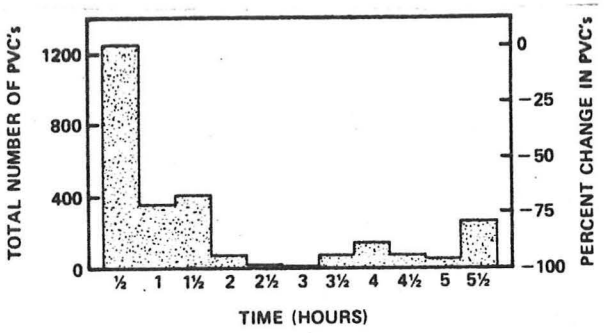

Figure 15. Spontaneous variability mimics a drug response (Ref. 110)

Despite these reports, it is fair to note that there is reasonable consistency in the occurrence of VEA (113). While gross numbers of VPBs may vary from one day to the next, it is unlikely that an individual patient would have large numbers of VPBs on one recording and few or no VPBs on a subsequent recording.

Exercise Testing

Although dynamic exercise has been advocated for assessment of the occurrence of VEA in normal subjects and in patients with cardiac disease, the consensus of opinion is that it is not as sensitive as prolonged periods of ambulatory monitoring for the detection of VEA either in any form or in its more complex forms. This applies equally to apparently healthy subjects (60), patients with coronary artery disease (61-63), and those with conditions such as hypertrophic cardiomyopathy (29) and mitral valve prolapse. It is interesting to note that in assessing prognosis after myocardial infarction, exercise-induced VEA was not considered a significant indicator (52, 114). In 123 patients who had uncomplicated myocardial infarctions, Starling et al (114) showed that exercise-induced angina, ST segment depression and an inadequate blood pressure response are all significant predictors of prognosis during a follow up period of 6 to 20 months; exercise induced VEA was not (Figure 16).

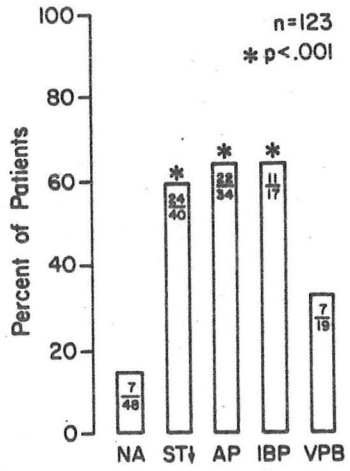

Figure 16. Future cardiac events related to each exercise response, NA=no abnormality; ST = ST segment depression; AP=angina pectoris; IBP=inappropriate blood pressure response. (Ref. 114).

In summary, ambulatory monitoring is superior to dynamic exercise in the identification of all forms of VEA irrespective of the type of cardiac disease that is under assessment.

CLASSIFICATION OF VEA

Table 6 shows the Lown grading system for the classification of ventricular arrhythmias detected by ambulatory monitoring (56). Since its introduction, this grading system has been adopted in most of the studies published in the seventies, depite some major reservations.

Table 6. The Lown grading system for ventricular arrhythmias

Grade	Characteristic
1	Uniform VPBs (< 30/hour)
2	Uniform VPBs (> 30/hour)
3	Multiform VPBs
4A	Couplets (2 VPBs consecutively)
4B	Ventricular tachycardia (3 or more VPBs consecutively)
5	R-on-T phenomenon

VPBs = Ventricular premature beats

from Lown and Wolf: Circulation 44: 130, 1971 (56)

These reservations have been discussed in depth by Bigger and colleagues (115) from data obtained from ambulatory monitoring studies done predischarge on 100 consecutive patients with an acute myocardial infarction. Only 12 of these patients had no VEA. Figure 17 illustrates the numbers of patients eligible for each Lown grade, those moving to a higher grade, and the numbers finishing in each grade. These results illustrate the four principal limitations of the Lown grading system. Firstly, each patient is confined to the highest grade of their VEA. Secondly, up to grade 2 reflects peak activity rather than hourly frequency. It is the latter than determines whether the VEA my be classified as frequent, and therefore considered for treatment. Thirdly, the Lown grading system implies that higher grades carry a higher risk, which is not necessarily the case, and lastly, it implies that each grade is mutually exclusive which is also not the case.

Regarding higher grades carrying a higher risk, frequent VEA (Lown grade II) has been shown to carry a significant risk of mortality in certain subsets of patients. Furthermore, it is now very evident that the R-on-T phenomenon does not deserve the highest grade, and may not require special classification at all. Engel et al (116) reviewed the issue of the R-on-T phenomenon and concluded in humans that it is not a critical determinant of primary

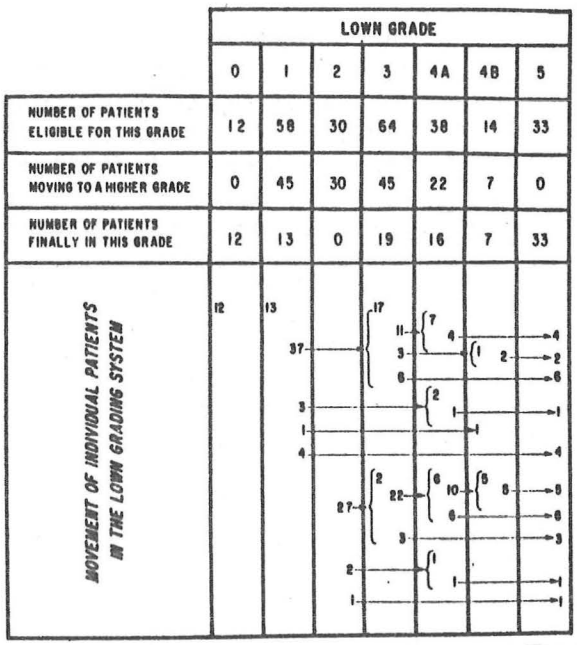

Figure 17. The movement of patients through the Lown grading system in the late hospital phase of myocardial infarction (Ref 56)

ventricular fibrillation complicating myocardial infarction, and that it is seldom documented to initiate ventricular tachycardia.

As a result of identifying these limitations, and because of the emerging literature showing that mny forms of VEA that were originally thought to be precursors of sudden death are not so, Bigger (3) has suggested a more topical and appropriate classification of VEA that may be used as a rough guide for management.

MANAGEMENT OF VEA

Bigger's classification (3) of VEA is suggested as a guideline for management on the basis of the patient's projected prognosis. As has been shown already, and as will be clearer after discussing this system of classification, this system is not completely satisfactory, with large "grey zones" where management remains debatable. VEA is divided into malignanat, potentially malignant and benign arrhythmias.

Malignant VEA

The three frequently recognized malignant, or lethal ventricular arrythmias are out-of-hospital ventricular fibrillation, recurrent sustained ventricular tachycardia and les torsades-de-pointes associated with the long Q-T syndrome.

Out-of-Hospital Ventricular Fibrillation

The characteristics of patients who survive out-of-hospital ventricular fibrillation are well described by the Seattle group (117). They have a high incidence of significant coronary artery disease, previous but not acute myocardial infarction, poor left ventricular function and of importance here, a high incidence of chronic complex VEA (117, 118). They also have a 25 to 30 per cent frequency of recurrent cardiac arrest, so-called recurrent sudden death (96). Treatment of these individuals is manadatory because of the recurrence rate and the high mortality. Methods of assessment of efficacy of antiarrhythmic therapy vary at each institution, but programmed electrical stimulation studies have appeared to produce favorable results (97, 119). Myerburg et al (118) have also shown that adequate plasma levels of antiarrhythmic drugs are sufficient to protect against recurrent ventricular fibrillation. They showed this to be the case despite an inability to suppress or abolish the VEA as detected by ambulatory monitoring.

Recurrent sustained ventricular tachycardia

The characteristics of patients who have recurrent sustained ventricular tachycardia are similar to those who survive out-of-hospital ventricular fibrillation. Seventy five per cent have coronary artery disease, although sustained ventricular tachycardia has been documented in young normals (121, 122). Wellars et al (123) has reported a very poor prognosis in patients who have sustained ventricular tachycardia post myocardial infarction. Treatment is essential in these patients and the assessment of efficacy of antiarrythmic therapy is most proficiently done by programmed electrical stimulation during electrophysiological studies (124). The importance of this

latter method is brought out by recent observations by Swerdlow et al (125), who reported that therapy failure demonstrated by programmed stimulation was a strong indicator of patient prognosis. Recently, several centers have reported the value of surgical excision of the myocardial arrhythmic source (124, 126).

Torsades-De-pointes and the long Q-T Syndrome

The characteristics of patients who present with the long Q-T syndrome with or without les torsades-de-pointes have already been discussed. The management of the correctable forms of the long Q-T syndrome is clear. Management of les torsades-de-pointes has been reviewed by Dr. Rude (78), and includes the use of beta-blockers, catecholamines, overdrive pacing and left stellate ganglionectomy (77).

Potentially malignant VEA

While it is clear that the treatment of malignant VEA is obviously essential, as implied by its classification, the management of potentially malignant VEA is the area of greatest debate. One guiding factor in the selection of who and who not to treat is documentation of the associated existence of cardiac disease. However, as will be seen, even the association of cardiac disease in these circumstances does not mandate therapy in the eyes of some investigators. Furthermore, it should be noted that virtually all the data used to determine prognosis in patients with potentially malignant VEA is generated from studies carried out on patients who had a myocardial infarction.

Frequent VEA

It is clear from Table 3, and has already been stated, that in postmyocardial infarction patients, VEA is a relatively common finding and is a statistical indicator of subsequent increased cardiac risk. The majority of these studies, however, either used no classification or used the Lown classification for identifying VEA. Bigger (3) has selected four studies (37, 42, 46, 127) and plotted mortality rate against the average hourly frequency of VPBs, ie. the number of VPBs recorded for 24 hours averaged over one hour. The results are shown in Figure 18. As can be seen the mortality rate increase plateaus at approximately 10 VPBs per hour, and patients with a higher frequency of VEA are at no greater risk. The mortality rate is thus 20 to 25 per cent at one year for patients with greater than 10 VPBS per hour.

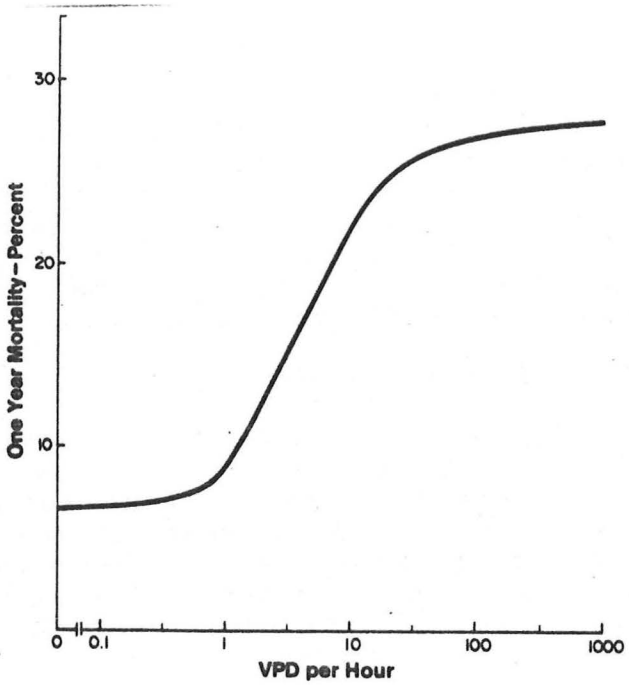

Figure 18. Mortality rate as a function of frequent VEA as defined by Bigger (3).

Two issues remain unresolved. Firstly, there are no data available to show specifically that reducing the frequency of VEA has a beneficial effect on postmyocardial infarction mortality rates. Secondly, it may not be appropriate to extrapolate the findings in postmyocardial infarction to other clinical circumstances.

Repetitive VEA

The complex feature of VEA of greatest prognostic value is its repetitiveness, as classified by Lown in grades 4A and 4B. Lown's grade 3 or multifocal VPBs and grade 5, the R-on-T phenomenon, have both been shown to be of little prognostic significance (116,127). Bigger (127) reviewed the ambulatory monitoring recordings of 400 postmyocardial infarction patients and found 15 per cent to have paired VPBs and 10 per cent to have both paired complexes and runs of 3 or more VPBs consecutively. Respectively, these patients had a 49 and 58 per cent mortality rate in a follow up period of 2 1/2 years. While other previous studies have not distinguished the nature of the complex VEA that was a prognostic fator, the fact remains that 10 of the postmyocardial infarction studies reported complex VEA to be a prognostic factor in subsequent cardiac events (37, 38, 40-42, 44, 46, 50-52).

The issue of asymptomatic, nonsustained ventricular tachycardia both postmyocardial infarction (43, 48) and in stable cardiac disease (57) being reported as benign and of no probable clinical significance, has already been raised. The majority of available data from studies of larger numbers of patients at least in the postmyocardial infarction setting would suggest that repetitive VEA in the presence of documented cardiac disease requires treatment.

VEA and left ventricular dysfunction

In 1977, Schulze et al (41) reported that the combination of complex VEA and a radionuclide-determined ejection fraction of less than 40 per cent represented an increased risk of subsequent cardiac events in postmyocardial infarction patients. Both Calvert et al (58) and Califf et al (59) have been able to statistically associate the severity of VEA and degree of left venticular dysfunction in patients with stable coronary artery disease.

Recently both the Multicenter Postmyocardial Infarction Research Group (53) and the MILIS group (54) have addressed the issue. The former study concluded that both frequent VEA (> 10 VPBs/hour) and a left ventricular ejection fraction of less than 40 per cent were independent prognosticators of poor outcome in a follow up period of one year. The MILIS group showed that the combination of repetitive VEA (two or more VPBs consecutively) increased the risk of sudden death in the follow up period of 2 years.

It is reasonable to conclude that although both frequent and repetitive VEA are independent variables affecting the prognosis of patients with cardiac disease, the association with documented left ventricular dysfunction greatly increases the mortality risks.

Benign VEA

The prevalence of VEA in an apparently healthy normal population has already been discussed. Although the prevalence of any VEA ranges from 10 to 100 per cent depending upon age the prevalences of frequent and repetitive VEA are both small, and in the young people, barely significant. The relatively few follow up studies carried out on normal subjects suggest that the prognosis of such individuals is excellent. Thus, even in the presence of VEA and in the absence of documented cardiac disease, antiarrhythmic therapy in these individuals is unwarranted.

Assessment of Drug Efficacy

Methods of detecting VEA have already been reviewed and some of their limitations have been outlined. Some of these limitations are of importance in the assessment of drug efficacy. It has already been shown how normal spontaneous variability of VEA recorded by ambulatory monitoring mimics a therapeutic response, and that a suppression of at least 85 per cent of VEA on consecutive 24-hour monitoring studies is necessary to demonstrate efficacy (110-112). Programmed electrical stimulation during electrophysiological studies has also been advocated to assess drug efficacy (78, 124, 125). While this procedure is highly specific, its sensitivity is markedly limited by the high proportion of false positive studies (128). The documentation of adequate plasma levels has been advocated for ensuring therapeutic effect (10, 129). This fails to take into consideration individual patient variability that is inevitable in assessing any drug efficacy (94). In addition to these various technical limitations, the cost effectiveness of these individual techniques adds to the limitations to their use.

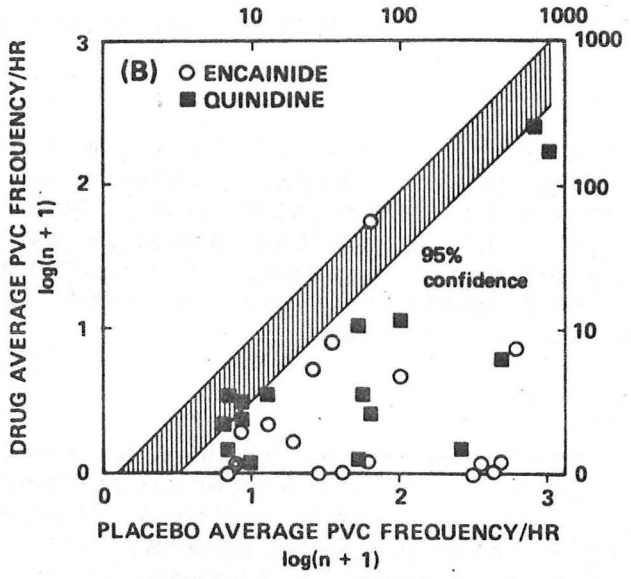

Figure 19. Responses of VEA to encainide and quinidine. The shaded area represents the 95 per cent confidence limits of spontaneous variability of VEA documented by two pre-drug monitoring studies. (Ref. 130)

Harrison has made the following recommendations to document drug efficacy (128).

1. For symptomatic patients, the abolition of symptoms is an obvious therapeutic goal.

2. The documentation of at least 85 per cent reduction in VEA by recurrent ambulatory monitoring studies. This may be achieved by ambulatory monitoring twice prior to the administration of the antiarrhythmic drug to determine the 95 per cent confidence limits of average VEA frequency (130). Subsequent monitoring studies are then able to indicate efficacy (Figure 19).

3. In patients where antiarrhythmic drugs are used for prophylaxis, plasma levels may be obtained (131).

Individual antiarrhythmic drugs have been covered comprehensively by Dr. Thomas Smitherman relatively recently (132).

Prophylaxis of Postmyocardial Infarction Patients

Antiarrhythmic Drugs

There are six clinical trials of antiarrhythmic agents involving 1675 postmyocardial infarction patients. They involved phenytoin (two) tocanide (two), mexilitene and aprindine (133-137). Although the drugs were uniformly effective in reducing the incidence of VEA, there was no evidence that per cent mortality was improved in the very small numbers of patients involved.

Beta-blocking drugs

Table 7 lists the major trials of beta-blocking agents and their effect on post-discharge mortality in postmyocardial infaction patients. These studies involve 12,001 patients and 6 beta-blocking agents. Only the study by Baber et al with propranolol showed no reduction in mortality in the treated group (141). The prophylactic effects of propranolol have been restudied by the BHAT Research Group (131) involving five times the number of patients and showed an effective reduction in mortality in the treated group. The study reported by Taylor et al (144) involving oxprenolol produced some unusual statistics. In patients entered into the study 4 to 16 weeks after

TABLE 7. DOUBLE-BLIND RANDOMIZED TRIALS TO DETERMINE THE EFFECT OF BETA-BLOCKING AGENTS ON MORTALITY AFTER MYOCARDIAL INFARCTION

Study	Yr	Drug	No. of Patients	Entry After MI (Days)	Follow up (Yrs)	Effect on Mortality
Multicenter International Study (138)	1977	Practolol	3038	7-28	1	Yes
Wilhelmasson et al (139)	1974	Alprenolol	230	28-42	2	Yes
Anderson et al (140)	1979	Alprenolol	480	1	1	Yes
Baber et al (141)	1980	Propranolol	720	2-14	1	No
Norwegian Multicenter Study (142)	1981	Timolol	1884	7-28	3	Yes
Hjalmarson et al (143)	1981	Metoprolol	1395	1	0.25	Yes
Taylor et al (144)	1982	Oxprenolol	417	4-16	6	Yes*
BHAT Research Group (131)	1982	Propranolol	3837	5-21	2	Yes

*In patients entered up to 16 wks, mortality less; if patients entered between 1 and 6 yrs, mortality increased.

myocardial infaction, follow-up showed a reduction in mortality in the treated group. However in those patients entered 1 to 7 years after their myocardial infarction, follow up revealed an increase in mortality in the treated group. Whether this adverse effect on mortality is attributable to the unique intrinsic sympathomimetic activity of oxprenolol remains to be demonstrated. Propranolol, metoprolol and timolol are available in the USA.

It is evident from these data that a suitable beta-blocking agent is effective in increasing longevity in patients with uncomplicated myocardial infarction for a documented period of up to 2 years.

SUMMARY

While it is not possible to come to a definite conclusion on every single individual in whom as some VEA is documented, certain guidelines are available to determine whether the VEA is benign, potentially malignant or malignant, and thus whether antiarrhythmic therapy should be initiated. It one takes into account the limitations of identification of etiology, of techniques for documentation, of difficulties in suitable classification, and of the antiarrhythmic agents themselves, suitable plans of management may be designed for each individual that need not be descried as cavalier.

REFERENCES

1. STRAUSS M.: Familiar medical quotations, Little, Brown and Co, Boston 1968, p. 271.

2. WINKLE RA: Measuring antiarrhythmic drug efficacy by suppression of asymptomatic ventricular arrhythmias. Ann Intern Med 9:480, 1979.

3. BIGGER JT: Definition of benign versus malignant ventricular arrhythmias: targets for treatment. Am J Cardiol 52:47C, 1983.

4. HINKLE LE, CARVER ST, STEVENS M: The frequency of asyptomatic disturbances of cardiac rhythm and conduction in middle-aged men. Am J. Cardiol 24:629, 1969

5. RODSTEIN M. WOLLOCH L, GUBNER RS: Mortality study of the significance of extrasystoles in an insured population. Circulation 44:617, 1971.

6. RAFTERY E.M, CASHMAN PMM: Long-term recording of the electrrocardioram in a normal population. Postgrad Med J 52(Suppl 7):32, 1976

7. CLARKE JM, SHELTON JR, HAMER J, TAYLOR S, VENNING GR: The rhythm of the normal human heart. Lancet 2:508, 1976.

8. KENNEDY HL, UNDERHILL SJ: Frequent or complex ventricular ectopy in apparently healthy subjects. Am J. Cardiol 38:141, 1976.

9. BRODSKY M, WU D, DENES P, KANAKIS C, ROSEN KM: Arrhythmias documented by 24 hour continuous electrocardiographic monitoring in 50 male medical students without apparent heart disease. Am J Cardiol 39:390, 1977.

10. VERBAAN CJ, POOL J, VAN WANROOY J: Incidence of cardiac arrhythmias in a presumed healthy population. Stott FD et al (Eds), International symposium on Ambulatory Monitoring, New York, Academic Press. 1977. p.1.

11. GOULDING L: Twenty-four hour ambulatory electrocardiography from normal urban and rural populations. Stott FD et al (Eds), International Symposium on Ambulatory Monitoring, New York, Academic Press 1977 p. 13

12. SCOTT O, WILLIAMS GJ, FIDDLER GI: Results of 24 hour ambulatory monitoring of electrocardiogram in 131 healthy boys aged 10-13 years. Br Heart J. 44:304, 1980

13. RABKIN SW, MATHEWSON FAL, TATE RB: Relationship of ventricular ectopy in new without apparent heart disease to occurrence of ischemic heart disease and death. Am Heart J 101:135, 1981

14. SOBOTKA PA, MAYER JH, BAUERNFEIND RA, KANAKIS C, ROSEN KM: Arrhythmias documeted by 24 hour continuous ambulatory electrocardiographic monitoring in young women without apparent heart disease. Am Heart J 101:753, 1981

15. GLASSER SP, CLARK PI, APPLEBAUM HJ: Occurrence of frequent complex arrhythmias detected by ambulatory monitoring: findings in an apparently healthy asymptomatic elderly population. Chest 75:565, 1979

16. CAMM AJ, EVANS KE, WARD DE, MARTIN A: The rhythm of the heart in active elderly subjects, Am Heart J 99:598, 1980

17. FLEGG JL, KENNEDY HL: Cardiac arrhythmias in a healthy elderly population. Chest 81:302, 1982

18. KENNEDY HL, PESCARMONA JE, BOUCHARD RJ, GOLDBERG RJ: Coronary artery status of apparently healthy subjects with frequent and complex ventricular ectopy. Ann Intern Med 92:179, 1980

19. DEBACKER G, JACOBS D, PRINEAS R, CROW R, VILANDRE J, KENNEDY H, BLACKBURN H: Ventricular premature contractions: a randomized non-drug intervention trial in normal men. Circulation 59:762, 1979

20. BELLET S, ROMAN L, KOSTIS J, SLATER A: Continuous electrocardiographic monitoring during automobile driving. Am J Cardiol 22:856, 1968

21. TAGGART P, GIBBONS D, SOMERVILLE W: Some effects of motor car driving on the normal and abnormal heart. Br Med J 4:130, 1969

22. TAGGART P, CARRUTHERS M, SOMERVILLE W: Electrocardiogram, plasma catecholamines and lipids, and their modification by oxprenolol when speaking before an audience. Lancet 2:341, 1973.

23. MOSS AJ, WYNAR B: Tachycardia in house officers presenting cases at grand rounds. Ann Intern Med 72:255, 1970

24. GAZES PC, SOVELL BF, DELLASTATIOUS JW: Continous radioelectrocariographic monitoring of football and basketball coaches during games. Am Heart J 78:509, 1969.

25. TAGGART P, PARKINSON P, CARRUTHERS M: Cardiac responses to thermal, physical and emotional stress. Br Med J 3:71, 1972.

26. LOWN B, TYKOCINSKI M, GARFEIN A, BROOKS P: Sleep and ventricular premature beats. Circulation 48:69, 1973

27. PICKERING G, GOULDING L, COBERN BA: Dimnal variation in ventricular ectopic beats and heart rate. Cardiovasc Med 2:1013, 1977

28. LOPES MG, RUNGE P, HARRISON DC, SCHROEDER JS: Comparison of 24 versus 12 hours of ambulatory ECG monitoring. Chest 67:269, 1975.

29. SAVAGE DD, SEIDES SF, MARON BJ, MYERS DJ, EPSTEIN SE: Prevalence of arrhythmais during 24 hour electrocardiographic monitoring and exercise testing inpatients with obstructive and nonobstructive hypertrophic cardiomyopathy. Circulation 59:866, 1979.

30. LOWN B: Sudden cardiac death: the major challenge confronting comtemporary cardiology. Am J Cardiol 43:313, 1979

31. WINKLE RA: Ambulatory electrocardiography and the diagnosis, evaluation and treatment of chronic ventricular arrhythmias. Prog Cardiovase Dis 23: 99, 1980.

32. TROUP PJ, SMALL JG, MILSTEIN V: Effect of electroconvulsive therapy on cardiac rhythm, conduction and repolarization. PACE 1:172, 1978

33. LEVY N, ABINADER E: Continuous electrocardiographic monitoring with Holter electrorecorder throughout the stages of gastroscopy. Dig Dis 22:1091, 1977

34. BOUGH EW, MYERS S: Cardiovascular responses to upper gastrointestinal endoscopy. Am J Gastroenterol 69:655, 1978.

35. ROESKE WR, HIGGINS C, KARLINER JS, BERK RN, O'ROURKE RA: Incidence of arrhythmias and ST-segment changes in elderly patients during barium enema studies. Am Heart J 90:688, 1975

36. Coronary Drug Project Research Group: Prognostic importance of premature beats follow myocardial infarction. JAMA 223:1116, 1973.

37. KOTLER MN, TABATZNIK B, MOWER MM, TOMINAGA S: Prognostic significance of ventricular ectopic beats with respect to sudden death in the late post infarction period. Circulation 47: 959, 1973

38. VISMARA LA, AMSTERDAM EA, MASON DT; Relation of ventricular arrhythmias in the late hospital phase of acute myocardial infarction to sudden death after hospital discharge. Am J Med 59:6, 1975

39. LURIA MH, KNOKE JD, MARGOLIS RM, HENDRICKS FH, KUPLIC JB: Acute myocardial infarction; prognosis after recovery. Ann Intern Med 85:561, 1976.

40. MOSS AJ, DECAMILLA JJ, DAVIS HP, BAYER L: Clinical significance of ventricular ectopic beats in the early posthospital phase of myocardial infarction. An J. Cardiol 39:635, 1977

41. SCHULZE RA, STRAUSS HW, PITT B: Sudden death in the year following myocrdial infarction. Am J Med 62:192, 1977

42. RUBERMAN W, WEINBlATT E, GOLDBERG JD, FRANK CW, SHAPIRO S: Ventricular premature beats and mortality ater myocardial infarction. N Engl J Med 297:750, 1977

43. ANDERSON KP, DECAMILLA J, MOSS AJ: Clinical significance of ventricular tachycardia detected during ambulatory monitoring after myocardial infarction. Circulation 57:890, 1978

44. BIGGER JT, HELLER CA, WENGER TL, WELD FM; Risk stratification after acute myocardial infarction. Am J Cardiol 42:202, 1978

45. DESOYZA N, BENNETT FA, MURPHY ML, BISSETT JK, KANE JJ: The relationship of paroxysmal ventricular tachycardia complicating the acute phase and ventricular arrhythmia during the late hospital phase of myocardial infarction to long term survival. Am J Med 64;377, 1978

46. MOSS AJ, DAVIS HT, DECAMILLA J, BAYER LW: Ventricular ectopic beats and their relation to sudden and nonsudden cardiac death after myocardial infarction. Circulation 60:998, 1979

47. DEBUSK RF, DAVIDSON DM, HOUSTON N, FITZGERALD J: Serial ambulatory electrocardiography and treadmill exercise testing following uncomplicated myocardial infarction. Am J Cardiol 45:547, 1980

48. MOLLER M, NIELSON BL, FABRICUS J: Paroxysmal ventricular tachycardia during repeated 24 hour ambulatory electrocadiographic monitoring of post myocardial infarction patients. Br Heart J 43:447, 1980

49. TAYLOR GJ, HUMPHRIES JO, MELLITS ED, PITT B, SCHULZE RA, GRIFFITHS LSC, ACHUFF SC: Predictors of clinical course, coronary anatomy and left ventricular function from acute myocardial infarction. Circulation 62:960, 1980

50. RUBERMAN W, WEINBLATT E, GOLDBERG JD, FRANK CW, CHAUDHARY BS, SHAPIRO S: Ventricular premature complexes and sudden death after myocardial infarction. Circulation 64:297, 1981

51. BIGGER JT, WELD FM, ROLNITSKY LM: Prevalence, characteristics and significance of ventricular tachycardia detected with ambulatory electrocardiographic monitoring in the late hospital phase of acute myocardial infarction. Am J Card 48:815, 1981

52. RAPAPORT E, REMEDIOS P: The high risk patient after recovery from myocardial infarction: recognition and management. J. Am Coll Cardio 1:391, 1983

53. The multicenter postinfarction Research Group: Risk Stratification and survival after myocardial infarction. N Engl J Med 309:331, 1983

54. MUKHARJ, J AND THE MILIS STUDY GROUP: late sudden death following acute myocardial infarction: multivariate analysis of risk factors. (in press)

55. MOSS AJ: Clinical significance of ventricular arrhythmias in patients with and without coronary artery disease. Prog Cardioverse Dis 23:33, 1980

56. LOWN B, WOLF M: Approaches to sudden death from coronary disease. Circulation 44:130, 1971

57. WINKLE RA, DERRINGTON DC, SCHROEDER JS: Characteristics of ventricular tachycardia in ambulatory patients, Am J Cardiol 39:487, 1977

58. CALVERT A, LOWN B, GORLIN R: Ventricular premature beats and anatomically defined coronary artery disease. Am J Cardiol 39:627, 1977

59. CALIFF RM, BURKS JM, BEHAR VS, MARGOLIS JR, WAGNER GS: Relationship among ventricular arrhythias, coronary artery disease, and angiographic and electrocardiographic indicators of myocardial fibrosis. circulation 57:725, 1978

60. EKBLOM B, HARTLEY LH, DAY WC: Occurrence and reproducibility o exercise-induced ventricular ectopy in normal subjects. Am J Cardiol 43:35, 1979

61. CRAWFORD M. O'ROURKE RA, RAMAKRISHNA N, HENNING H, ROSS J JR; Comparative effectiveness of exercise testing and continous monitoring for detecting arrhythmias in patients with previous myocardial infarction. Circulation 50:301, 1974

62. NIXON JV, PENNINGTON W, RITTER W, SHAPIRO W: Efficacy of propranolol in the control of exercise-induced or augumented ventricular ectopic activity. Circulation 57:115, 1978

63. POBLETE, PF, KENNEDY HL, CARALIS DG: Detection of ventricular ectopy in patients with coronary heart disease and normal subjects by exercise testing and ambulatory electrocardiography. Chest 74:402, 1978.

64. INGHAM RE, ROSSEN RM, GOODMAN DJ, HARRISON DC: Ambulatory electrocardiographic monitoring in ideopathic hypertrophic subaortic stenoasis (abstr.). Circulation 52 (suppl II) II-93, 1975

65. MCKENNA WJ, CHETTY S, OAKLEY CM, GOODWIN JF: Arrhythmia in hypertrophic cardiomyopathy: exercise and 48 hour ambulatory electrocardiographic assessment with and without beta ardrenergic blocking therapy. Am J Cardiol 45:1, 1980

66. MCKENNA WJ, DEANFIELD J, FARUQUI A, ENGLAND D, OAKLEY CM, GOODWIN JF: Prognosis in hypertrophic cardiomyopathy: role of age and clinical, electrocardiographic and hemodynamic features. Am J Cardiol 47:532, 1981

67. ANDERSON KP, STINSON E, DERBY GC, DYER PE, MASON JW: Vulnerability of patients with obstructive hypertrophic cardiomyopathy to ventricular arrhythmia induction in the operating room. Am J Cardiol 51:811, 1983

68. HUANG SK, MESSER JV, DENES P: Significance of ventricular tachycardia in ideopathic dilated cardiomyopathy. Am J Cardiol 51:507, 1983

69. MARKIEWICZ W, STONER J, LONDON E, HUNT SA, POPP RL: Mitral valve prolapse in one hundred presumably healthy females. Circulation 23:464, 1976.

70. SBARBARO JA, MEHLMAN DJ, WU L: A prospective study of mitral valvular prolapse in young men. Chest 75:555, 1979.

71. WINKLE RA, LOPES MG, FITZGERALD JW, GOODMAN DJ, SCHROEDER JS, HARRISON DC: Arrhythmias in patients with mitral valve prolapse. Circulation 52:73, 1975

72. DEMARIA AN, AMSTERDAM EA, VISMARA LA, NEUMANN A, MASON DT: Arrhythmias in the nitral valve prolapse syndrome. Ann Intern Med 84:656, 1976

73. WEI JY, BULKLEY BH, SCHAFFER AH, GREENE HL, REID PR: Mitral valve prolapse syndrome and recurrent ventricular tachyarrhythmias. Ann Intern Med 89:6, 1978.

74. JERESATY RM: Sudden death in the mitral valve prolpase click syndrome. Am J Cardiol 37:317, 1976

75. KLEIGER RE, SENIOR RM: Long term electrocadiographic monitoring of ambulatory patients with chronic airway obstruction. Chest 65:483, 1974

76. DESSERTENNE F: La tachycardie ventriculaire a deux foyers opposes variable. Arch Mal Coeur 59:263, 1966

77. SMITH WM GALLAGHER JJ: "Les torsade de pointes": an unusual ventricular arrhythmia. Ann Intern Med 93:578, 1980

78. RUDE RE: Ventricular tachycardia. Medical Grand Rounds. UTHSCD, 1981

79. JERVELL A, LANGE-NIELSON F: Congenital deafmutism, functonal heart disease with prolongation of the Q-T interval, and sudden death. Am Heart J 54:59, 1957

80. ROMANO C, GEMME G, PONGIGLIONE R: Aritmie cardiache rare dell, eta pediatrica. Clin Pedriatr 45:656, 1963

81. WARD OC: New familiar cardiac syndrome in children, J Ir Med Assoc 54:103, 1964

82. MOSS AJ, MCDONALD J: Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long Q-T syndrome. N Engl J Med 285:903, 1971.

83. SCHWARTZ PJ, WOLF S: Q-T interval prolongation as a predictor of sudden death in patients with myocardial infarction. Circulation 57:1074, 1978

84. JAMES TN, ZIPES DP, FINEGAN RE, EISELE JW, CARTER JE: Cardiac gaglionitis associated with sudden unexpected death. Ann Intern Med 91:727, 1979

85. BEKHEIT S, ALI A: QT interval in ideopathic prolapsed mitral valve. Am J Cardiol 41:374, 1978

86. BURCH GE, MYERS R, ABILDSKOV JA: New electrocardiographic pattern observed in cerebrovascular accidents. Circulation 9:719, 1954

87. SINGH BN, GAARDNER TD, KANAGAE T, GOLDSTEIN M, MONTGOMERY JZ, MILLS H: Liquid protein diets and torsade de points. JAMA 240:115, 1978

88. LOEB HS, PLETRAS RJ, GUNNAR RM, TOBIN JR JR: Paroxysmal ventricular fibrillation in two patients with hypomagnesemia. Circulation 37:210, 1968

89. REYNOLDS EW, VANDER ARK CR: Quinidine syncope and delayed repolarization syndromes. Mod Conc Cardiovasc Dis 55:117, 1976

90. TZIVONI D, KAREN A, STERN S, GOTTLIEB S; Disopyramide-induced torsade-de-pointes. Arch Intern Med 141:946, 1981

91. SCHOOMAKER FW, OSTEEN RT, GREENFIELD JC: Thioridazine - induced ventricular tachycadia controlled with an artificial pacemaker. Ann Intern Med 65:1076, 1966.

92. KAREN A, T ZIVONI D, GAVISH D, LEVI J, GOTTLIEB S, BENHORIN J, STERN S: Eteiology, warning signs and therapy of torsade-de-points. Circulation 64:1167, 1981

93. SMITH TW, HABER E: Digitalis. N. Engl J Med 289:1125, 1973

94. SHAPIRO W: Correlative studies of serum digoxin levels and arrhythmias of digitalis intoxication. Am J Cardiol 41:852, 1978

95. EJVINSSON G: Effect of quinidine on plasma concentrations of digoxin. Br Med J 1:279, 1978.

96. LIBERTHSON RR, NAGEL EL, HIRSCHMAN JC, NUSSENFELD SR: Prehospital ventricular defibrillation: prognosis and follow up course. N Engl J Med 291:317, 1974

97. RUSKIN JN, MCGOVERN B, GARAN H, DIMARCO JP, KELLY E: Antiarrhythmic drugs: a possible cause of out-of-hospital cardiac arrest. N Engl J Med 309:1302, 1983

98. VELEBIT V, PODRID P, LOWN B, COHEN BH, GRABOYS TB: Aggravation and provacation of ventricular arrhythmias by antiarrhythmic drugs. Circulation 65:886, 1982

99. FOWLER NO, MCCALL D, CHOUT, HOLMES JC, HANENSON IB: Electrocardiographic changes and cardiac arhythmias in patients receiving psychotropic drugs. Am J Cardiol 37:223, 1976.

100. LEFRANK E, PITHA J, ROSENHEIM S: A clinico-pathologic analysis of adriamycin cardiotoxicity. Cancer 32:302, 1973.

101. BANNER AS, SUNDERRAVAN EV, AGARWAL MK, ADDINGTON WW: Arrhythmogenic effects of orally administered bronchodilators. Arch Intern Med 139:434, 1979

102. CROFT C: Personal observation, 1984

103. WEAVER WF, BURCHELL HB: Serum potassium and the electrocardiogram in hypokalemia. Circulation 21:505, 1960

104. HOLLAND OB, NIXON JV, KUHNERT L: Diurmetic-induced ventricular ectopic activity. Am J Med 70:762, 1981

105. HARRINGTON JT, ISNER JM, KASSIRER JP: A national obsession with potassium. Am J Med 73:155, 1982

106. PAPADEMSTRIOU V, FLETCHER R, KHATRI IM, FREIS ED: diuretic diuret hypokalemia in uncomplicated systemic hypertension: effect on plasma potassium correction on cardiac arrhythmias. Am J Cardiol 52:1017, 1983.

107. CHIANG BN, PERLMAN LV, OSTRANDER LD, EPSTEIN FJ: Relationship of premature systoles to coronary heart disease and sudden death in the Tecumseh epidemiological study. Ann Intern Med 70:1059, 1969

108. HOLTER NJ: New method for heart studies. Science 134:1214, 1961.

109. KENNEDY HL, CHANDRA V, SAYTHER KH, CARALIS DG: Efectiveness of increasing hours of continuous ambulatory electrocardiography in detecting maximal ventricular ectopy. Am J Cardiol 42:925, 1978

110. WINKLE RA: Antiarrhythmic drug effect mimicked by spontaneous variability of ventricular ectopy. Circulation 57:1116, 1978

111. MORGANROTH J, MICHELSON EL, HOROWITZ LN, JOSEPHSON ME, PEARLMAN AS, DUNKMAN WB: Limitations of routine long-term electrocardiographic monitoring to assess ventricular ectopic frequency. Circulation 58:408, 1978

112. MICHELSON EL, MORGANOTH J: Spontaneous variability of complex ventricular arrhythmias detected by long-term electrocardiographic recording. Circulation 61:690, 1980

113. MISNER JE, IMREY PB, SMITH L: Secular variations in frequency of premature ventricular contractions in untreated individuals. J Lab Clin Med 92:117, 1978

114. STARLING MR, CRAWFORD MH, KENNEDY GT, O'ROURKE RA: Exercise testing early after myocardial infarction: predictive value For subsequent unstable angina and death. AM J Cardiol 46:909, 1980

115. BIGGER JT, WENGE TL, HEISSENBUTTEL RH: Limitations of the Lown grading system for the study of human ventriculr arrhythmias. Am Heart J 93;727, 1977

116. ENGEL TR, MEISTER SG, FRANKL WS: The "R-on-T" phenomenon; an update and critical review. Ann. Intern med 88:221, 1978

117. BAUM RS, ALVAREZ H, COBB LA: Survival after resuscitation from out-of-hospital ventricular fibrillation. Circulation 50:1231, 1974

118. GOLDSTEIN S, LANDIS JR, LEIGHTON R, RITTER G, VASU CM, LANTIS A, SEROKMAN R: Characteristics of the resuscitated out-of-hospial cardiac arrest victim with coronary artery disease. Circulation 64;977, 1981

119. SPIELMAN S, FARSHIDI A, HOROWITZ LN, JOSEPHSON ME: Ventricular fibrillation during programmed ventricular stimilation: incidence and clinical implications. Am J Cardiol 42:913, 1978

120. MYERBURG RJ, CONDE C, SHEPS DS, APPEL RA, KIEM L, SUNG RJ, CASTELLANOS A: Antiarrhythmic drug therapy in survivors of prehospital cardial arrest: comparison of effects on chronic ventricular arrhythmias and recurrent cardial arrest. Circulation 59:855, 1979

121. COHN LJ, DONOSO E, FRIEDBERG CK: Ventricular tachycardia. Prog. Cardiovasc Dis 9:29, 1966

122. PEDERSEN DH, ZIPES DP, FOSTER PR, TROUP PJ: Ventricular tachycardia and ventricular fiberillation in a young population. Circulation 60:988, 1979

123. WELLENS HJJ, BAR FWHM, VANAGT EJDM, BRUGADA P: Medical treatment of ventricular tachycardia: considerations in the selection of patients for surgical treatment. Am J Cardiol 49:186, 1982

124. JOSEPHSON ME, HOROWITZ LN: Electrophsiological approach to therapy of recurrent sustained ventricular tachycardia. Am J Cardiol 43:631, 1979

125. SWERDLOW CD, WINKLE RA, MASON JW: Determinants of survival in patients with ventricular tachyarrhythmias. N. Engl J Med 308:1436, 1983

126. HOROWITZ LN, HARKEN AH, KASTOR JA, JOSEPHSON ME: Ventricular resection guided by epicardial and endocardial mapping for treatment of recurrent ventricular tachycaria. N. Engl J Med 302:397, 1982

127. BIGGER JT, WELD FM: Analysis of prognostic significance of ventricular arrhythmias after myocardial infarction. Br Heart J 45:717, 1981

128. HARRISON DC: Methods for documenting antiarrhythmic efficacy. Am J Cardiol 52:37C, 1983

129. GAUGHAN CE, LOWN B, LANIGAN J, VOUKYDIS P, BESSER EW: Acute oral testing for determining antiarrhythmic drug efficacy. Am J Cardiol 38: 677, 1978

130. SAMI M, KRAEMER H, HARRISON DC, HOUSTON N, SHIMASAKI C, DEBUSK RF: A new method for evaluating drug efficacy. Circulation 62:1172, 1980.

131. Beta-blocker Heart Attack Trial Research Group: A randomized trial of propranolol in patients with acute myocardial infarction. JAMA 247:1707, 1982

132. SMITHERMAN TC: Drug treatment for disorders of cardiac rhythm: past, present and future. Medical Ground Rounds. UTHSCD, 1982

133. COLLABORATIVE GROUP: Phenytoin after recovery from myocardial infarction: controlled trial in 568 patients. Lancet 2:1055, 1971

134. PETER T, ROSS D, DUFFIELD A: Effect on survival after myocardial infarction of long term treatment with phenytoin. Br Heart J 40:1356, 1978.

135. BASTION BC, MCFARLANE PW, MCLAUGHLAN 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: 1047, 1980

136. RYDEN L, ARNMAN K, CONRADSON TB, HOFVENDAHL S, MORTENSEN O, SMEDGARD P: Prophylaxis of ventricular tachyarrhythmias with intravenous and oral tocainide in patients with and recovering from acute myocardial infarction. Am Heart J 100:1006, 1980

137. CHAMBERLAIN DA, JEWITT DE, JULIAN DG: Oral mexiletine in high risk patients after myocardial infarction. Lancet 2, 1324, 1980

138. Multicenter International Study: Reduction in mortality after myocardial infaction with long term beta-adrenoceptor blockade. Br Med J 2:419, 1977

139. WILHELMSSON C, WILHELMSSON L, VEDIN JA, TIBBLIN G, WERKO L: Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. Lancet 2:1157, 1974.

140. ANDERSEN MP et al: Effect of alprenolol on mortality among patients with definite or suspected acute myocardial infarction. Lancet 2:865, 1979

141. BABER NS, EVANS DW, HOWITT G, THOMAS M, WILSON C, LEWIS JA, DAWES PM, HANDLER K, TUSON R: Multicentre post-infarction trial of propranolol in 49 hospitals in the UK, Italy and Yugoslavia. Br Heart J 44:96, 1980

142. The Norwegian multicenter Study Group: Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 304:801, 1981

143. HJALMARSON A et al: Effect on mortality of metoprolol in acute myocardial infarction. Lancet 2:823, 1981

144. TAYLOR SH, SILKE B, EBBUTT A, SUTTON GC, PROUT BJ, BURLEY DM: A long-term prevention study with oxprenolol in coronary artery disease. N Engl J Med 307:1293, 1982