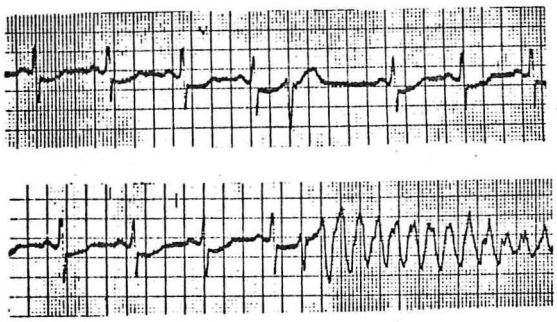
VENTRICULAR ECTOPIC ACTIVITY:
SIGNIFICANCE AND MANAGEMENT



MEDICAL GRAND ROUNDS

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CONTENTS

HISTORICAL NOTES

"When in his flight from Mahmúd of Ghazne he came incognito to Jurján or Gurgán (the ancient Hyrcania) by the Caspian Sea, a relative of the ruler of that province lay sick with a malady which baffled all the local doctors. Avicenna, though his identity was then unknown, was invited to give his opinion, and, after examining the patient, requested the collaboration of someone who knew all the districts and towns of the province, and who repeated their names while Avicenna kept his finger on the patient's pulse. At the mention of a certain town he felt a flutter in the pulse. 'Now', said he 'I need someone who knows all the houses, streets and quarters of this town'. Again when a certain street was mentioned the same phenomenon was repeated, and once again when the names of the inhabitants of a certain household were enumerated. Then Avicenna said: 'It is finished. This lad is in love with such-and-such a girl who lives in such-and-such a house, in such-and-such a street, in such-and-such a quarter of such-and-such a town; and the girl's face is the patient's cure'. So the marriage was solemnized at a fortunate hour chosen by Avicenna, and thus the cure was completed."

Attributed to Avicenna (980-1037) by Browne, EG. (1921) Arabian Medicine Cambridge University Press p.84

"While I was with the Turkish emperor Sultan Suleiman Sachus I got to know of a certain Turkish soldier who in an acute fever always had a dicrotic pulse: which after the illnes had subsided was in no way changed, with signs indicating with certainty the convalescence of the body; wherefrom I inferred that nature had given him this type of pulse. It is therefore most expedient that people when they are well should often meet the doctors to whom they entrust themselves during illness. For the family doctor or his friend can easily remember what the pulse was yesterday (i.e. recently) during health when he has already been taken ill; and he will duly notice how much it has changed. If indeed you should encounter a bad and serious pulse in a patient whom you do not know and whose arteries you have not previously touched before he was taken ill, remember this rule: If from all the other signs the disease appears to be without danger, it should be realized that the terrifying pulse is [just] a natural phenomenon, or was in fact present before this illness, because of some evident cause."

From Joseph Struthius' (1510-1578) *Sphygmicae artis iam mille ducentos annos perditae & desideratae libri V* (1555)

"Some books speak of intermitting pulses as dangerous signs, but, I think, without reason; for such trivial causes will occasion them, that they are not worth regarding in any illness, unless joined with other signs of more moment."

Heberden, 7 July 1768.

"On the whole it is wise to assume that ectopic beats are innocent, and to judge organic disease on other grounds....Treatment includes fresh air, exercise, a healthy physiological life and excluding provocative factors such as tobacco and alcohol....Reassurance is important, and should be unconditional and convincing, for ectopic beats rarely constitute a complaint except in those prone to anxiety."

Paul Wood. 1968. Diseases of the heart and circulation. 3rd ed. J. B. Lippincott, Philadelphia, 256 p.

ILLUSTRATIVE CASE REPORTS

Patient [redacted], [redacted] is a 73 year old [redacted] male who was first seen at [redacted] in 1962 with palpitations and shortness of breath. The patient gave a history of having had short episodes of palpitations several times over the preceeding 2-3 years. The patient noted the onset of palpitations 4 days prior to admission which continued until the morning of admission when the patient developed moderate shortness of breath and right-sided chest pain with radiation into his jaw. The patient was noted to have a pulse of approximately 220; the EKG was interpreted as supraventricular tachycardia. This was controlled with digitalization, but subsequently he developed premature ventricular contractions. The patient was given procaine amide 250 mg q6h which abolished the occurrence of recorded PVC's. Subsequently, the digitoxin and procaine amide were both discontinued but the patient again developed a tachycardia and consequently, both medications were restarted. Over the ensuing 11 years, the patient was totally asymptomatic and was continued on digitalis and varying doses of procaine amide.

In 1968, the patient was noted to be hypertensive with a BP of 160/105 and was started on 4 mg of naqua per day. The patient was noted to have cardiomegaly with left ventricular enlargement on x-ray study.

In [redacted] 1974, the patient presented with bigeminy and multifocal PVC's. The patient was initially felt to be digitalis toxic, but the concurrent digitoxin level was 6.6 ng/ml. The patient was treated with 500 mg of pronestyl q4h and noted subsequently to develop 20-30 PAC's per minute and consequently started on additional quinidex 300 mg q8h. Discharge: the patient was discharged on this regimen of medication but subsequently reduced his dosage of procaine amide to 500 mg qid.

In [redacted] 1974, at routine follow-up the patient was noted to have atrial flutter with a 4 to 1 block and was admitted for cardioversion. The patient was continued on pronestyl 500 mg qid and quinidex 300 mg q8h and spontaneously converted to normal sinus rhythm. Subsequently, the patient had no ventricular ectopic activity recorded on casual EKG's. He now has left atrial "overload" by EKG and a grade II/VI holosystolic apical murmur which had not been previously noted.

Case Report #2

A 31 year old [redacted] male sought evaluation for the need of coronary angiography.

This patient had reported "skips in the heartbeat" to his physician 2 years prior to the present evaluation. ECG was alleged to show one PVC/20 seconds. They disappeared and returned 1 year prior to evaluation and were reported to occur predominantly at rest and to be variable in frequency. Inderal 10 mg qid and digitoxin 0.1 mg after initial digitalization were associated with initial suppression of palpitations, but later they were said to be present at a rate of "8 per minute". A cardiovascular workup was carried out approximately 5 months ago which revealed multifocal PVC's plus a premature nodal contraction at rest. A double Master's test was reported to show 1 mm of ST segment depression in V4 (pt. taking digitoxin 0.1 mg/d). One mg of atropine was administered and resulted in an increase in heart rate and complete disappearance of all premature beats. Coronary angiography was seriously considered.

The patient continued to note palpitations especially when he was resting and expressed some concern about them. In the previous year, apparently in response to admonitions from his physician, the patient had lost 35 lbs. and stopped smoking 3 years ago. There was no history suggestive of angina pectoris. Family history was negative for premature coronary artery disease; the father developed angina pectoris in his early 60's. The patient had a responsible position subjecting him to high pressures and deadlines in a show business associated company.

Physical examination was negative save for occasional premature beats. EKG revealed a sinus rhythm at 65, S1, S2, S3 syndrome and one sinus pause and one premature junctional beat.

At this point, the patient was begun on 20 mg of propanolol q6h. He had discontinued both propanolol and digitoxin 6 weeks previously.

One month later he reported very occasional palpitations. A continuous recording of lead 2 showed a heart rate of 55 with slight sinus arrhythmia and no premature beats at rest or with postural or respiratory maneuvers.

Two months later the patient reported only occasional palpitations which did not bother him much. His mood was better, and a long strip of lead 2 did not reveal any arrhythmias. Exercise test was performed to a maximum heart rate of 160 bpm at 3 min. 40 sec. at 900 kpm. There was no chest pain or dyspnea. The patient stopped because of generalized fatigue. No premature beats of any type were seen before, during or following excercise.

In this patient who had no clearcut signs of associated organic heart disease, reassurance and beta-blockade with propanolol partially suppressed the palpitations subjectively and was associated with their absence on repeated recordings at rest and during a maximal exercise procedure.

Case Report #3

[redacted] - First [redacted] admission for 18 year old [redacted] man with chief complaint: Non-specific abdominal pain. Pain for several weeks. Admitted for frequent PVC's. Asymptomatic except for occasional atypical chest pain, regular palpitations, and sometimes dizziness without passing out after strenuous exertion (runs a 10.3 100 yard dash on track team). P.E. normal with premature beats. CXR - normal. Routine lab - normal. ECG - Frequent unifocal PVC's with runs of quadrigeminy. Exercise test - stopped at 600 KPM because of asymptomatic ventricular tachycardia (3 consecutive PVC's seen twice). Maximum heart rate at this level 120/min. Started on diphenylhydantoin - no response. Switched to quinidine, and responded with resolution of arrhythmia. A repeat exercise test to 1050 KPM x 3 minutes without arrhythmia or ECG changes. Discharged on Quinidex 300 mg t.i.d.

DISCUSSION OF

GROUPED REFERENCES AND ILLUSTRATIVE DATA

A. Population studies - general

The historical notes on page 1 demonstrate that wisdom concerning the significance of an irregular pulse has been available for many centuries. The case reports on pages 2 and 3 describe conventional clinical approaches to the problem in our community. Nevertheless, the coronary care unit experience, the cumulative results of various population studies and improvements in methodology have focused on the problem of sudden death and the identification of asymptomatic individuals unusually susceptible to sudden death. It is now agreed upon that the bulk of sudden death is associated with advanced ischemic heart disease and that the mechanism is electrical and therefore potentially reversible. The precise electrical phenomena visualized to be the culprit in most cases is illustrated on the cover of this protocol.

That a palpable incidence of ventricular ectopic activity can be found in the general population by whatever technique employed is amply illustrated in the tables from the interesting book by Scherf and Schott on pages 1, 2, and 3 of Appendix A. A suggested grade of the severity of ventricular ectopic activity is on page 1, Appendix A.

The population studies cited further confirm the presence of both supraventricular and ventricular ectopic activity in ambulant asymptomatic populations. The incidence of this activity increases with age as does the complexity of the rhythms found. When this activity is unassociated with other clear evidences of organic heart disease, it is very difficult to demonstrate increased mortality by either insurance statistics or by recent, careful epidemiologic studies. The Tecumseh study, ref. 4, initially published evidence that the PVC was a good predictor of sudden cardiac death. This was apparently confirmed by the study of Hinkle, et al. ref. 5. Further analysis showed that in Tecumseh the PVC by itself was not as important as either other evidences of heart disease or the PVC in the setting of other evidences of heart disease, ref. 8. In Hinkle's study the sudden cardiac deaths occurred in patients who had upon initial examination strong evidence of organic heart disease or hypertension. The Framingham study, ref. 6, and a recent study in North Carolina, ref. 12, as well as more recent reviews from insurance statistics, ref. 9, appear to confirm the point of view that the PVC in a general, asymptomatic population is not a disproportionate predictor of subsequent sudden cardiac death unless a) the identified ventricular ectopic activity is complex, in which case b) there is usually associated evidence of organic heart disease or hypertension. The current interest of 12 insurance companies are summarized in Appendix A, page 3 and the rating system of a nationally-known Dallas based life insurance company is provided on pages 4 and 5 of Appendix A. An excessive expectation of mortality is indicated by the number 50 or greater. This latter is provided to demonstrate current business practices which seem on the basis of previously described data to be slightly biased in favor of the company in the category 3. Premature Contractions.

B. Interesting clinical observations and clues

These recent studies describe the association of R waves interrupting T waves almost invariably with serious overt heart disease and in such patients, a poor prognosis. The postextrasystolic T wave changes originally described by Levine, et al. ref. 12, have more recently been explained as a normal physiological phenomenon, ref. 15, which may be exaggerated in the presence of an abnormal myocardium.

Lamb described a variety of arrhythmias including ventricular ectopic activity associated with breath holding, hyperventilation and Valsalva maneuvers which can rarely result in or be associated with other arrhythmias leading to brief periods of cardiac arrest, ref. 13. See also Wildenthal, K; Fuller, DS and Shapiro, W: Paroxysmal atrial arrhythmias induced by hyperventilation. Am. J. Card. 21:436, 1968. Sleep is generally associated with a reduction in ventricular ectopic arrhythmia but not in every patient, ref. 16. Monitoring of unrestricted patients indulging in cigarette smoking did not reveal any dysrhythmic activity. Cardiac arrhythmias in sudden death have been associated with subarachnoid hemorrhage, ref. 18, and the interesting mechanisms involved are presented and discussed in ref. 72, 74, 80, 81, and 84. It is well known that emotion and psychologic pressure may enhance or bring out ventricular ectopic arrhythmia. These may complicate drug therapy and provide serious clinical problems. The interesting animal model experiments of Hockman, Mauck and Hoff have shown that electrical stimulation in discrete areas of the brain can produce sympathetically mediated reflexes (blocked by beta-blockade) leading to almost every clinically described arrhythmia.

Reference 19 discusses the frequency of ventricular ectopic activity in the mitral prolapse syndrome but could not correlate them with either symptoms or subsequent prognosis. They did note that the 24-hour ECG in this patient population was more sensitive in picking up ventricular ectopic activity than either exercise tests or conventional 12-lead ECG.

C. Ventricular ectopic activity in ischemic heart disease

In group studies of patients with ischemic heart disease, i.e. documented myocardial infarction, the presence of PVC's is going to have a positive correlation with death because they are very common in this population. The exact figure apparently will depend upon the technique of monitoring. The yield increases with the utilization of holter monitoring and exercise testing particularly maximal exercise testing. While the Coronary Drug Project Group, ref. 27, 29 have by sophisticated, statistical analyses demonstrated the PVC to have independent power in predicting subjects susceptible to sudden death, it does seem clear that increasing complexity of ventricular ectopic activity especially increased frequency, couplets, runs of ventricular tachycardia and R/T phenomena focus more sharply on the truly susceptible individual.

These findings in association with significant myocardial damage appear to increase the likelihood of subsequent sudden cardiac death, ref. 33.

The clinical challenge then becomes defined and has been well described by Dr. Lown (Am. J. Med. 46:705, 1969) and especially well in ref. 25. The major limitation surrounds the shortcomings of presently available therapy; and until safe, effective measures are available, the prophylactic employment of antiarrhythmic drugs will require more precise identification of the potential victims at highest risk. For any given individual, one must know which type of VPC is important, is the risk to the patient related to the condition under which ventricular ectopic activity is discovered by the physician, and if a certain VPB is important, is it a transient phenomenon or commonly present in the susceptible individual. If the ideal drug were available, it would be acceptable to treat many patients including large numbers who perhaps are not at high risk in order to prevent mortality in the included patients who were at high risk. However, in absence of the ideal drug the previous admonitions are still operative.

Selected supporting data are presented in Appendix A, pages 6-9.

D. Clinical observations in paroxysmal and sustained ventricular tachyarrhythmias (? pre-lethal) - outside of the CCU

Repeated observations by respected clinicians have described paroxysmal ventricular tachycardia occasionally recurring for many years in patients without identifiable heart disease, ref. 34-39. Idiopathic recurrent ventricular fibrillation has been described, ref. 40. This syndrome has a much more uncertain prognosis. Drug therapy has been felt to be effective in both types of syndromes. In 1952, Drs. Harvey and Levine postulated that this type of mechanism might be the explanation of death from fright - a particularly interesting possibility in the light of the neurophysiologic studies cited previously by Hockman, Mauck and Hoff. Dr. Charles Fisch, ref. 41, admonishes, however, that clinical diagnosis by conventional electrocardiography may at times be so fraught with error that when ventricular tachycardia is said to occur in the absence of heart disease, one should be suspicious of supraventricular tachycardias with aberrant conduction unless fusion beats, captures or HIS bundle studies demonstrate the accuracy of the diagnosis.

More recent experience from Seattle, ref. 42, with recurrent ventricular fibrillation further defines this syndrome. The salient features were that 73% of the patients who had recurrent ventricular fibrillation had clear evidence of ischemic heart disease. Of those who with their initial episode had had an associated myocardial infarction, 5% had subsequent ventricular fibrillation or sudden cardiac death while of 138 with "primary ventricular fibrillation" that is unassociated with an acute myocardial infarction, 31% had recurrent ventricular fibrillation or sudden cardiac death. Thirty-three percent of these episodes occurred within 12 weeks; the median time from the first episode was 20 weeks, the mean 28 weeks and the range 2-104 weeks.

Immediately prior to the episode, 33% had experienced low activity or sleep, 40% occurred during routine activity, 16% occurred in association with vigorous activity or high emotion(3 immediately after coitus), 4% during heavy alcohol consumption. Symptoms preceded the occurrence in 6 of 38 or 16% of the witnessed events. Dr. James Warren in a second editorial on this subject, ref. 43, points out once again that it is advantageous to have a myocardial infarction in association with an episode of ventricular fibrillation and that thus far trials of prevention of recurrence have not been successful (73% of those in ref. 42 had been under therapy though it might have been considered inadequate). Dr. Warren reiterates the call for better modes of treatment.

E. Exercise-induced VEA - in health and disease

Despite the admonition by Bourne, ref. 44, that "malignant" PVC's appeared with exercise and "benign" PVC's disappeared with exercise in 1927, ventricular ectopic activity has not become a standardized end-point in exercise testing. The early studies of Lamb and Hiss, ref. 48, demonstrated that in the main, normal persons developed PVC's at heart rates over 150. Recent studies have tended to confirm this impression in a rough fashion, see especially ref. 60. That exercise can be dangerous is amply demonstrated by the complications observed during training or jogging, ref. 53 and 54. In the athletic population cardiac death when it occurs during competitive stresses has usually been found to be associated with congenital or acquired cardiovascular abnormalities when examined at autopsy, ref. 56. Gooch and McConnell, ref. 55, have demonstrated the relative benignity of these arrhythmias in patients without cardiovascular disease as compared to those with cardiovascular disease when subjected to submaximal exercise testing. Astrand, ref. 50, has documented the increasing incidence with age upon stress testing. Blackburn and colleagues, ref. 53, suggest strongly that physical conditioning diminishes the incidence and complexity of premature ventricular complexes after physical conditioning at any given level of stress. This type of stress apparently can be safely applied to many patients after documented myocardial infarction prior to hospital discharge, ref. 64 and Appendix C. Studies correlating angiographic findings have illustrated the inability of the treadmill test to predict the location of coronary disease, ref. 66, but with increasing severity of coronary angiographically demonstrated lesions, the incidence and severity of VEA on exercise increases, ref. 65 and 68.

Exercise stress testing is vastly superior to routine electrocardiograms for the exposure of ventricular ectopic activity (ref. 69) and can provide useful information in population surveys, ref. 70, and in evaluating the status of patients with clinical disease, ref. 71, in a safe laboratory situation. While diagnoses based on ventricular ectopic activity revealed by exercise will be fraught with error, the normal patient will very rarely demonstrate high-grade VEA with exercise even at heart rates in excess of 150.

F. Mechanisms - Emphasizing

The literature concerning the electrophysiological bases for arrhythmias has exploded in the past 15 years. These references are designed to merely provide ready access to the literature and emphasize the little-known area and the possible role of the central nervous system and the concepts of re-entrant activity particularly as elucidated in the excellent articles by Han, ref. 77 and Surawicz, ref. 78 and Vassalle, ref. 79. The effects of ischemia are discussed in these articles. The effects of acute coronary occlusion in the animal model on the ventricular fibrillation threshold are described by Axelrod, et al., ref. 82, Lanigan, et al., ref. 83. One of several abstracts discussing the concept of the protective zone as developed in Dr. Lown's laboratory is included, ref. 83.

G. Treatment of VEA - mostly in disease

Basic concepts and drug interactions are discussed under Section I. In Section II, the potential importance of recent publications from Seattle and Boston are listed. Briefly, these investigators - Gey and his colleagues ref. 94, 95, 97 and Jelinek and his colleagues ref. 96 - have suggested that exercise stress testing be used to demonstrate the efficacy of drug therapy. In general, I think these are very important concepts. The results demonstrate the inadequacy of the drugs tested. The toxic effects of quinidine and pronestyl in maximum therapeutic dosage occurred more frequently than suppression of the arrhythmia for which they were prescribed. This type of work will have to be continued and applied to additional agents as they become available.

III. Beta-adrenergic blockers - exciting, but with careful patient selection dangers are evident

Patients must be carefully selected in order to avoid the toxic and potential lethal effects of beta-adrenergic blockers. While there is evidence that they suppress ventricular ectopic activity, ref. 106, there is conflicting evidence as to their efficacy in the prevention of sudden cardiac death in patients following acute myocardial infarction. Two recent reports on a beta-blocker alprenol, ref. 112 and 113, show initial promise for this alternate agent. Reference114 is an excellent discussion of clinical pharmacology of propanolol.

IV. Lidocaine - elegant in the CCU - are we ready to have it self-administered?

When administered intravenously, clearly an effective drug much closer to the ideal than other available agents. Oral absorption is poor so that it is unsuitable for long-term management of susceptible patients. Some authors are ready for studies that include self-administration to highly susceptible patients upon the development of symptoms and prior to their entry to hospital, ref. 117. A study of this sort would not be simple since it would require a large enough population of susceptible individuals over a long enough time to come to clinical significance. It would also require the mobilization of many community resources as amply outlined by Dr. Lown (Am. J. Med. 46:705, 1969 and ref. 25).

V. Procainamide

Despite its usefulness in the acute therapy of ventricular ectopic activity and its apparent usefulness in the coronary care unit, ref. 121, the drug is unsuitable for long-term out-patient management under most circumstances, ref. 122 and 124. See supporting data in Appendix A.

VI. Quinidine

A high incidence of toxicity with long-term therapy at doses designed to avoid toxic plasma levels. The bulk of this toxicity is non-cardiovascular. Nevertheless, quinidine syncope has been reported in approximately 4% of patients on conventional dosages (1.2 - 1.8 gm/day) and not always in association with high blood levels although Dr. Storstein, ref. 125, believes it is nearly always associated with high blood levels. Nevertheless, of the available drugs quinidine and the beta-blockers may be the safest in selected patients and with suitable monitoring, for the suppression of ventricular ectopic activity at the present time although the data in ref. 96 and 97 make it difficult to be enthusiastic.

VII. Surgical techniques. Carefully selected patients do benefit

It is becoming clear that appropriately selected patients may be cured by appropriate surgical procedures. In the light of these data and particularly that in ref. 135, one might well wish to perform suitable diagnostic studies for possible surgery in patients manifesting pre-lethal arrhythmias who might be suitable candidates for one of the several surgical procedures available.

VIII. Electricity - effective in CCU - possible for highly susceptible patients - if they can be identified and gadget proved safe

"Thump-version" has been effective in one of our post-myocardial infarction patients at home and on the wards, ref. 138. Mirowski and colleagues describe the potential efficacy of an implanted standby automatic defibrillator which is not yet available, ref. 139.

IX. Dilantin

In acute arrhythmias complicating ischemic heart disease, dilantin has been effective in a minority. Nevertheless, there is suggestive evidence from a collaborative study, ref. 142, that at less-than-therapeutic blood levels ventricular ectopic activity was suppressed although sudden death was not. A subset of these patients, however, suggested that with properly maintained therapeutic blood levels sudden death might conceivably be reduced in post-myocardial infarction patients. This probably requires further investigation.

X. Bretylium

Bretylium appears to be useful in selected situations.

XI. Mexiletine

Chronic oral administration at supposedly therapeutic plasma levels appears to be associated with toxicity in 50% or more of the patients.

XII. A probably not yet obsolete integrated approach to treatment and prevention in the susceptible patient

Dr. Lown and his colleagues provide an excellent discussion of ventricular tachyarrhythmias and their treatment. Their approach to prevention includes 1) ambulatory monitoring, 2) exercise stress, 3) the assessment of the efficacy of digitalis in selected patients, 4) testing the effect of antiarrhythmic drugs both for toxicity and for efficacy by stress testing and monitoring, 5) the realization that ultimate decisions concerning therapy might require a month or more of out-patient management, 6) attention to relevant psychologic problems.

H. Results of application of quantitative electrocardiography in a Beverly Hills cardiological office practice

The discussion by Dr. Bleifer and his colleagues, ref. 151, describes the technique of holter monitoring and the results obtained in the various clinical problems. While the data presented in this paper is highly selected, it does illustrate the value of the technique. The data is reasonably convincing in showing increasing incidence of ventricular tachycardia in association with increasing complexity of premature ventricular contractions.

The holter technique looking at 50 or 100,000 heart beats instead of the 70 beats or less seen on the conventional electrocardiogram or automated techniques performing the same function, ref. 31, have amply demonstrated the unreliability of conventional electrocardiography and conventional CCU monitoring techniques in picking up the entirety of the ventricular ectopic activity or for that matter, any other transient electrocardiographic changes that the patient may demonstrate. Thus, some attention will have to be paid by present and future investigators to the data base utilized for survey type and predictive type studies. Fortunately, the trends divined by simpler techniques seem to be in the main confirmed by these more sophisticated applications. However, the selection of patients susceptible to sudden death, the testing of the efficacy of various modes of therapy, the evaluation of which PVC is the most dangerous and under what circumstances for a given patient will undoubtedly require further applications of these techniques as well as associated computer aids.

SUMMARY

Ventricular ectopic activity can be graded into forms which have increasing danger to patients. The forms of ventricular ectopic activity seen in healthy, ambulatory populations and even during the stress of maximal and submaximal exercise testing is not associated with an increased risk of death in the absence of evidence of associated organic heart disease, hypertension or multiple risk factors for ischemic heart disease. Statistically, complex forms of ventricular ectopic activity are associated with increased risk of sudden cardiac death in patients with clear evidence of associated organic heart disease, hypertension and multiple risk factors.

Available modes of therapy are far from ideal in that they are associated with a high incidence of toxicity and a poor record of long-term suppression of ventricular ectopic activity.

The advice of Struthius, Heberden and Paul Wood as outlined on page 1 would seem applicable to the healthy patient presenting with ventricular ectopic activity. The rare patient with paroxysmal ventricular tachycardia and primary ventricular fibrillation will be an exception to this rule.

The selection of patients for therapy will generally be restricted to those with obvious signs of heart disease, usually ischemic heart disease, and presenting with easily elicited complex premature ventricular contractions, paroxsyms of ventricular tachycardia or ventricular fibrillation. The sophisticated and intensive approach to therapy outlined by Lown, ref. 150, would seem appropriate in such patients. Selection of any patient for therapy of ventricular ectopic activity considered potentially dangerous must be viewed in the light of the dangers and inadequacies of the presently available therapeutic agents.

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APPENDIX A. ILLUSTRATIVE DATA

Grading of Ventricular Ectopic Activity with 24 Hours Ambulatory Monitoring and with Treadmill Exercise

	Monitoring	Exercise
Grade 0	No arrhythmia	No arrhythmia
Grade 1	Isolated unifocal VPBs Less than 30/hr or 1/min	Isolated unifocal VPBs Less than 3/min
Grade 2	Isolated unifocal VPBs More than 30/hr or 1/min	Isolated unifocal VPBs More than 2/min
Grade 4	a.) couplets b.) ventricular tachycardia	a.) couplets b.) ventricular tachycardia
Grade 5	Early cycle VPBs	Early cycle VPBs

Ref. 32

INCIDENCE OF EXTRASYSTOLES AMONG THE GENERAL POPULATOIN, HOSPITAL PATIENTS GENERALLY AND CARDIAC PATIENTS

Number of Subjects	Number of Extra-systoles	Per Cent		Author
2,651	17	0·6	Isolated religious community. Ages over 15. Incidence about the same in men and women.	Goldbarg *et al.* (1970)
5,129	95	1·9	Tecumseh community. Only " frequent " extrasystoles, i.e. 10 per cent of beats or over. Ages 16 and over. More prevalent among men than women. Increasing with age in both sexes	Ostrander *et al.* (1965)
5,129	264	5·1	Tecumseh community. Follow-up	Chiang *et al.* (1969
500	12	2·4	Canadian Air Force Recruits	Stewart and Manning (1944)
1,000	15	1·5	American Air Force Recruits	Graybiel *et al.* (1944)
67,375	748	1·1	American Air Force Recruits (excluding parasystole)	Averill and Lamb (1960)
122,043	1,749	1·4	American Air Force Recruits. Complementing preceding study	Hiss and Lamb (1962)
5,124	194	3·8	Life Insurance Applicants	Leslie (1941)
10,000	1,503	15·0	Patients electrocardiographed 1914–1931 at Massachusetts General Hospital	White (1944)
25,000	3,034	12·0	Patients electrocardiographed 1934–1943 at Massachusetts General Hospital	White (1944)
16,810	—	1·0	Patients electrocardiographed 1940–1942 at Metropolitan Hospital, New York. Electrocardiograms are taken routinely	Scherf
12,473	286	2·3	General Hospital; medical cases	Laake (1949)
6,000	270	4·5	—	Unghváry (1938)
2,500	—	*ca.* 70	Patients examined for cardiac complaints. Extrasystoles either deduced from history or present on examination	Holzmann (1965)
500	—	*ca.* 20	Consecutive series referred to a Cardiographic Department	Campbell (1929)
66,707	3,359	*ca.* 5	Records obtained in a Cardiac Department. In 2,504 (3·8 per cent) of the total and 75 per cent of those with extrasystoles) associated with myocardial disease	Dreifus (1966)

Ref. 153

DISTRIBUTION OF EXTRASYSTOLES ACCORDING TO THEIR SITE OF ORIGIN

Number of Tracgs. exam'd	Number of Extrasystol.	Per cent	Ventr.	Per cent	Supraventric.	Ventr. and Supraventric.	Remarks	Author
1,000	15	1·5	8	53	7	0	Young healthy aviators	Graybiel *et al.* (1944)
500	12	2·4	9	77	3	0	Young healthy aviators	Stewart *et al.* (1944)
10,000	1,503	15·5	974	65	529	0	Patients in general hospital	White (1944)
25,000	3,304	12·1	2,007	66	1,027	0	Patients in general hospital	White (1944)
12,473	286	2·3	181	64	105		Patients in general hospital	Laake (1949)
6,000	216	3·6	98	45	57	61	Hospital patients	Unghváry (1938)
3,269	251	6·8	167	67	84		Only cases without organic heart disease	Nathan (1949)
?	194		120		61	6	Only cases with extrasystoles examined. In 7 cases origin undetermined	Leslie (1941)
500	114	22·8	70	61	44		Patients of a Cardiographic Department	Campbell (1929)
5,600	86	1·5	52	60			Children under 16 attending cardiac clinic	Landtman (1947)
?	1,142		758	66	384	0	Only cases with extrasystoles examined	Ungerleider and Gubner (1942)
24,000	398	1·9	141	62	38	49	Only in 228 cases extrasystoles classified	Dauwe (1938)
941	160	17·0	74		60		Only patients over 51. In 26 cases origin of extrasystoles undetermined	Martínez (1949)
300	38	12·6	15	39	19	4	Ambulatory patients over 60. 55·6 per cent were 70–79	Fox *et al.* (1942)
100	20	20·0	15	75	5	0	Patients over 70	Eliaser and Kondo (1941)
315	108	34·2	57	53	51	0	Patients aged 75–96 without cardiac disease	Willius (1931)
385	123	31·9	83	68	40	0	Patients aged 75–96 with cardiac disease	Willius (1931)
700	231	33·0	140	60	91	0	Total of Willius' series	
100	31	31·0	10	32	21	0	Patients aged 80–103. Averaged age 84·2	Wosika *et al.* (1950)
?	850		526	62	321	0		Holzmann (1960)
67,375	748	1·1	419	56	329	0	Air Force recruits (excl. parasystole)	Averill and Lamb (1960)
122,043	1,749	1·4	952	55	797	0	Air Force recruits	Hiss and Lamb (1962)
2,042				*ca.* 9 of total	*ca.* 6·3 per cent of total		Series incl. 662 patients with cardiovascular disease and 188 with hypertension	Nohara (1962)
1,070	105	9·8		*ca.* 83	*ca.* 17		In 36 patients (34·3 per cent) extrasystoles were assoc. with organic heart dis., in about one third with tension and anxiety	Foley and Yee (1963)
5,129	264	5·1	185	70	79	0	Tecumseh community	Chiang *et al.* (1969)

INCIDENCE OF EXTRASYSTOLES IN MIDDLE AND OLD AGE

Age Group	Number examined	Number with Extrasystoles	Per cent	Remarks	Author
Over 51	941	160	17	52 per cent aged 51–60	Martínez (1949)
Over 60	300	38	12·6	Ambulatory patients	Fox *et al.* (1942)
60–90	102	9	8·8	Non-cardiac patients	Taran and Kaye (1942)
Over 70	100	20	20	" " "	Eliaser and Kondo (1941)
Over 70	100	23	23	" " "	Levitt (1939)
Over 70	100	28	28	" " "	McNamara (1949)
75–96	700	231	33	108 without, 123 with cardiac disease. *See also* Table 15–8	Willius (1931)
80–103	100	31	31	Consecutive cases. Average age 84·2	Wosika *et al.* (1950)
65–100	602	150	24·9	216 men, 386 women	Taran and Szilagyi (1958)

Ref. 153

INCIDENCE OF EXTRASYSTOLES IN CHILDREN

Type of Group	Number exam'd	Number with Extra-systoles	Per cent	Remarks	Author
Normal children	2,672		2·2		Lyon and Rauh (1939)
	259	2	0·8		Shokhooff and Taran (1938)
	100	1	1		Perry (1931)
	100	2	2		Hafkesbring *et al.* (1927)
Schoolchildren	1,782	40	2·2	Ages: under 10 to 19	Lyon and Rauh (1939)
Children amongst patients of all ages with extra-systoles	226	7	3·1	Ages: 10 to 19	Cowan and Ritchie (1922)
	100	3	3	up to 14	Smith (1924)
Hospital patients generally	1,000	48	4·8	Diagnosis made only by clinical impression	Visco (1911)
	400	0	0		Antell (1921)
Children attending cardiac clinic	5,600	86	1·53	Children under 16. In most cases predisposing factor present, e.g. infection. Good prognosis. Includes 200 normal controls	Landtman (1947)
	782	35	4·4	Ages 2½–14½	Lyon and Rauh (1939)
Children with cardiac disease	100	1	1	Rheumatic heart disease	Drawe *et al.* (1937)
	100	0	0	Congenital heart disease	Drawe *et al.* (1937)
	468		4·3		Lyon and Rauh (1939)

What 12 insurance companies are interested in

Company	Number of es per minute	Runs of es	Age of patient	Persistency	Rate of basic rhythm	Appearance or disappearance after exertion	Multiform es	Changes in T waves of post-extrasystolic beat
A			+					
B			+			+		
C	+		+					
D			+	+		+	(+)	(+)
E							+	
F	+		+			+	not now	
G	+	less now	(+)					
H			+			+	+	+
I	+		+			+		
J		+	+			+	+	?
K	+		+			+	+	+
L	+					+		

es = extrasystoles (+) = postpone ? = probably of some influence on rating

Ref. 153

HEART DISORDERS – (Continued)

The following factors may vary these ratings: age and sex of applicant, history of chest pain, other cardiovascular abnormalities and whether or not there has been progressive deterioration or long periods of stabilization of the electrocardiogram.

2. Arrhythmia not listed elsewhere.

   To include sino-auricular block, A-V nodal rhythm and wandering pacemaker.

   Sinus arrhythmia – a change in pulse rate associated with respiration. Found in most healthy children and young adults. If noted in applicants over age 50, an electrocardiogram should be obtained; otherwise, disregard.

   Sino-auricular block and a wandering pacemaker may indicate cardiac pathology and should be evaluated by the Medical Director.

3. Premature Contractions
   a. Supraventricular
   c. Ventricular

   If the premature contractions decrease, remain the same or do not increase by more than three per minute;

AT REST:	Under age 50	Over age 50
1 - 10	0	25
11 - 20	25	75
21 - 30	75	150
Over 30	150	200 to Decline

Robitz

   If the premature contractions appear or increase by more than four following exercise (single premature beat may be disregarded):

AT REST:	Under age 50	Over age 50
2 - 10	50	75
11 - 20	75	150
21 - 30	150	250
Over 30	250	350 to Decline

   d. Unusual

   This group includes such changes as bigeminy, trigeminy, multiple foci, ST or T wave changes in post-extrasystolic beats, or other unusual features.

   [illegible] Add +50 - up to other debits

5. Paroxysmal Tachycardia
   a. Supraventricular

   A sudden attack of rapid, regular, increased pulse rate varying in duration from a few hours to several days. It starts and ends suddenly and is generally recognized by the individual.

   APS – Electrocardiogram at H.O. discretion
   No WP or ADB if rated over +100.

   Few short attacks per year (less than four attacks and duration less than 12 hours).

Last attack within 2 years	0 - 50
3rd year and later	0

   More frequent (more than four attacks per year) or duration of attack greater than twelve hours.

Last attack within 2 years	50-100-up
3rd year and later	0

HEART DISORDERS – (Continued)

b. Ventricular
Within 2 years — Postpone
2 years and later — 200-up

7. Auricular Flutter or Fibrillation

A totally irregular irregularity of the pulse which may be constant or paroxysmal.
Present — Decline
History of
Less than four episodes of less than one day duration, no other cardiac abnormality

	Under age 40	Over age 40
Within 1 year	150-Decline	Usually Decline
2nd year	75-150	200-Decline
3-5 years	50-75	100-200
6-10 years	0-50	50-100
11th year and later	0	0

More frequent or of longer duration — RMD

8. Auriculoventricular Block
a. Incomplete block

Pulse rate under 95 on electrocardiogram:

PR Interval	Under age 50	Over age 50
0.21–0.25	50	75
0.26–0.29	75	150
0.30 and over	150	250

If condition stable for 5 years, decrease above debits by 1/3; if stable for 10 years, decrease debits by 1/2. If PR interval has been progressively increasing, add + 50 to decline depending upon degree and age.

Pulse rate over 95 with PR interval greater than 0.23 seconds — RMD

b. Incomplete block with dropped beats

	Under age 50	Over age 50
Occasional dropped beats	Add +25 to the above ratings	
Wenkebach Phenomena (MOBITZ I)	50	50
Atrial: Ventricular beats; PERIODIC DROPPED VENTRICULAR BEATS (MOBITZ II):		
4:3 BLOCK	150	250
2:1 BLOCK	200	300-Decline
3:1 and over BLOCK	Usually Decline	Decline

c. Complete Block (3rd degree block)
With or without history of Stokes-Adams Syndrome — Usually Decline

(Heart block with other cardiac impairments should be referred to the Medical Director for Individual Consideration.)

9. Wolff-Parkinson-White Pattern
False bundle branch block. Frequently associated with increased susceptibility to paroxysmal tachycardia.

	Under age 35	Age 35 and over
No episodes of tachycardia	25-50	50-75
History of tachycardia	75-100	100-175

*Mortality of Individuals with Extrasystoles without Other Abnormalities**

Type of extrasystole	Entrants	Actual deaths	Expected deaths	Ratio actual to expected deaths
Supraventricular				
Simple	83	15	12.69	118%
Complex	39	6	6.22	96%
Ventricular				
Simple	359	56	59.79	94%
Complex	123	21	17.34	121%
All	604	98	96.04	102% (83% to 123%)†

*Standard insurance risks in the absence of extrasystoles.
†95% confidence limit.

*Mortality of Individuals with Ventricular Extrasystoles and Other Abnormalities**

Type of other abnormality	Entrants	Actual deaths	Expected deaths	Ratio actual to expected deaths
Rating for blood pressure and/or cardiac condition	42	15	6.70	223%
No rating for blood pressure or cardiac condition	44	8	6.10	131%
All	86	23	12.80	180% (114% to 269%)†

*Rated up to 195% expected mortality for conditions other than extrasystoles.
†95% confidence limit.

Mortality of Individuals with Extrasystoles without Other Abnormalities by Response to Exercise

Issue age (years)	Entrants	Actual deaths	Expected deaths	Ratio actual to expected deaths
	Decreased or Remained Same after Exercise			
Under 45	181	19	24.40	78%
45 and over	90	29	21.43	135%
All	271	48	45.83	105% (75% to 135%)
	Increased			
Under 45	46	5	7.74	65%
45 and over	16	5	2.71	185%
All	62	10	10.45	96% (43% to 180%)*

*95% confidence limit.

An insurance study

Ref. 9

Population Studies

Relationship of Selected Antecedent ECG Abnormalities to Incidence of Sudden Death in the Tecumseh Population (30 Years of Age or Older)

ECG findings	Minnesota code	No. sudden death		No. observed in total population		Six-year incidence of sudden death per 1,000 population
Bilateral BBB syndrome	$II_1 + VII_2$	3	(68.6)*	4	(69.3)	750
Left BBB	VII_1	5	(59.6)	18	(63.2)	277
Old myocardial infarction	I_1	5	(62.6)	26	(60.5)	192
Ventricular premature beats	$VIII_1$	10	(65.1)	165	(57.6)	61
Left ventricular hypertrophy	III_1	6	(74.1)	124	(58.1)	48
First degree A-V block	VI_3	3	(57.6)	100	(53.4)	30
Normal ECG (no codable items)	None	7	(49.8)	2,700	(45.3)	2.6

*( ) Mean age in years of the group.

Tecumseh 1970
Ref. 8

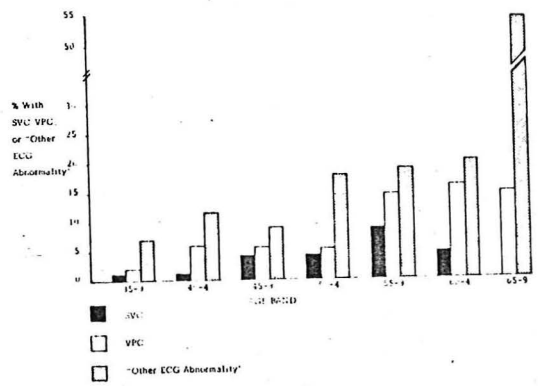


Figure 1

Prevalence of SVC, VPC, and other ECG abnormalities by 5-year age bands in Canton study.

Ref. 12

Relative Risk of Mortality Associated with Various ECG Abnormalities for Age Band 50–59

ECG abnormality	1-hour SD	24-hour SD	All CHD deaths
VPC (with or without "other ECG abnormality") (N = 29)	1.5	2.4	1.8
"Other ECG abnormality" (with or without VPC) (N = 57)	1.2	2.3	2.5
VPC without "other ECG abnormality" (N = 25)	0.9	2.6	1.6
"Other ECG abnormality" without VPC (N = 53)	0.8	2.4	2.5
VPC and "other ECG abnormality" (N = 4)	5.4	5.4	3.3

Abbreviations: SD = sudden cardiac death; CHD = coronary heart disease.

Ref. 12

Table 1.—Mortality According to Ectopic Beat Characteristics*

Ectopic Beat Characteristics*	Number of Men	Total Mortality No.	Total Mortality %	Sudden Coronary Deaths No.	Sudden Coronary Deaths %
All men with base-line ECG	2,035	256	12.6	111	5.5
No ectopic beats	1,764	198	11.2	87	4.9
Any ectopic beat	271†	58	21.4†	23	8.5‡
No VPB	1,800	205	11.4	88	4.9
VPB any, no SVPB	221	48	21.7§	23	10.4§
VPB 1-9/100 beats, no SVPB	177	37	20.9§	16	9.0‖
VPB ≥10/100 beats, no SVPB	44	11	25.0‖	7	15.9§
VPB any	235	51	21.7§	23	9.8§
VPB 1-9/100 beats	190	40	21.1§	16	8.4
VPB ≥10/100 beats	45	11	24.4‖	7	15.6‖
No SVPB	1,985	246	12.4	110	5.5
SVPB any, no VPB	36	7	19.4	1	2.8
SVPB 1-9/100 beats, no VPB	28	5	17.9	1	3.6
SVPB ≥10/100 beats, no VPB	8	2	25.0	0	0
SVPB any	50	10	20.0	1	2.0
SVPB 1-9/100 beats	38	8	21.1	1	2.6
SVPB ≥10/100 beats	12	2	16.7	0	0
VPB alone	221	48	21.7	23	10.4
VPB plus SVPB	14	3	21.4	0	0
VBP not in pairs or runs	225	47	20.9	22	9.8
VPB in pairs or runs	10	4	40.0	1	10.0
VPB uniform	196	43	21.9	20	10.2
VPB multiform	39	8	20.5	3	7.7
VPB uniform pairs	8	4	50.0	1	12.5
VPB multiform pairs	2	0	0	0	0
VPB, right ventricular	63	14	22.2	3	4.8
VPB, left ventricular	68	15	22.1	9	13.2
VPB, origins in both ventricles	18	3	16.7	1	5.6
VPB, undetermined origin	86	19	22.1	10	11.6
No postectopic negative T-wave change	257	56	21.8	22	8.6
Postectopic negative T-wave change	14	2	14.3	2	14.3
VPB, compensatory	221	48	21.7	23	10.4
VPB, interpolated	14	3	21.4	0	0
VPB, not bigeminy	231	50	21.6	23	10.0
VPB, bigeminy	4	1	25.0	0	0
VPB without bizarre QRS	141	29	20.6	13	9.2
VPB with bizarre QRS	94	22	23.4	10	10.6
Not fusion beats	227	47	20.7	21	9.3
Fusion beats	8	4	50.0	2	25.0
T-R′ interval <0.20 sec	51	16	31.4	6	11.8
T-R′ interval ≥0.20 sec	171	33	19.3	20	11.7
SVPB without aberrant conduction	47	9	19.1	1	2.1
SVPB with aberrant conduction	3	1	33.3	0	0
SVPB, uniform	43	9	20.9	1	2.3
SVPB, multiform	7	1	14.3	0	0

*Three-year follow-up in Coronary Drug Project. There were 256 deaths in 2,035 placebo treated men. VPB indicates ventricular premature beats; SVPB, supraventricular premature beats.
†$P < .01$ compared to deaths when no ectopic beat was present.
‡$P < .05$ compared to deaths when no ectopic beat was present.
§$P < .01$ compared to deaths when no VPB was present.
‖$P < .05$ compared to deaths when no VPB was present.

Table 3.—Prognostic Value of Ectopic Beat Characteristics*

Ectopic Beat Characteristic	t-Value	t-Value Adjusted for Age	t-Value Adjusted for Age and for 6 Primary Risk Factors†	t-Value Adjusted for 20 Clinical Risk Factors‡	t-Value Adjusted for 31 Combined Risk Factors§
VPB, any (≥1/100 beats)	4.22 (2.53)	4.03 (2.43)	3.91 (2.37)	2.93 (1.92)	2.64 (2.08)
VPB, exact frequency (per 100 beats)	2.62 (1.70)	2.51 (1.65)	2.55 (1.66)	2.04 (1.49)	1.74 (1.35)
VPB plus runs and T-R′ interval	5.10 (3.11)	4.94 (3.03)	4.89 (3.01)	4.19 (2.72)	3.86 (2.79)

*There were 248 deaths among 1,971 placebo-treated patients during this three-year follow-up by The Coronary Drug Project. Numbers in parentheses are t-values for the relationship of ventricular premature beats to 105 sudden coronary deaths.
†Levels of cholesterol, triglyceride, 1-hr glucose tolerance, systolic blood pressure, relative weight, cigarette usage.
‡Six factors of previous column, *plus* age, race, Coronary Drug Project risk class, number of prior infarcts, interval from last myocardial infarction, New York Heart Association class, congestive failure, roentgenographic heart size, use of digitalis or diuretics, angina pectoris, intermittent claudication, physical inactivity, serum uric acid level.
§Clinical factors of previous column *plus* 11 electrocardiographic findings, Q-QS waves, ST-segment depression, negative T waves, ST-segment elevation, heart rate, abnormal axis, high left R waves, atrioventricular conduction defect, ventricular conduction defect, atrial fibrillation, VPB and SVPB.

Ref. 29

After myocardial infarction, Davis, CA. 1975

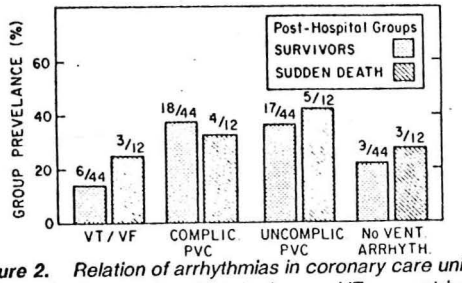


Figure 2. *Relation of arrhythmias in coronary care unit to sudden death after hospital discharge. VT = ventricular tachycardia; VF = ventricular fibrillation; complic = complicated; uncomplic = uncomplicated; PVC = premature ventricular contractions; vent. arrhythm. = ventricular arrhythmias.*

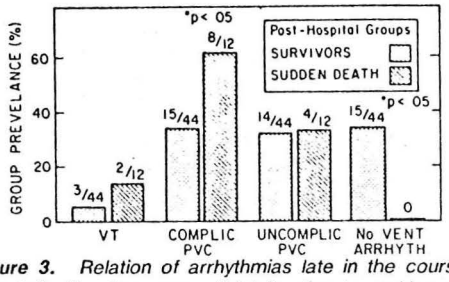


Figure 3. *Relation of arrhythmias late in the course of hospitalization for myocardial infarction to sudden death after hospital discharge.*

Ref. 33

Observations During Exercise

ncidence of Ventricular Arrythmias Observed During Maximal Treadmill Exercise Testing

Age Group (yr)	Patients Studied (no.)	All VPC	Frequency of VPC		Paired VPC	Multifocal VPC	Ventricular Tachycardia
			Occasional	Frequent			
25–34							
N	266	77 (29%)	55 (70%)	22 (30%)	6 (2.2%)	3 (1.1%)	1 (0.4%)
CVD	16	7 (44%)	3 (43%)	4 (57%)	0	0	0
35–44							
N	237	81 (34%)	55 (68%)	26 (32%)	11 (5.0%)	8 (3.4%)	4 (1.7%)
CVD	46	25 (54%)	13 (52%)	12 (48%)	6 (13.0%)	3 (6.5%)	2 (4.4%)
45–54							
N	58	25 (43%)	12 (48%)	13 (52%)	3 (5.0%)	1 (1.8%)	1 (1.8%)
CVD	27	13 (48%)	4 (31%)	9 (69%)	3 (11.0%)	3 (11.0%)	3 (11.0%)

CVD = patients with definite or suspected cardiovascular disease; N = normal subjects; VPC = ventricular premature complexes.

Heart Rate at Time of Appearance of Ventricular Premature Complexes During Exercise Testing

Age Group (Yr)	Heart Rate	
	<150/Min	≥150/Min
25–39		
N	28 (24%)	88 (76%)
CVD	15 (70%)	7 (30%)
40–54		
N	17 (25%)	50 (75%)
CVD	14 (60%)	9 (40%)

Abbreviations as in Table IV.

Ref. 60

Observations during exercise and after conditioning

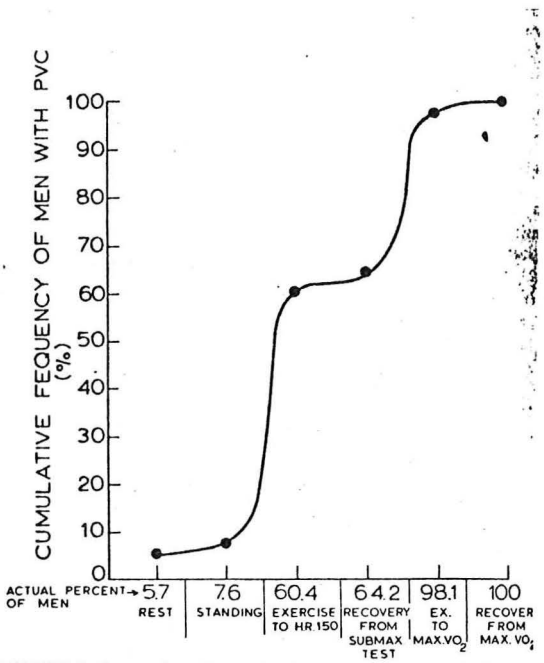


FIGURE 3. Proportion of men having premature ventricular contractions detected at various stages of a progressive stress test.

Ref. 63

Change in Frequency of Premature Ventricular Contractions (PVC) Associated with the Physical Conditioning Program (Penn State, First versus Final Round)

	Men with PVC During Submaximal Test (no.) (first round)	Men with Reduced Frequency of PVC (no.) (final round)	Men with Same or Greater Frequency of PVC (no.) (final round)
Exercise group (no. = 49)	19	15	4
Control group (no. = 49)	16	8	8

$\chi^2 = 3.203$; $P = 0.07$

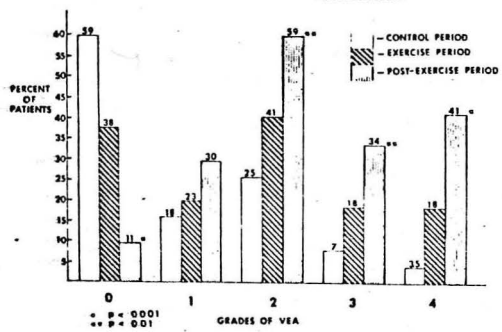
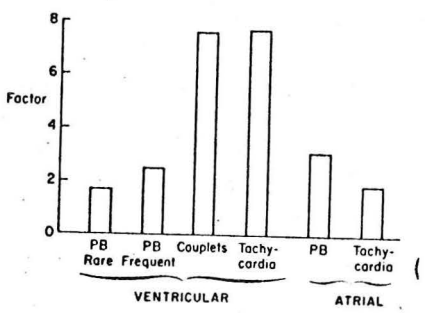


Figure 1. Distribution of Grades of Ventricular Ectopic Activity (VEA) during Three-Minute Control, Exercise and 10-Minute Post-exercise Recovery Periods in 56 Patients with Coronary Heart Disease Exhibiting Arrhythmia with Exercise.



Importance of monitoring post-exercise rest period Ref. 32

Factor by which exercise increases arrhythmic activity Ref. 69

[redacted] Comparison of Exercise Response in 66 CHD Males, Matched for Maximum Heart Rate, 33 of Whom Terminated Exercise Because of Angina and 33 Because of Fatigue

Basis for Stopping Exercise	Age (yr)	Duration of Exercise (min)	Maximum Heart Rate (beats/min)	VEA		
				Any VPB	Frequent VPB	Couplets/VT
Angina pectoris	57	5.2	133	8 (24.2%)	2 (6.1%)	0
Fatigue	56	6.3	133	11 (33.3%)	4 (12.1%)	2 (6.1%)

[redacted] Comparison of Exercise Response in Two Age-matched Subgroups Each Consisting of 64 men*

Clinical Subgroup	Age (yr)	Duration of Exercise (min)	Maximum Heart Rate (beats/min)	VEA		
				Any VPB	Frequent VPB	Couplets/VT
Normal	49	11.2	165	12 (18.8%)	2 (3.1%)	1 (1.6%)
CHD	49	8.3	149	24 (37.5%)	15 (23.4%)	4 (6.3%)

*The CHD patients stopped exercise because of fatigue.

[redacted]. Reproducibility of Ventricular Arrhythmias in 27 Patients Who Had More Than One Exercise Test

Grade of Arrhythmia	Patient	Test No.	Test With Specific Arrhythmia	Reproducibility*
VT/couplets	3	15	9	6/12 = 50%
VT/couplets/frequent VPBs	10	50	25	15/40 = 37.5%
Total VEA†	16	72	33	17/56 = 30%

*No. of tests with arrhythmia − no. of identifying tests for specific arrhythmia ÷ total tests − no. of identifyin specific arrhythmia.

†Ventricular ectopic activity.

Comparison of Conventional Electrocardiographic Monitorin with Automated Arrhythmia Analysis for Detection of Arrhythmias in 31 Coronary Care Unit Patients with Acute Myocardial Infarction

Arrhythmia	Conventional ECG Monitor		Automated Arrhythmia Detection Systen	
	no. of Pa-tients	% of Total	no. of Pa-tients	% of Total
Premature ventricular contractions (PVC)	20	64.5	31	100
Serious ventricular arrhythmias	5	16.1	29	93.5
Multifocal PVC	2	6.5	27	87.1
Consecutive PVC	4	13.0	24	77.4
PVC >5/min	3	9.7	8	25.8
Bigeminy	2	6.5	7	22.6
"R on T" phenomenon	1	3.2	4	13.0
Ventricular fibrillation	1	3.2	1	3.2
Premature atrial contractions	14	45.2	30	96.8
A-V dissociation with junctional rhythm or idioventricular tachycardia	0	0	5	16.1
Atrial fibrillation	2	6.5	2	6.5
Asystole	1	3.2	1	3.2
Complete heart block	1	3.2	1	3.2
Junctional tachycardia	1	3.2	1	3.2

The importance of technics is illuminated by this comparative study from Cincinnati

Ref. 31

[redacted]. Details of Patients With PVT and Normal Hearts

SEX	AGE	PRECIPITATING FACTORS	TYPE OF PVT
M	15	Emotional excitement	Persistent
M	21	Emotional excitement	Intermittent
F	56	Severe diarrhea of unknown origin	Intermittent
M	49	Surgical removal of chromophobe adenoma of pituitary gland under general anesthesia with ether and Pentothal	Persistent
M	23	Consumption of 15 cans of beer	Intermittent
M	39	Hypokalemia in a patient with nephrosis	Intermittent

Many cases of this sort are now questioned, but the original observers were often brilliant clinicians

Ref. 37

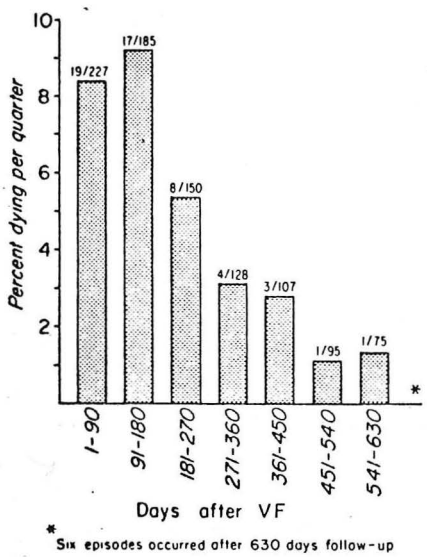


Figure 1. Per Cent Recurrent Ventricular Fibrillation or Sudden Death (or Both) per Quarter after Resuscitation from a Previous Episode of Out-of-Hospital Ventricular Fibrillation (VF).

Fifty-nine episodes occurred in 228 patients with known status on June 1, 1974. The fractions above each bar indicate:

$$\frac{\text{no. of episodes of fibrillation or sudden death per quarter}}{\text{no. of survivors followed and alive at mid quarter.}}$$

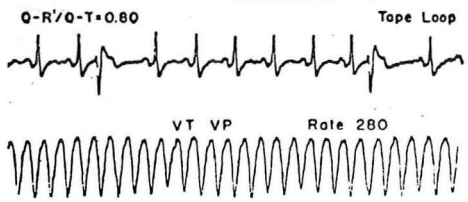


Fig. 5. In patients with acute myocardial infarction early extrasystoles trigger $VT_{(VP)}$, analogous to the disorder produced in animals.

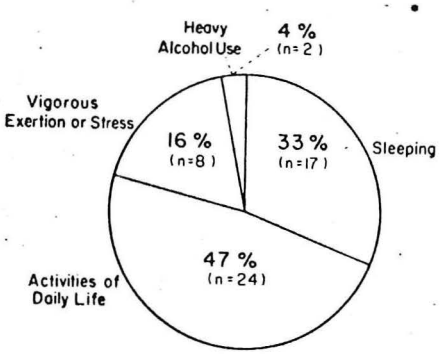
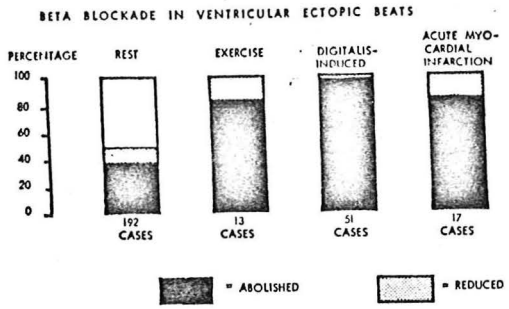


Figure 2. Activity at the Time of Recurrent Ventricular Fibrillation or Sudden Death (or Both) in 51 Episodes.

In 13 cases activity immediately before circulatory arrest could not be determined.

In recurrent ventricular fibrillation a myocardial infarction may be of value

Ref. 42, 43



–Summary of the effects of beta-adrenergic blockade on ven beats.

Ref. 106

Course of 39 Patients Receiving Procaine Amide

Course	No. of pts
Early reactions	9
Late reactions	14
Stopped drug without symptoms	7
Death on therapy	1
Remaining on drug 18 months	8
Total	39

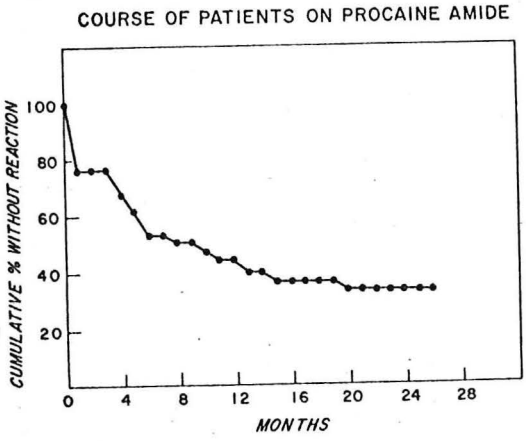


Figure 1

Time course of toxic reaction in patients on prolonged procaine amide therapy.

The problem of procaine amide

Ref. 124

Arrhythmias in First 6 Months of Study

Group	Pts monitored	Frequent VPB's	Couplets or VT	
Control	23	12	6	$P < 0.10$
Procaine amide Rx	21	10	1	
Procaine amide D/C	12	9	2	

Abbreviations: VPB = ventricular premature beat; VT = ventricular tachycardia; D/C = discontinued.

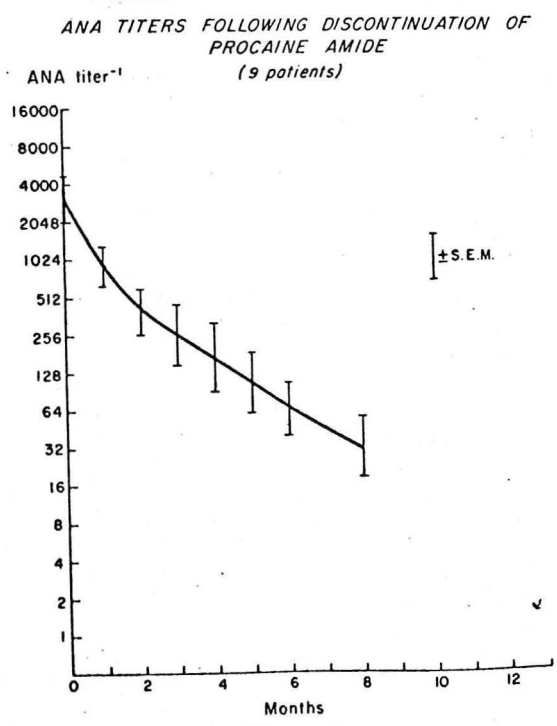


Figure 5

Time course of ANA titer following discontinuance of procaine amide in nine patients. The mean value returns to normal (<1:32) 8 months after stopping therapy.

Summary of 10 Quinidine Reactions

Cases	Previous use of quinidine	Known drug allergy	Other background information	Cumulative dosage of quinidine this course, Gm.	Total dosage day of syncope, Gm.	Quinidine blood level, mg.-L	Syncope hours after last dose	Number of attacks	ECG during attack	ECG quinidine effect	ECG quinidine toxicity	Rhythm after recovery	Digitalis maintenance
1 [redacted]	None known	Sulfonamides	History of syncopal attacks	3.8	1.6	–	3½	1	Ventricular fibrillation	0	0	–	+
2 [redacted]	None known	None	–	4.4	2.0	–	6½	1	–	+	0	Sinus rhythm	+
2 [redacted]	1 course	None	–	4.4	0.4	–	3	1	Ventricular flutter	+	Premature ventricular contractions	Sinus rhythm	+
3 [redacted]	None known	None	Ventricular irritability for years	0.9	0.8	–	3½	1	Ventricular fibrillation	0	0	Sinus rhythm	+
4 [redacted]	None known	None	History of epilepsy; on Dilantin	7.4	2.0	16.2	1	11	Ventricular fibrillation	0	0	Atrial fibrillation	+
5 [redacted]	1 course	None	–	6.0 + 4.0 procaine amide	1.2 + 0.75 procaine amide	2.8	2½	10	Ventricular flutter	0	0	Atrial fibrillation	+
6 [redacted]	4 or 5 courses	Ephedrine	–	5.8 + 6.0 procaine amide	0.8 + 1.0 procaine amide	6.8	3	4	–	+	0	Sinus rhythm	+
7 [redacted]	None known	Penicillin	–	22.2	2.4	20.5	2	1	–	+	0	Atrial fibrillation	+
7 [redacted]	1 course	Penicillin	–	1.2	0.8	6.3	3	1	–	0	0	Atrial fibrillation	+
8 [redacted]	4 courses	None	–	2.4 quinidine gluconate	0.9 quinidine gluconate	4.0	2	5	Ventricular flutter	+	Premature ventricular contractions	Sinus rhythm	+

Result of Antiarrhythmic Therapy Against Ventricular Ectopic Activity in 23 Patients

	Procaine amide						Quinidine					
	3.0 g/day			6.0 g/day			1.2 g/day			1.8 g/day		
Pts.	Effective	Toxic	Serum level mcg/ml	Effective	Toxic	Serum level mcg/ml	Effective	Toxic	Serum level mcg/ml	Effective	Toxic	Serum level mcg/ml
1	No	No	4.4	Yes	+++	7.0	Yes	No	3.3	—	—	—
2	Yes	No	6.8	—	—	—	No	No	4.6	Yes	No	8.6
3	No	+	6.4	No	++	11.6	No	+++	—	—	—	—
4	No	No	4.0	Yes	++	10.9	No	+++	—	–	—	—
5	No	No	6.0	No	No	10.1	No	+	5.6	—	—	—
6	No	No	4.4	Yes	No	8.6	Yes	No	3.4	—	—	—
7	Yes	No	2.9	—	—	—	Yes	No	2.7	—	—	—
8	No	No	8.5	—	—	—	No	+	3.4	No	+	4.7
9	—	+++	—	—	—	—	No	++	3.3	No	+++	—
10	No	No	5.8	No	No	14.9	—	—	—	No	No	3.7
11	No	+	4.1	No	+	9.4	No	No	1.4	No	No	2.7
12	No	No	6.4	No	No	10.9	No	No	2.7	No	++	3.6
13	Yes	No	5.0	—	—	—	No	No	3.0	Yes	No	5.0
14	No	No	—	No	No	16.5	No	+	1.2	No	No	4.6
15	No	No	3.6	No	++	9.0	No	+	1.3	—	—	—
16	No	No	—	No	+++	—	No	No	1.9	Yes	+	4.2
17	No	No	3.2	Yes	+++	9.4	No	No	4.7	No	No	5.1
18	No	+	3.1	No	++	4.4	No	+	4.4	No	+++	9.7
19	Yes	++	11.5	—	—	—	—	—	—	Yes	No	3.2
20	No	No	2.2	No	+	4.4	No	No	2.6	No	No	5.0
21	No	+	7.5	No	+++	—	No	No	0.2	No	+	5.2
22	No	++	4.1	—	—	—	No	No	2.7	No	+	3.2
23	No	+	4.8	No	No	8.4	No	No	1.4	No	No	2.9

The danger of quinidine, above, Ref. 129. Neither quinidine nor procaine were effective during exercise, Ref. 96

Mechanisms for cardiac arrhythmias

I. Abnormal automaticity	*II. Abnormal conduction*	*III. Coexisting abnormalities of automaticity and conduction*
A. *Site of impulse initiation* 1. Normal (sinoatrial node) 2. Abnormal a. Atrial specialized fibers b. A-V junctional fibers c. His-Purkinje fibers d. Atrial fibers in A-V valves B. *Normal automatic mechanism* 1. Abnormal Rate a. Tachycardia b. Bradycardia 2. Abnormal rhythm a. Premature impulses b. Delayed impulses c. Absent impulses C. *Abnormal automatic mechanisms* 1. Afterdepolarizations 2. Incomplete repolarization 3. Other a. Oscillatory depolarizations at low membrane potential b. Other	A. *Causes of impaired conduction* 1. Partial depolarization 2. Incomplete repolarization 3. Reduced responsiveness 4. Anatomical discontinuity 5. Abnormal response B. *Slowing and block* 1. Sinoatrial block 2. Atrioventricular block 3. His bundle block 4. Bundle branch block 5. Purkinje fiber block C. *Unidirectional block & reentry* 1. Ordered reentry a. Sinoatrial node and junction b. A-V node and junction c. His-Purkinje system d. Purkinje fiber-muscle junction e. Abnormal A-V connections (WPW) 2. Random reentry a. Atrial muscle b. Ventricular muscle	A. *Phase 4 depolarization & impaired conduction* 1. Specialized cardiac fibers B. *Abnormal automaticity & impaired conduction* 1. Specialized cardiac fibers a. Afterdepolarizations b. Other 2. Other cardiac fibers C. *Parasystole*

Ref. 90

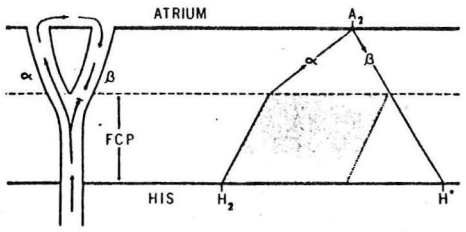


Figure 2. Mechanism of Reciprocal Beats. (Adapted From Moe and Mendez[1]).

The diagram at the left shows longitudinal dissociation of the upper level of an atrioventricular node into two effective pathways, "α" and "β", joining in a final common pathway (FCP). An early premature response initiated in the His bundle (H_2) is assumed to be blocked at junction of FCP with β, but propagates through the α pathway to atrial tissue and returns through β to the FCP. A ventricular echo H* (schema at right) will occur provided the conduction time from FCP to atrium and return exceeds the refractory period of FCP (indicated by stippled area).

Moe and Mendez
New Eng. J. Med. 288:250, 1973

Factors That May Enhance Vulnerability to VF

1. Large mass of myocardium
2. Local depolarization
3. Increased automaticity of Purkinje fibers
4. Transformation of nonpacemaker into pacemaker fibers
5. Slow conduction
   A. Localized focal block, or preexcitation
   B. Generalized*
6. Uniformly prolonged refractoriness (duration of action potential)
7. Increased nonuniformity of refractoriness
   A. Altered differences between Purkinje and ventricular fibers
   B. Increased dispersion of refractoriness in the ventricular myocardium

* Includes changes in membrane responsiveness

Ref. 78

APPENDIX B. DRUG TREATMENT - from Bellet, S. 1971. Clinical disorders of the heart beat. 3rd ed. Lea & Febiger, Philadelphia

Qualities of an Ideal Antifibrillatory Drug

1. Restores disturbances in cardiac electrophysiology to normal without impairing cardiac function
2. Increases automaticity of the S-A node when it is depressed
3. Decreases automaticity of ectopic foci when it is elevated
4. Restores subnormal conductivity to normal, thus abolishing local islands of refractory tissue that may become foci for re-entry
5. Does not have an undue negative inotropic effect
6. Does not cause excessive parasympathetic or sympathetic stimulation

Relative Efficacy of Antiarrhythmic Drugs in the Treatment of Premature Contractions and Tachyarrhythmias of Atrial or Ventricular Origin

Drug	*Atrial*	*Ventricular*
Digitalis	++	0
Quinidine	++	++
Procaine amide	++	++
Lidocaine	+	++
Diphenylhydantoin	+	++
Antazoline	+	+
Propranolol	+	+
Alprenolol	+	+
Acetylcholine	+	0
Prostigmine	+	0
Edrophonium	+	0

B. *Drugs that Slow Tachyarrhythmias and Tend to Abolish Premature Beats (Atrial and/or Ventricular)*:
1. Quinidine
2. Procaine amide
3. Potassium
4. Lidocaine
5. Bretylium
6. Beta blocking agents (propranolol and alprenolol)
7. Diphenylhydantoin
8. Antazoline
9. Digitalis (occasionally)

Summary of Pharmacologic Effects of Beta-adrenergic Receptor Blocking Agents Presently in Clinical Use.

Drug/Isomer		*Beta-Blocking Effect*	*Sympathomimetic Effect*	*Local Anesthetic Quinidine-like Effect*
Propranolol	L	+	0	+
	D	0	0	+
Alprenolol	L	+	+	+
(H 56/28)	D	0	0	+
ICI 45,763 (Kö-592)		+	0	+
Trasicor		+	+	+
Butidrine		+	+	+
Sotalol (MJ 1999)		+	0	0
INPEA		+	−	0
ICI 50,172		+	+	0

Propranolol (Inderal)

A. Mechanisms of Action. (Beta-blocking agents other than propranolol may not exert all of the effects of propranolol, *e.g.*, Sotalol does not exert action 2)

1. Beta adrenergic blockade
2. Direct quinidine-like depressant effects

B. Indications

1. Sinus tachycardia (in selected cases)
   - *a.* Pheochromocytoma
   - *b.* Thyrotoxicosis
   - *c.* Strong anxiety factor
2. Atrial flutter or fibrillation in conjunction with digitalis
3. Recurrent supraventricular tachyarrhythmias in W-P-W
4. Repetitive supraventricular tachycardias
5. Tachycardias associated with exercise

C. Toxicity. (May be accentuated in the presence of hepatic or renal disease)

1. Slows cardiac rate and aggravates bradycardia and congestive heart failure
2. Causes airway obstruction and decreased ventilatory function
3. May exacerbate hypoglycemic tendencies in certain patients
4. Nausea
5. Vomiting
6. Diarrhea or constipation
7. Mental depression

D. Contraindications

1. Slow heart rate
2. Second degree or complete A-V heart block
3. Cardiogenic shock
4. In conjunction with myocardial depressant anesthetics
5. Congestive heart failure
6. Digitalis toxicity with A-V conduction disturbances
7. Bronchial asthma
8. Allergic rhinitis during the pollen season

Hemodynamic Effects

Little or no effect with average doses. With large doses, depressant action involves the entire circulatory system.

1. In normal subjects (oral administration)
   a. Fall in arterial blood pressure (due to vasodilatation of systemic arterioles)
   b. Right ventricular pressure, cardiac output and blood volume unchanged
2. In patients with cardiovascular disease (oral administration)
   a. Lowers blood pressure
   b. No change in cardiac output if it is normal; will be raised toward normal if a low cardiac output is due to an arrhythmia that has been corrected by quinidine.

Plasma Levels

Electrocardiographic changes and clinical effects often do not parallel the plasma levels.

1. With plasma levels of 4 to 8 mg./L., some slowing of heart rate; P–R interval not affected or only slightly prolonged; changes in S–T segment and T waves; lengthening of Q–T interval
2. With higher plasma levels, further slowing of heart rate, increased widening of QRS complexes and further increase in P–R interval
3. With marked cardiotoxicity, marked widening of QRS and ventricular standstill occur

Electrocardiogram

1. Early changes (in order of occurrence)
   a. Notching of T wave (from superimposition of U wave)
   b. Increase in Q–T interval
   c. T waves decrease in amplitude and may become inverted
   d. Depression of S–T segment
2. Later changes
   a. Widened and often notched P wave
   b. Prolonged P–R interval
   c. Slowing of atrial rate leading to atrial standstill
   d. Notable lengthening of Q–T interval
   e. Widening of QRS leading to ventricular tachycardia, ventricular fibrillation, or a slow idioventricular rhythm.

Indications

1. Conversion to normal sinus rhythm and prophylactic treatment of the following arrhythmias:
   a. Premature beats (atrial, junctional and ventricular)
   b. Paroxysmal atrial and nodal tachycardia and ventricular tachycardia
   c. Atrial flutter and fibrillation (drug of choice for conversion in the latter)
   d. Occasionally ventricular flutter or fibrillation
2. To prevent the recurrence of the arrhythmias listed above
   a. After conversion
   b. As maintenance therapy after cardioversion
3. In resuscitative attempts of patients with ventricular flutter (exclusive of that associated with A–V heart block) (in doubt)
4. Use prior to and as an adjunct to countershock

QUINIDINE

Contraindications, Precautions, and Adverse Reactions

A. Contraindications:

1. History of serious reaction to drug (*e.g.*, purpura, hypotension, fever, skin reaction, thrombocytopenia)
2. Ventricular flutter or fibrillation; Stokes-Adams attacks if associated with complete A–V heart block (not contraindicated in ventricular fibrillation in sudden cardiac arrest not associated with complete A-V block)
3. Complete A-V heart block unless patient is paced
4. Partial A–V block

B. Give With Caution in:

1. Bundle branch block
2. Severe heart failure
3. Hyperpotassemia
4. Patients receiving anticoagulants
5. Azotemia
6. Pregnancy
7. Use with extreme caution or omit in those developing cardiac toxic effects: ventricular paroxysmal beats, ventricular tachycardia or flutter while on the drug

C. Adverse Reactions:

1. Fever
2. Skin reactions
3. Thrombocytopenia
4. Purpura
5. Ectopic beats or ventricular tachycardia
6. Tinnitus
7. Respiratory distress
8. G. I. (anorexia, vomiting, nausea)

Untoward and Toxic Effects of Quinidine Administration

Clinical

1. Allergic (skin rashes, fever and thrombocytopenic purpura)
2. Cinchonism
3. Gastrointestinal
4. Cerebral
5. Respiratory
6. Blood Dyscrasias
   a. Hemolytic anemia
   b. Leukopenia
   c. Hypoplastic thrombocytopenia
   d. In combination with anticoagulants: hypoprothrombinemic hemorrhage due to depression of vitamin K-sensitive hepatic clotting factor synthesis

Cardiovascular

1. Heart Failure
2. Hypotension
3. Embolic phenomena (indirect effect of restoration to normal sinus rhythm)
4. Electrocardiogram
   a. Depression of atrial activity, leading to atrial standstill
   b. Widening QRS complexes which may precipitate ventricular flutter and/or fibrillation
   c. Arrhythmias produced
      (1) Increasing bradycardia and P-R interval prolongation followed by idioventricular rhythm and cardiac standstill
      (2) Multifocal ectopic ventricular premature beats with runs of ventricular tachycardia; may lead to convulsive seizures
      (3) Idioventricular rhythm and complete cardiac standstill
      (4) Ventricular fibrillation

QUINIDINE

Procaine Amide

A. Electrophysiology and Pharmacologic Effects

1. Reduces cardiac excitability, thereby raising the threshold for stimulation
2. Increases effective refractory period of atrium, ventricle and Purkinje-fiber-papillary muscle junction
3. Depresses automaticity of His-Purkinje system
4. Direct effects tend to depress excitability and conductivity, which lead to prolongation of P-R and QRS
5. Tends to reduce vagal tone
6. In toxic doses, procaine amide causes enhancement of automaticity, severe depression of excitability, and conduction prolongation of action potential and of the effective refractory period
7. Antagonizes cardiac effects of epinephrine and possibly acetylcholine

B. Hemodynamic Effects (Has primary depressant action)

1. Decreases cardiac output
2. Decreases blood flow through pulmonary vascular bed
3. Causes fall in pulmonary artery pressure
4. Causes slight hypotension; when blood pressure is already lowered, the decline may be marked

C. Electrocardiographic Effects (Similar to quinidine)

1. Q_1T interval (electrical systole) prolonged (not invariable as with quinidine)
2. T wave amplitude decreased (T wave inversion occasionally with large doses)
3. P-R interval occasionally prolonged
4. QRS complex widening is a sign of toxicity

D. Indications

1. Atrial and junctional premature beats and paroxysmal atrial tachycardia associated with W-P-W
2. Ventricular premature beats and ventricular tachycardia
3. Prophylactic use during myocardial infarction to protect against ventricular tachycardia or fibrillation once ventricular premature beats are observed
4. Active treatment during cardiac catheterization and anesthesia and surgery. Routine use is not recommended
5. Tachyarrhythmias during digitalis toxicity
6. Prophylaxis for postcountershock arrhythmias

E. Methods of Administration

1. *Oral administration:* 250 mg. to 0.5 gm. every four to six hours (preferred method)
2. *Intramuscular administration (preferred parenteral route):* 0.5 to 1.0 gm. of gluconate or hydrochloride repeated every four to six hours. This route is simpler and less toxic than the intravenous
3. *Intravenous administration* (not for routine use; only in cases of urgency with continuous ECG monitoring): 0.5 to 3.0 gm. after initial 100 mg. at rate of 100 mg. every four minutes. This route is indicated when conversion to normal sinus rhythm is urgent, in shock-like states, and during anesthesia and surgery. It should be accomplished under electrocardiographic and blood pressure monitoring, as well as with necessary equipment for countershock, defibrillation, pacemaking and cardiac compression

Toxic Effects - Procaine

A. Cardiovascular Effects
1. Hypotension
2. Other cardiotoxic effects
   a. May enhance automaticity of ventricular pacemakers
   b. Marked slowing of sinus rate
   c. Bizarre ventricular tachycardias
   d. Ventricular fibrillation
3. Fatalities

B. Gastrointestinal System
1. Anorexia
2. Nausea and vomiting

C. Central Nervous System Effects (Minimal central stimulatory effects)
1. Transient psychoses (visual and auditory hallucinations)
2. Mental depression

D. Allergic Manifestations
1. Systemic lupus erythematosus-like syndrome
2. Hypersensitivity reactions (antinuclear antibody and LE cells)
3. Anemia, hyperglobulinemia and leukopenia
4. Urticaria and skin rash
5. Agranulocytosis
6. Chills and fever

Treatment of Toxicity
1. Discontinuance of drug
2. Vasopressor agents in hypotensive patients
3. Molar sodium lactate
4. Artificial pacemaker with slow heart rates
5. Countershock in presence of ventricular tachycardia
6. Steroids, if SLE syndrome is not reversed by simple discontinuance of drug

Electrophysiologic Effects of Lidocaine

S–A Node. No effect with doses in therapeutic range

Atria. Slight dose-related increase in partial refractoriness and threshold to stimulation

A–V Junction. Minimal prolongation of A–V conduction time

His-Purkinje System
1. Depresses automaticity
2. Prolongs relative refractory period
3. Depresses conduction velocity slightly
4. Raises threshold to stimulation
5. Does not alter action potential morphology

Ventricles
1. Decreases excitability
2. Does not alter resting or action potential
3. Does not affect refractoriness
4. Moderate depression of intraventricular conduction velocity
5. Abolishes multiple responses to premature beats
6. Reduces the maximal rate of stimulation to which ventricles can respond

TABLE 45-1. Effect of Lidocaine on Ventricular Arrhythmias

	No. of Subjects	*Terminated*	*% Success*
Frequent ventricular premature beats	518	426	82
Ventricular tachycardia	68	61	90
Ventricular fibrillation	4	1	25
Total	590	488	83%

(Bigger and Heissenbuttel, courtesy of Prog. Cardiov. Dis.)

Lidocaine

A. Indications

1. Frequent ventricular premature beats
2. Ventricular bigeminy
3. Ventricular tachycardia
4. Ventricular arrhythmias associated with
   a. Digitalis toxicity
   b. Electric countershock

B. Toxicity (These effects may appear at lower dosages than usual in patients with liver disease)

1. May detrimentally slow ventricular rate in
   a. Sinus bradycardia
   b. S-A heart block
   c. A-V heart block
2. Drowsiness
3. Paresthesia
4. Decreased hearing
5. Convulsions

C. Contraindications

1. History of hypersensitivity to local amide anesthetics
2. Complete A-V heart block
3. Intraventricular block
4. S-A heart block

Indications

1. Acute ventricular arrhythmias associated with anesthesia, cardioversion, catheterization and cardiac surgery
2. Prevention of recurrent arrhythmias of ventricular origin
3. Digitalis-produced ventricular arrhythmias and digitalis toxicity as manifested by both ectopic beats and incomplete A-V block
4. Certain cardiac arrhythmias of central origin
5. Electric countershock: prevention of postconversion arrhythmias, especially in digitalized patients

Toxicity - Lidocaine

1. *Circulatory Effects*
   a. Hypotension
   b. Bradycardia
   c. Transient atrioventricular block, prolonged A-V conduction
   d. Ventricular standstill and death
   e. Impaired myocardial contractility and peripheral vasodilatation
2. *Respiratory Effects*
   a. Respiratory depression and arrest
3. *Hematologic Effects*
   a. Anemia, pancytopenia
   b. Reticuloendothelial disorders, including malignant lymphoma, infectious mononucleosis
   c. Megaloblastic anemia (sometimes)
4. *Allergic Effects*
   a. Agranulocytosis with leukopenia, thrombocytopenia
   b. Jaundice and hepatitis
   c. Morbilliform rash or fatal hemorrhagic erythema multiforme
5. *Central Nervous System*
   a. Nystagmus, tremors, ataxia, cerebellar degeneration, giddiness, diplopia, blurring of vision, ptosis, slurring of speech
   b. Fatigue and drowsiness
   c. Insomnia and irritability
6. *Other Effects*
   a. Gastric upsets
   b. Hyperplasia of the gums
   c. Metabolic
      (1) Megaloblastic anemia
      (2) Low PBI
      (3) Depressed adrenal cortical function
   d. Hypertrichosis
7. *Effects of Other Drugs*
   a. Dicumarol, sulfaphenazole, and phenylbutazone—increase the half-life of DPH
   b. Phenobarbital—decreases the half-life of DPH

Indications - Digitalis

1. Supraventricular ectopic rhythms, accompanied by fast rates
2. In the presence of atrial fibrillation, atrial flutter, and atrial or junctional tachycardia
3. Ventricular premature contractions accompanied by or resulting from congestive heart failure
4. Use cautiously in presence of varying degrees A-V heart block
5. Not indicated in therapy of arrhythmias commonly associated with digitalis toxicity until this etiology ruled out:
   a. PAT with block
   b. Ventricular premature beats
   c. Bigeminal rhythm
   d. "True" ventricular tachycardia

Manifestations of Digitalis Toxicity

	Common	*Uncommon*
Cardiac	Bradycardia, S–A block, sinus arrhythmias, all degrees A–V block (sometimes with paroxysmal tachycardia), A–V junctional rhythm (including premature beats, coupled ventricular premature beats, and paroxysmal tachycardia)	Atrial fibrillation, atrial flutter, ventricular tachycardia and fibrillation, complete A–V heart block
ARRHYTHMIAS THAT HAVE A HIGH PROBABILITY OF BEING CAUSED BY DIGITALIS TOXICITY	Multifocal ventricular premature beats, A–V junctional tachycardia, A–V dissociation, PAT with block	
Extracardiac		
GASTROINTESTINAL	Anorexia, nausea, vomiting	Diarrhea
VISUAL	Alterations in color perception, scotomata, blurring, shimmering, micropsia, macropsia	Amblyopia
NEUROLOGIC	Headache, fatigue, insomnia depression	Convulsions, delirium
ALLERGIC	None	Urticaria, eosinophilia
ENDOCRINE	None	Gynecomastia

Electrolytes Employed in Therapy

A. Potassium

1. Effective in the abolition of certain arrhythmias
   - *a.* Arrhythmias resulting from digitalis toxicity (see page 1072)
   - *b.* Arrhythmias associated with hypopotassemia
   - *c.* Ectopic beats (when refractory to quinidine or procaine amide)—supraventricular or ventricular
2. Untoward and toxic effects
   - *a.* Hyperpotassemia
   - *b.* Cardiac and extracardiac effects
3. Electrocardiographic effects
   - *a.* Increased amplitude of T wave
   - *b.* Increase in QRS width (0.12 to 0.14 sec.)
   - *c.* Slow idioventricular rhythm
   - *d.* Cardiac arrest

B. Calcium

1. Indications
   - *a.* Arrhythmias associated with hypocalcemia
   - *b.* Occasionally effective in supraventricular tachycardia
   - *c.* To neutralize hyperpotassemia during resuscitative procedures after cardiac arrest
2. Untoward and toxic effects
   - *a.* Relative contraindication or use with caution in digitalized hearts
   - *b.* May produce hypercalcemia and result in premature beats, paroxysmal tachycardia, especially in diseased hearts

C. Magnesium

1. Of limited value except in selected cases of arrhythmias resulting from digitalis toxicity

Molar Sodium Lactate and Sodium Bicarbonate

A. Cardiac Actions

1. Decreases acidosis, may produce alkalosis
2. Decreases extracellular potassium
3. Enables endogenous and exogenous epinephrine and norepinephrine to be effective
4. Vagolytic effect
5. Increases cardiac volume--leads to direct cardiac stimulation
6. Lactate effects

B. Indications

1. Hyperpotassemia
2. Treatment of Stokes-Adams attacks
3. As supplement to vagolytic and sympathomimetic drugs
4. Cardiac arrest (in certain instances)

C. Toxic Effects and Contraindications

1. Severe heart damage with overt or impending heart failure
2. Increased frequency of premature beats following infusion
3. Hypopotassemia
4. Alkalosis

Parasympathetic Blocking Agents

A. Atropine: Blocks the effects of acetylcholine; may be used to abolish arrhythmias produced by vagal hyperactivity; action is short-lived, and side effects are often disturbing

1. *Indications*
   a. Employed to combat parasympathetic effects and as a temporary measure in:
      (1) Sinus bradycardia caused by overactive vagal tone, especially in bradyarrhythmias
      (2) Sinus (respiratory) arrhythmia, to relieve symptoms, if present
      (3) S-A block caused by overactive vagal tone
      (4) Atrial flutter with slow ventricular rate associated with myocardial infarction
      (5) Atrial fibrillation with slow ventricular rate
      (6) Partial A-V heart block due to parasympathetic overactivity
      (7) To combat toxic digitalis effects of vagal origin
   b. Employed as a diagnostic aid to evaluate the degree of vagal tone in:
      (1) Complete A-V heart block
      (2) A-V junctional rhythm, to accelerate rate of impulse formation by diminishing vagal tone
      (3) Differential diagnosis between atrial arrhythmias (brings out a hidden retrograde P wave, as in midnodal rhythm, in the electrocardiogram)
2. *Toxicity*
   a. Serious side effects are uncommon in the human with the commonly administered doses
   b. In toxic doses, dryness of mouth, disturbed speech, and in very large doses, weakening of pulse, marked pupillary dilatation, hallucinations, coma, and death

B. Methantheline (Banthine): Has atropine-like effects, but has two-thirds the potency of atropine. It has fewer side effects than atropine, and the action is more sustained

1. *Indications*
   a. Similar to those of atropine.
2. *Toxicity*
   a. Dryness of mouth, blurred vision, restlessness, and fatigue
   b. Neostigmine counteracts serious untoward effects

Proarrhythmic Drugs

Digitalis: Produces arrhythmias in toxic doses or in the presence of electrolyte imbalance

Other Antiarrhythmic Agents: Quinidine, procaine amide, and potassium salts may produce ventricular arrhythmias

Diuretics: Cause arrhythmias by producing hypopotassemia

Xanthines (Aminophylline and Caffeine): Produce myocardial stimulation and diuretic effects

Thyroid Extract: May cause hyperthyroidism and its associated arrhythmias

Sympathomimetic Amines: May cause arrhythmias because of their initial sympathetic and later parasympathetic effects

Alkalinizing Agents: Sodium bicarbonate and molar sodium lactate may cause premature beats, ventricular tachycardia and ventricular fibrillation

Meperidine and *Morphine:* Occasionally produces ectopic rhythms by blocking vagal impulses

Heroin: Produces slow ventricular rate and atrial fibrillation, occasionally

Thioridazine (Mellaril): May cause electrocardiographic changes, PVC's and tachyarrhythmias

Imipramine Hydrochloride (Tofranil): Electrocardiographic changes and fatal arrhythmias associated with overdosage

Fluoroalkane Gases: Produces sinus bradycardia, A–V heart block and sudden death

Nicotine: Major action is transient stimulation and then secondary, more persistent depression

APPENDIX C. SUMMARY OF PRELIMINARY STUDIES UNDERWAY, CARDIOVASCULAR SECTION DALLAS VAH

A. Effects of acute intravenous and oral and chronic oral propanolol on exercise induced-VEA.

8 patients (3 CHD, 2 negative coronary angios, 3 syncope and/or palpitations without angios)

1. IV - 6/8 > 60% reduction PVC's
2. Acute oral - 6/8 > 60% reduction PVC's
3. Chronic oral - 3/5 > 60% reduction PVC's
4. 7 pts had couplets and/or VT - 6/7 abolished
5. 3 pts had VT - 3/3 abolished

B. Exercise testing to end-point up to target heart rate 120/min - 16 pts 3 weeks after documented myocardial infarction.

Negative	ST shifts	Pain	Ex-induced VEA
9	4	2	1

C. Holter monitoring 4-6 hrs.; 18 pts. 3 and 6 weeks after documented myocardial infarction.

	3 weeks	6 weeks
VEA	5	3*
None	13	10
Total	18	13

*No VEA at 3 weeks