Prognostic Significance of Ventricular Ectopic Beats with Respect to Sudden Death in the Late Postinfarction Period

By Morris N. Kotler, M.D., Bernard Tabatznik, M.D., Morton M. Mower, M.D., and Suketami Tominaga, M.D.

SUMMARY
The role of ventricular dysrhythmias as determinants of sudden coronary death (SCD) was studied prospectively in 160 male survivors of myocardial infarction, all under 65 years of age and in New York Heart Association (NYHA) functional class I or II. Twelve-hour electrocardiographic recordings were taken in all patients at serial intervals and analyzed for frequency and type of ventricular ectopic beat (VEB). Eighty percent showed VEB's on at least one tape recording. There have been 14 SCD's in a follow-up period ranging between 30 and 54 months, 12 in 87 patients (13.8%) with significant VEB's (frequent, unifocal, multifocal, paired or coupled, and ventricular tachycardia), and only two in 66 patients (3%) with absent or infrequent VEB's ($P < 0.02$).

Although the number of patients in this study is small, the results show that all complex VEB forms together were associated with an excess risk of SCD, notwithstanding the absence of SCD in 27 patients with ventricular parasystole. It is suggested that the differential association with SCD between ventricular extrasystoles and parasystole in the late postinfarction period may have bearing on the mechanism of ventricular fibrillation and SCD.

Additional Indexing Words:
Holter monitoring
Coronary risk factors
Ventricular parasystole
Coronary Drug Project
Ventricular fibrillation

THE RECENT interest in the ventricular ectopic beat is attributable to coronary care unit experience which defined its role as a precursor of ventricular fibrillation in acute myocardial infarction. However, there is very little available data on the prevalence and prognostic significance of ventricular dysrhythmias in long-term survivors of myocardial infarction. The purpose of this report is to provide such information in a group of free-living middle-aged men with a history of myocardial infarction, using serial Holter continuous electrocardiographic recordings for identifying ventricular dysrhythmias.  

Materials and Methods

The study population consisted of 160 male participants in the Coronary Drug Project (CDP) at the Sinai Hospital Clinic in Baltimore. The CDP is a National Heart and Lung Institute Collaborative Study, a long-term randomized double-blind trial to evaluate the effectiveness and safety of several lipid-lowering drugs in prolonging the life of patients with prior myocardial infarction. The study design of the CDP and its more recent modifications are reported in detail elsewhere. There are 53 participating clinics, of which the Baltimore Sinai Clinic is one, in the CDP. The drugs under study are 2.5 mg/day of mixed conjugated estrogens; 5.0 mg/day of mixed conjugated estrogens; 1.8 g/day of clofibrate; 6.0 mg/day of dextrothyroxine; 3.0 g/day of nicotinic acid; and a lactose placebo.

Eligible men were those with one or more documented myocardial infarcts who were between the ages of 30 and 64 years at the time of enrollment. All had survived their most recent infarct by at least 3 months and were free of recent deterioration of their cardiac manifestations, free of a specified list of life-threatening diseases, and were neither on insulin nor on...
anticoagulant therapy. Using criteria outlined by NYHA, all patients were in functional class I or II.

At the time of enrollment in the project and prior to randomization into treatment groups, a series of baseline measurements were made on each patient in accordance with a common protocol. Twelve-lead ECG's recorded at entry were sent to the CDP Electrocardiographic Center at the University of Minnesota and analyzed for Q-wave abnormalities and S-T depression according to defined criteria. In addition, as an ancillary study to the CDP, all 160 patients in the Sinai Hospital Clinic had electrocardiographic tape recordings during 10-12 continuous hours of routine daily activity, using the Holter Avionics technic of recording. These recordings were repeated at eight monthly intervals, and in some instances more frequently. Standard 12-lead electrocardiograms with 6-in. strips were taken at annual intervals or more frequently depending on clinical indications. Each patient kept a diary of activities and symptoms during the recording period. Sudden death was defined as death occurring instantaneously or within 1 hour of the onset of symptoms.

Analysis of ECG Tape Recordings

The continuous ECG data were reduced and analyzed according to a technic described previously. Tape-recorded electrocardiograms are played on a Viking model 87 tape deck at 7½ in/sec. The signal is introduced into a high-speed cardiacheterometer which produces a sawtooth wave pattern whose height is proportional to the instantaneous R-R interval. The pattern is recorded on a Sanborn Twin Beam Model 62 recorder at 2.5 mm/sec, producing a photographic record called a “rhythm scan.” Abnormal areas such as ventricular ectopic beats are easily identified for reproduction in standard electrocardiographic format, using the Avionics electrocardiograph.

All tapes were analyzed for arrhythmias and conduction disturbances. Special attention was directed to the presence or absence of ventricular parasystole.

The “rhythm scan” analysis was used as a screening device for identifying parasystole, since the presence of significant variations in coupling intervals is readily identified by the technic. Areas showing slowly progressive variation of coupling intervals were reproduced in real time and standard yet strict criteria were used for diagnosis of parasystole. These included at least the first two of the following three criteria: (1) varying coupling intervals, (2) interectopic intervals divisible by a shorter fixed interval, either manifest or calculated, and (3) fusion beats. Equivocal cases were classified as extrasystoles rather than parasystole.

Ventricular ectopic activity was also identified and classified according to the following grading system:

- grade 0 = No ventricular ectopic beats
- grade 1 = less than 10 unifocal ventricular ectopic beats per hour
- grade 2 = greater than 10 unifocal ventricular ectopic beats per hour
- grade 3 = multiform ventricular ectopic beats
- grade 4 = ventricular ectopic beats in pairs or couplets
- grade 5 = three or more successive ventricular ectopic beats

Each patient was accorded the highest grade identified on any Holter recording. By February 1, 1972, a total number of 660 standard electrocardiograms and 717 Holter recordings were available for analysis. On this date all patients had been followed between 30 and 54 months.

Results

Prevalence and Characteristics of Ventricular Ectopic Beats

Twenty-four patients (15%) showed one or more ventricular ectopic beats on the ECG taken at entry to the study (fig. 1). The incidence rose to 34.4% when 660 serial standard ECG’s, averaging four per patient, were analyzed. The initial Holter recordings at entry showed ventricular ectopic beats in 43% of patients. When 414 Holter tapes, averaging two to three per patient, were analyzed, ventricular ectopic beats were identified in 62.5% of patients.

By February 1, 1972, at which time 717 Holter tapes, averaging four to five per patient, had been analyzed, 128 (80%) of the patients showed ventricular ectopic beats on at least one recording. Only 32 (20%) showed no ventricular ectopic beats at any time (grade 0). Thirty-six patients (22.5%) were classified as having infrequent unifocal ventricular ectopic beats (grade 1); 28 patients (17.5%) had frequent unifocal ventricular ectopic beats greater than 10 per hour (grade 2); 28 (17.5%) had multiform ectopic beats (grade 3); in

![Figure 1](http://circ.ahajournals.org/)

See Results for description.

Circulation, Volume XLVII, May 1973
ARRHYTHMIAS AND SUDDEN DEATH

32 (20%) they occurred in pairs or couplets (grade 4), and four cases (2.5%) had brief runs of ventricular tachycardia (grade 5).

Closer analysis of the ventricular ectopic beat characteristics showed ventricular parasystole in three patients in grade 2, four in grade 3, 18 in grade 4, and two in grade 5. A Q-RVerb/QT interval <1 was observed in only seven cases, five of which had parasystole with an occasional ectopic beat occurring on the downslope of the T wave.

**Ventricular Ectopic Beats in Relation to Sudden Coronary Death**

There were 21 deaths in the 30-54 month range of follow-up, six due to recurrent myocardial infarction with pump failure, one due to cerebral hemorrhage, and 14 sudden and unexpected, occurring instantaneously or within an hour of onset of symptoms (fig. 2). Excluding the seven nonsudden death patients, the incidence of SCD was 9.2%.

With only the initial 72-sec 12-lead electrocardiogram considered, 10 of 131 patients (7.6%) without ventricular ectopic beats died suddenly compared with four of 22 patients (18.2%) with ventricular ectopic beats. When 660 serially recorded 12-lead electrocardiograms were analyzed the incidence of SCD was 19.2% with ventricular ectopic beats as compared to 2.9% without ventricular ectopic beats.

Classification of the 717 tapes by grade showed one sudden death in each of the groups with no ectopic beats (grade 0) and infrequent unifocal ectopic beats (grade 1); five in the 26 (19%) patients with frequent unifocal ectopic beats (grade 2); five in 28 (18%) patients with multiform ventricular ectopic beats (grade 3); none in the 30 patients with paired or coupled ventricular ectopic beats (grade 4); and two in three patients with paroxysmal ventricular tachycardia (grade 5). One patient (in grade 2) had shown a Q-RVerb/QT interval <1.

**Ventricular Parasystole**

Ventricular parasystole was recognized on the Holter tape recordings in 27 of the 160 patients, an incidence of 16.8%. Eighteen showed paired ectopic beats.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2**

See Results for description. The numerator refers to the number of sudden coronary deaths and the denominator to the total number of patients in each category.
beats (grade 4), representing the minimal manifest
interectopic interval and presumably the discharge
rate of the ectopic focus. An example is shown in
figure 3. In patients with multiform ventricular
ectopic beats without couplets corresponding to
grade 3, at least one focus was found to be
parasystolic in four patients. Three patients with
frequent unifocal ectopic beats without couplets
(grade 2) showed parasystole, and two patients
had a parasystolic ventricular tachycardia (grade
5). There were no instances of SCD in the 27
patients who had a parasystolic rhythm. This may
explain the apparent benignity of grade 4 patients
in whom the incidence of parasystole was 56% (18
of 32 patients). In those patients who died of
recurrent myocardial infarction two of the six
patients had parasystole.

Prognostic Importance of Ventricular Ectopic Beats
in the Presence of Other Risk Factors

Figure 4 shows the relationship between ectopic
beat characteristics and sudden death and in
addition examines this relationship according to the
presence or absence of other clinical risk factors,
considered individually. This two-way analysis
demonstrates whether or not VEB's act indepen-
dently of these other risk factors. It is not, however,
a test of other risk factors in relation to sudden
death.

For this analysis, patients in grade 0 and 1 (as
determined by serial tape analyses) have been
combined to characterize a population with infre-
quent ectopic activity. Mortality rates in this group
are compared with patients in grades 2-5 represen-
ting significant ventricular ectopic activity. The
difference between the sudden death rate in the former
group (3%) and the latter group (13.8%) is signifi-
cant at a P value of 0.018 using Fisher's exact test
of statistical analysis.6 (fig. 4, col. 1).

In the remaining columns of figure 4, the two-
way relationship between VEB's and five selected
risk factors is displayed. In each comparison
patients with significant VEB (grades 2-5) show a

![Figure 3](http://circ.ahajournals.org/)

Parasystole in a patient with couplets. The upper strip shows the longer interectopic interval which mea-
sures 360 hundredths of a second, a multiple of the shortest interectopic interval which measures 60 hun-
dredths of a second. The middle and lower strips of the same patient show slight variation in the manifest
interectopic interval discharge rate with resultant longer calculated interectopic intervals.

Circulation, Volume XLVII, May 1973
ARRHYTHMIAS AND SUDDEN DEATH

higher incidence of SCD independent of the individual risk characteristics. Comparisons were also made with the following demographic, clinical, and electrocardiographic characteristics: age, number of infarcts, interval between the last myocardial infarct and entry to the study, angina pectoris, systolic hypertension, serum cholesterol, serum triglyceride, glucose intolerance, cardiomegaly on X-ray, relative body weight, cigarette smoking, history of congestive heart failure, risk group based on number of infarcts and presence or absence of major complications at the time of infarction, physical activity, digitalis usage, diuretic therapy, supraventricular arrhythmias, S-T depression, presence or absence of abnormal Q waves, tall R wave in V₅, intraventricular conduction disturbance, and resting heart rate. In each instance VEB's appear to act independently with respect to SCD.

Influence of Antiarrhythmic Drug Therapy

It is possible that the administration of antiarrhythmic drugs could have affected both the grading of VEB's in this population. One hundred eight of the 160 cohorts were not on any antiarrhythmic agent at any point in the study period. The remainder were on one of the following medications, either singly or in combination: propranolol, quinidine, procainamide, and atropine, with or without digitalis. Many patients were on propranolol for angina pectoris rather than for arrhythmias. Digitalis alone was not considered an antiarrhythmic agent in this analysis. Seventeen of 68 patients (25%) graded 0 and 1 were on antiarrhythmic therapy compared with 35 of 92 (38%) graded 2-5. Fifteen of the 17 patients on therapy in grades 0 and 1 were on propranolol because of angina. Thus it appears most unlikely that appreciable numbers of patients were falsely classified into lower grades because of suppressive drug therapy.

Excluding the seven cases of nonsudden death, there were six sudden deaths in 49 patients (12.2%) receiving antiarrhythmic drug therapy compared with eight in 104 patients (7.7%) not on antiarrhythmic agents. In those patients with significant VEB's (grades 2-5) five of 32 (15.6%) on antiarrhythmic drugs died suddenly compared with seven of 55 (12.7%) not on therapy. None of these differences is statistically significant. However, these results negate the possibility that the presence or absence of antiarrhythmic therapy was an

![Figure 4](http://circ.ahajournals.org/)

See Results for description. The numerator refers to the number of sudden coronary deaths and the denominator to the total number of patients in each category.
important factor in either preventing or predisposing to sudden coronary death. Because of the uncontrolled conditions of the study, the higher death rate in the treated group should not be interpreted as indicative of the ineffectiveness of antiarrhythmic medications.

Discussion

As would be expected, longer periods of electrocardiographic monitoring yield an increasing incidence of ventricular ectopic activity.\textsuperscript{14} It is perhaps noteworthy that 10 of 14 sudden coronary deaths in this study occurred in patients whom serial conventional 12-lead electrocardiograms showed ventricular ectopic activity (fig. 2). It might seem reasonable that if VEB's are indeed precursors of ventricular fibrillation in a postinfarction population, those patients at particular risk can be identified from standard ECG without recourse to continuous ECG monitoring. Support for this viewpoint is provided in the CDP Research Group reports.\textsuperscript{8, 15} in which ventricular ectopic activity was found on the standard ECG in 11.5% of 2030 placebo-treated patients at entry to the project. Despite the low sensitivity of the standard ECG in identifying ventricular ectopic beats, the latter proved to be a significant independent prognostic finding with respect to subsequent mortality. The 3-year mortality in men showing VEB's on standard ECG was about twice that in men with no VEB's (21.7% vs 11.4%; \textit{P} < 0.01). A multivariate analysis was used in that study to adjust for 31 demographic, clinical, and electrocardiographic findings simultaneously.

On the other hand, continuous ECG monitoring during routine daily activity provides accurate information on the quality as well as the prevalence of ventricular ectopic activity not available on the standard ECG. The overall prevalence of ventricular ectopic activity in this study population (80%) is remarkably similar to that reported by Lown, Klein, and Hershberg\textsuperscript{16} in the acute phase of myocardial infarction (80%), and by Moss, Schnitzler, Green and Decamilla\textsuperscript{17} in the early convalescent period following infarction (72%). However, ventricular tachycardia occurred in only 2.5% of our study population, a figure that compares with the 4% incidence of Moss et al.,\textsuperscript{17} but contrasts with the 28% incidence of Lown et al.\textsuperscript{16} in acute infarction. Since long periods of monitoring occurred in all three studies, it seems likely that the tendency to develop lethal arrhythmia in the acute phase of infarction relates to a lowered threshold for ventricular tachycardia and ventricular fibrillation in the first 5–7 days.\textsuperscript{16}

The recognition of ventricular parasystole also is understandably enhanced by the use of long recording periods. We identified 27 unequivocal instances of parasystole in our study population of 160 patients. This incidence of 16.8% is considerably higher than the incidence of 1.7% in acute myocardial infarction reported by McKendrick and Salazar,\textsuperscript{18} and 0.67% (37 of 5479) in healthy flying personnel reported by Myburgh and Lewis.\textsuperscript{19} The ectopic discharge rate was clearly identified in 18 of our 27 cases in the form of coupled or paired ventricular ectopic beats (fig. 3), and these cases of parasystole contributed heavily to our grade 4 category. A remarkable feature of our study was the complete absence of sudden death in our patients with ventricular parasystole, although two patients died of recurrent myocardial infarction. If this trend continues over a period of time, this observation raises important theoretic and practical considerations regarding the mechanism and prevention of ventricular fibrillation. It is generally agreed that parasystole is an expression of regular impulse formation in an ectopic focus outside the sinoatrial node, this focus being independent of and protected from all other impulses.\textsuperscript{20} The mechanism for such independent impulse formation is considered to be automaticity, in the form of spontaneous diastolic depolarization of Purkinje cells. On theoretic grounds, it may be difficult for a highly organized automatic rhythm to degenerate into a disorganized one such as ventricular fibrillation; on clinical evidence it is exceptional for rapid automatic rhythms such as accelerated idioventricular rhythm and parasystolic ventricular tachycardia to progress to ventricular fibrillation.\textsuperscript{21, 22} On the other hand, there is no general agreement on the genesis of the simple ventricular extrasystole coupled in a fixed relationship to the preceding sinus beat. If this type of ventricular ectopic beat is indeed the result of reentry of the same impulse that caused the preceding depolarization, it suggests the possibility that increased tendency for reentry might be prerequisite for the development of ventricular fibrillation. The practical consequence of this theory in terms of selecting patients for vigorous antiarrhythmic drug prophylaxis is obvious.

Notwithstanding the limitations of this report imposed by a small numerator (14 sudden deaths over a period of follow-up ranging between 30 and 54 months), a relatively small denominator (160 participants), and a variable encompassing 80% of

\textit{Circulation, Volume XLVII, May 1973}
the study population uncovered by a highly sensitive technic of serial periods of continuous electrocardiographic monitoring, we feel justified in concluding that ventricular extrasystoles show independent predictive properties with respect to sudden coronary death. We were unable to demonstrate similar properties for any of the other risk factors analyzed. Such "statistically nonsignificant" results are to be expected when the sample size and number of events are small, and in no way deny a possible role for these risk factors. However, when "statistically significant" results are obtained in spite of a small sample size and number of events, it is very likely that observed differences are meaningful. Our results are in general agreement with current hypotheses about the mechanisms of sudden death in both the acute and late phases of myocardial infarction and are consistent with the large body of data provided by the Coronary Drug Project Research Group report and other studies.

Several other factors that might have influenced the results merit comment. The possible effect of antiarrhythmic drug therapy in either preventing or predisposing to sudden coronary death was considered. Our findings clearly show that antiarrhythmic medications neither led to inaccurate classification of patients into the lower grades of ectopic activity, nor obviously affected the prognosis in either direction. Because of the random and uncontrolled administration of these agents it would be misleading to regard these results as an index of the inefficacy of such medication. It has not been possible to date to analyze the role of the lipid-lowering agents on the results. Because of the double-blind nature of the CDP, this analysis must await the termination of the study. However, two of the original treatment schedules, high-dose estrogens and dextrothyroxine, have been discontinued. Four of our 14 sudden coronary deaths occurred in patients on dextrothyroxine, one death occurred in a patient on the high-dose estrogen schedule, and one in a patient on known placebo at the time of death. The remaining eight deaths occurred in patients either on low-dose estrogen, nicotinic acid, clofibrate or placebo. It seems very unlikely on the available data, with such a small number of events and so many treatment groups that any single treatment schedule would have contributed in a significant manner to sudden death.

Another factor worthy of consideration is the possibility that some clinical factor which may have been the primary risk factor led us to apply more tapes in certain patients than in others, thereby identifying a higher prevalence of ventricular ectopic beats in patients at greater risk. In point of fact, the main reason for patients receiving an unequal number of tape studies was technical rather than clinical. For example, patients were often unwilling to wear a recorder at certain times, or may have missed clinic visits. The fact that those patients in the sudden death group received a total of 45 tape recordings or an average of 3.2 per patient as compared with an average of 4.6 per patient in the survivors indicated that there was no bias for frequency of recordings in patients at higher risk.

It should be appreciated that any population of infarct survivors is a select group, particularly in this study where patients regarded as functional NYHA class III or IV were excluded. Therefore, our data does not bear on the role of ventricular ectopic beats in patients with advanced heart disease on the one hand or in a premorbid population on the other, although studies in these populations suggest a similar role for the more complex forms of ventricular ectopic activity (frequent unifocal, multifocal, and ventricular tachycardia) as a determinant of sudden death. Nor does our data relate to the independent prognostic significance of additional risk factors. Studies employing larger cohorts and utilizing more sophisticated statistical models do indeed provide relevant information on the prognostic significance of serum lipids, hypertension, diabetes, age, relative body weight, cigarette smoking (Coronary Drug Project Research Group: Unpublished data), congestive heart failure at the time of infarction, major arrhythmias in the acute phase, and electrocardiographic pattern characteristics in survivors of myocardial infarction. Along these lines our results do define certain population groups at greater or lesser risk of sudden death. For example, the patient with ventricular ectopic beats and S-T segment depression on the ECG would seem to be at high risk, particularly if he is a cigarette smoker; conversely, the nonsmoker with no or rare unifocal ventricular ectopic beats and absence of pathologic Q waves on the ECG would seem to have an excellent prognosis. It is hoped that the technics employed in this study will help define population groups at risk of sudden death in order to develop effective methods of prophylaxis, pharmacologic or electronic.
Acknowledgment

We are indebted to Dr. Jeremiah Stamler and members of the Editorial Review Board of the Coronary Drug Project for their careful review of the manuscript.

References

Prognostic Significance of Ventricular Ectopic Beats with Respect to Sudden Death in the Late Postinfarction Period

MORRIS N. KOTLER, BERNARD TABATZNIK, MORTON M. MOWER and SUKETAMI TOMINAGA

Circulation. 1973;47:959-966
doi: 10.1161/01.CIR.47.5.959

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1973 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/47/5/959

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at: http://circ.ahajournals.org//subscriptions/