Natural History of Cardiac Arrhythmias
and their Prevention with Quinidine in Patients
with Acute Coronary Insufficiency

By Saul S. Bloomfield, M.D., Donald W. Romhilt, M.D.,
Te-Chuan Chou, M.D., and Noble O. Fowler, M.D.

SUMMARY
In a prospective controlled clinical trial the natural history of cardiac arrhythmias and their prevention with prophylactic quinidine therapy were studied in 23 patients with acute coronary insufficiency without myocardial infarction. After a loading procedure, 300 mg of quinidine sulfate or placebo was administered orally every 6 hours for up to 5 days under balanced, random, double-blind conditions. An automated arrhythmia detection system was used to quantify arrhythmias from stored continuous electrocardiographic tape recordings.

The frequency of ventricular and supraventricular arrhythmias tended to increase progressively on each successive day of study in placebo-treated patients. By contrast, in quinidine-treated patients all arrhythmias were quantitatively lower on each day of therapy and did not show a tendency toward progressive daily increases. In the placebo group there was an average of 140 premature ventricular contractions (PVC's) per day on the first day which increased to 600 PVC's per day by the fifth day, whereas with quinidine there was an average of 40 PVC's per day or less throughout the 5 days of study ($P < 0.01$). The daily increase in ventricular arrhythmias in placebo-treated patients with acute coronary insufficiency during the 5 days is in contrast to the natural history of patients with documented myocardial infarction who have a marked daily decrease in the frequency of ventricular arrhythmias during the first 5 days. Significant arrhythmia suppression with quinidine was present when mean blood quinidine concentration reached a steady state above 4 mg/liter at the end of the first day of therapy. Adverse reactions to quinidine were not observed. On the basis of these data, quinidine sulfate given prophylactically at a dosage producing modest blood concentrations appeared to be both effective and safe for the prevention of ventricular and supraventricular arrhythmias that occurred during the first 5 days after an episode of acute coronary insufficiency without infarction.

Additional Indexing Words: Coronary heart disease
Antiarrhythmic drug
Premature ventricular contractions
Coronary care unit

The high incidence of ventricular arrhythmias following acute myocardial infarction has been well documented and has led to treatment programs, both therapeutic and prophylactic, aimed at suppressing these arrhythmias with the intent of reducing mortality. In the coronary care unit initial emphasis was directed toward patients with verified myocardial infarction, but more recently patients with acute coronary insufficiency without infarction have received considerable attention. In a previous communication, we reported a clinical trial which demonstrated the efficacy of prophylactic quinidine sulfate for the prevention of arrhythmias following uncomplicated acute myocardial infarction in 55 patients. During the same period we also studied 25 patients whose presenting symptoms were similar, but the diagnosis of acute myocardial infarction was not subsequently verified. The purpose of this report is to describe the incidence and natural history of arrhythmias and their prevention with quinidine sulfate in 25 patients with acute coronary insufficiency.
Methods

Patient Selection Criteria

On accession to study, the 25 patients were under 70 years of age and had a history of coronarylike pain during the previous 24 hours. Twenty-two patients had severe substernal chest pain lasting longer than 30 min while three patients had multiple episodes of substernal chest pain lasting 15–20 min which were more severe and lasted longer than previous episodes of angina pectoris. The electrocardiogram of 19 patients had either S-T-segment elevation suggestive of an acute injury pattern (three patients) or marked T-wave inversion consistent with myocardial ischemia (16 patients). One patient had marked S-T-segment depression and five patients had nonspecific abnormalities of the S-T segment and T wave. Two patients had an old myocardial infarction on the electrocardiogram. The following complications were absent at the onset of study: shock, atrioventricular block, bundle-branch block, severe heart failure, uremia, coma, or an existing arrhythmia. The diagnosis of acute myocardial infarction was excluded on the basis of an evaluation by two independent observers utilizing the following criteria: (1) daily electrocardiograms which failed to reveal the development of pathologic Q waves, and (2) daily serum enzyme determinations (creatinine phosphokinase, serum glutamic oxaloacetic transaminase, lactic dehydrogenase) which did not demonstrate a rise.

Patients under study were admitted to either the Cincinnati General, Jewish, or Veterans Administration Hospitals. At all three hospitals, patients received uniform management, including routine nasal administration of oxygen for 48 hours, opiates for analgesia, barbiturates for sedation, and heparin as an anticoagulant. No antiarrhythmic agent except the study medication was administered during the trial. It was planned to remove from study any patient who developed a recognized arrhythmia which required specific therapy, or any patient who developed heart block, shock, uremia, or heart failure requiring digitalis therapy. Also, any patient with evidence of quinidine toxicity by symptomatology or by QRS prolongation greater than 25% from the pretreatment tracing on conventional electrocardiograms taken twice daily was removed from the trial. Data were collected for 5 days on 20 patients and for 2 days on five patients unless any of the above-named complications occurred earlier. In the latter eventualities, data collected up to the time of withdrawal from study were retained for inclusion in the analysis.

Design of Trial

The trial compared a quinidine-treated group of patients with a control group receiving indistinguishable placebos under double-blind conditions. Attending physicians and staff nurses also were unaware of which patients received quinidine, and the investigators remained blind until after the data had been analyzed. Upon entering the study patients were randomly allocated to one of the two treatment groups according to a predetermined schedule. The randomization provided for stratification of patients according to sex and hospital, with equal balancing of treatments within strata. Since the trial was a between-subject comparison, each patient was studied with only one form of treatment.

Experimental medications consisted of quinidine sulfate, 300 mg, or placebo in identical coded capsules. Three oral doses were given fasting at 3-hour intervals as a loading procedure, followed by one dose every 6 hours before meals for the remainder of the study period. If necessary, the drug code for any patient could be broken without revealing the treatment received by other patients. The decision to remove a patient from study was always made before the code for that patient was broken.

Evaluation of Response

Results of treatment with quinidine and placebo were evaluated with continuous electrocardiographic tape recordings using the Holter-Avionics recorder for the entire time the patient was being studied. The stored tapes with the continuous electrocardiogram for the entire study period were subsequently played back at real time and analyzed with a Hewlett-Packard automated arrhythmia detection system. The automated arrhythmia detection system recognized arrhythmias by two criteria: (1) change in R-R interval by more than 20%; (2) widening of the QRS by more than 0.015 sec as compared with the average of four normal QRS complexes for that patient. The instrument was set to printout automatically intermittent electrocardiograms which contained a complete record of all arrhythmias, including single ectopic beats fulfilling either of these two criteria. The time of each episode of arrhythmia to the nearest minute was recorded on the electrocardiogram by an automated time stamp. All electrocardiographic printouts by the automated arrhythmia detection system were read, and each arrhythmia or premature ventricular contraction was identified and quantified from the electrocardiographic printout on an hour-by-hour basis by the investigators. From this analysis each arrhythmia or single premature ventricular contraction was verified visually by the investigators, and all artifacts were excluded.

The efficacy of quinidine in preventing arrhythmias was determined by a comparison between the two treatment groups with respect to the occurrence of the following arrhythmias: premature ventricular contractions (PVC's), serious ventricular arrhythmias, and premature supraventricular contractions. All arrhythmia data were statistically analyzed for treatment differences by the Mann-Whitney U test (two-tailed) with the use of a computer program specially written for this purpose.

In all patients, blood quinidine levels were determined at the sixth and ninth hours after entry into study, i.e., before and 3 hours after the end of the loading period, and then once or twice daily for the remaining days immediately before administration of a dose of drug. Blood quinidine concentration was

*Serious ventricular arrhythmias were defined according to the criteria set by Low: PVC's of more than five/min, multifocal, "R on T," consecutive in runs of two or more or bigeminy.
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determined in all samples by an automated adaptation of the protein precipitation spectrophotofluorometric method.14

Results
Patient Characteristics and Results of Randomization

Electrocardiographic tape recordings for 23 of these 25 patients were acceptable for processing and analysis and the data presented concern this group of 23 patients. Electrocardiographic data for the two excluded patients were uninterpretable owing to technical problems with the tape recordings. Three patients in the placebo group and two in the quinidine group were studied for only 48 hours. The 23 patients included 13 men and 10 women.

Twelve patients comprised the placebo group and 11 the quinidine-treated group. Group characteristics of these patients on entry into study are shown in table 1. The two treatment groups were similar in all baseline characteristics examined at the time of entry except for sex distribution, Q-T interval, and numbers of patients on maintenance digitalis therapy. Especially noteworthy was the time at which study drugs were started in relation to the onset of the acute episode; the mean interval was 16 hours in both the placebo and quinidine groups.

After entry into the study, the numbers of patients in each treatment group receiving concomitant medications including opiates, barbiturates, and heparin were equal. An exception, however, was diuretic therapy which was given to five placebo-treated patients but only one quinidine-treated patient. The fact that more placebo-treated patients than those treated with quinidine received digitalis (table 1) and diuretics before and after entering the study was probably due to chance. The possibility is raised, however, that despite the randomization of patients to the two treatment groups, the discrepancy between the groups in administered diuretics and digitalis might have contributed in some way to observed differences in arrhythmia activity associated with the two treatments.

Effect on Arrhythmias

Data on arrhythmias for the entire duration of study in all 23 patients were completely analyzed and form the basis of this report. The mean number of PVC's per day was significantly lower (P < 0.01 or better) in the quinidine-treated patients than in the placebo patients on each of the 5 days of the study (fig. 1). The mean number of PVC's per day in quinidine-treated patients stayed at a rather constant low level throughout the 5 days of study, i.e., 40 PVC's per day or less. By contrast, in placebo-treated patients the mean number of PVC's tended to increase progressively on each successive day. On the first day there was an average of 140 PVC's and these increased progressively during the course of the 5 days, until a maximum of 600 PVC's was reached on the fifth day. A parallel pattern was observed with respect to the mean number of

Table 1

<table>
<thead>
<tr>
<th>Characteristics of Treatment Groups on Entry into Study</th>
<th>Placebo group</th>
<th>Quinidine group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Sex (no.):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Women</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Age (mean yr ± SEM)</td>
<td>55 ± 2</td>
<td>53 ± 2</td>
</tr>
<tr>
<td>Weight (mean kg ± SEM)</td>
<td>74.3 ± 3.8</td>
<td>73.9 ± 2.3</td>
</tr>
<tr>
<td>Interval between acute episode and entry (mean hr ± SEM)</td>
<td>16 ± 1.7</td>
<td>16 ± 2.2</td>
</tr>
<tr>
<td>History of previous infarction (no. of pt)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Maintenance digitalis therapy (no. of pt)</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Serum enzymes (mean ± SEM):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum SGOT (U/ml)</td>
<td>43 ± 7</td>
<td>45 ± 6</td>
</tr>
<tr>
<td>Maximum LDH (U/ml)</td>
<td>519 ± 40</td>
<td>464 ± 44</td>
</tr>
<tr>
<td>Maximum CPK (U/ml)</td>
<td>29 ± 12</td>
<td>43 ± 10</td>
</tr>
<tr>
<td>Blood chemical findings (mean ± SEM):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/100 ml)</td>
<td>17 ± 1</td>
<td>15 ± 2</td>
</tr>
<tr>
<td>Serum potassium (mEq/liter)</td>
<td>4.2 ± 0.2</td>
<td>4.3 ± 0.1</td>
</tr>
<tr>
<td>Serum sodium (mEq/liter)</td>
<td>137 ± 1</td>
<td>138 ± 1</td>
</tr>
</tbody>
</table>

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Occurrence of arrhythmias during each day of prophylactic quinidine or placebo therapy.

episodes of serious ventricular arrhythmias and to a lesser degree the mean number of premature supraventricular contractions (fig. 1). These data indicate that prophylactic quinidine therapy quantitatively reduced ventricular arrhythmias of all degrees of severity and also reduced premature supraventricular contractions, especially after the first day of treatment. They also suggest that a natural daily increase in both ventricular and supraventricular arrhythmias occurred in the placebo patients during the 5 days which followed an episode of acute coronary insufficiency without infarction.

Because the initial 48 hours after entry were considered to be a very critical period for development of ventricular arrhythmias, the data on ventricular arrhythmias for this period were examined during each of eight successive 6-hour intervals (fig. 2). The mean number of PVC's per 6-hour interval throughout the first 48 hours of study, including the first 6 hours, was lower in the quinidine-treated patients than in the placebo-treated patients, with placebo-quinidine differences reaching statistical significance at the end of 24 hours. Similarly the mean number of serious ventricular arrhythmias per 6-hour interval was lower in the quinidine-treated patients than in placebo patients during these 48 hours except for the first 6-12 hours (fig. 2). These data suggest that during the initial 48 hours after acute coronary insufficiency, quinidine afforded protection against ventricular arrhythmias, but that owing to the natural history of these arrhythmias the protection was more obvious after than during the first 24 hours.

Withdrawals from Study and Side Effects

Five patients were removed from study before the end of the study period (table 2). Two patients, who were not receiving digitalis, in the quinidine group were removed early from study because of the development of 2:1 atrioventricular block on the second day of study in one patient and atrioventricular dissociation 5 hours after entry into the study in the other. Two placebo-treated patients were removed from the study early; one when it was discovered that the prescribed study medication had been omitted inadvertently, and the other was removed early by error. Finally, one patient in the quinidine group died of subarachnoid hemorrhage at the end of the first day of study. On postmortem examination significant coronary artery disease (>50% narrowing in two vessels) was present in this patient and myocardial infarction was absent. On the average, quinidine-treated patients did not have appreciable widening of the QRS complex or prolongation of P-R and Q-T intervals, nor did they show greater changes in heart rate and arterial pressure than patients given placebo. Side effects of nausea, vomiting, diarrhea or QRS prolongation greater than 25% of the
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![Graphs showing PVC and serious ventricular arrhythmias](image)

**Figure 2**

Occurrence of ventricular arrhythmias during initial 48 hours of prophylactic quinidine or placebo therapy.

pretreatment tracing did not occur in any placebo or quinidine-treated patient.

**Blood Quinidine Concentration**

Mean blood quinidine concentrations at various times after entry into study are shown in figure 3. At the sixth hour, the blood quinidine level was 3.3 ± 0.5 (mean ± SEM) mg/liter. A maximum mean concentration of 5.2 ± 0.5 mg/liter was reached by the ninth hour after which a steady state was in effect. From the arrhythmia data, it would appear that significant arrhythmia suppression with quinidine was present when steady state blood levels had been achieved.

On the basis of these data, quinidine sulfate given prophylactically at a dosage producing modest blood concentrations appeared to be both effective and safe for the prevention of ventricular and supraventricular arrhythmias that occurred during the first 5 days after an episode of acute coronary insufficiency without infarction.

**Discussion**

In an earlier report on the efficacy of prophylactic quinidine against cardiac arrhythmias after

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of pt.</th>
<th>Heart block</th>
<th>Drug not received</th>
<th>Other</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>12</td>
<td>0</td>
<td>1</td>
<td>1*</td>
<td>2</td>
</tr>
<tr>
<td>Quinidine</td>
<td>11</td>
<td>2</td>
<td>0</td>
<td>1†</td>
<td>3</td>
</tr>
<tr>
<td>Totals</td>
<td>23</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

*By error.
†Died of subarachnoid hemorrhage.
Acute myocardial infarction, the present authors observed that over the course of the first 5 days following acute myocardial infarction there was a natural daily decline in numbers of supraventricular and ventricular arrhythmias of all degrees of severity. This progressive decrease in arrhythmias was present in both untreated (placebo) and quinidine-treated patients, such that the highest frequency of arrhythmias occurred on the first day after acute myocardial infarction, and by the fifth day arrhythmias were virtually absent. By contrast, the data reported in the present paper show that in coronary heart disease patients with acute coronary insufficiency without infarction there is a reversal in the natural history of arrhythmias (fig. 4). In untreated (placebo) patients with acute coronary insufficiency the lowest frequency of all arrhythmias occurred on the first day of study with progressive daily increments such that by the fifth day the frequency of cardiac arrhythmias was still increasing. Although this increase in PVC’s is rather marked in figure 4, it still represents only one PVC every 2–3 min on day 5 and could represent a baseline level of PVC’s for this group of patients. This difference in natural history of arrhythmias in patients with acute coronary insufficiency without infarction compared with patients having acute infarction is difficult to explain and certainly was not anticipated. These data suggest that there is increasing excitability of myocardial tissue in patients with acute coronary insufficiency, and decreasing excitability of the myocardium in patients with acute infarction. However, it is possible that PVC’s actually decreased during the initial period of observation in the patients with acute coronary insufficiency because of treatment.
with oxygen, analgesics, and sedatives, and later returned to their baseline level.

The protection afforded by quinidine in preventing the development of arrhythmias, although present in the early hours after an acute episode, did not reach statistical significance until the end of 24 hours. This contrasts with the findings in patients with acute myocardial infarction where the same dosage regimen of quinidine was found to afford significant protection as early as the sixth hour after initiation of therapy. One possible explanation for this difference could be a need for higher blood levels of quinidine in patients with acute coronary insufficiency without infarction. This is supported by the observation that arrhythmia suppression in the latter patients occurred only when mean blood quinidine concentrations reached a steady state in excess of 4 mg/liter whereas in patients with acute infarction, arrhythmia suppression was present with mean concentration as low as 2.5 mg/liter. This finding raises the possibility that arrhythmias following acute myocardial infarction are more easily suppressed by quinidine than arrhythmias in coronary heart disease without acute myocardial infarction. However, other factors could also account for the difference in arrhythmia protection with quinidine between coronary insufficiency and infarct patients. These factors include differences in the natural history of arrhythmias in these two clinical conditions which, as already mentioned, would tend to show significant differences between treated and untreated patients as early as the first day in patients with acute infarction but only later in patients with acute coronary insufficiency. Furthermore, the number of coronary insufficiency patients studied was less than half that of the myocardial infarction patients (N=55) so that significant differences between treated and untreated coronary insufficiency patients might be difficult to demonstrate in the early hours when arrhythmias were quantitatively at a lower level of frequency.

The effectiveness of quinidine in protecting patients with acute coronary insufficiency against arrhythmias was matched by its apparent lack of significant toxicity. In view of the efficacy and safety of prophylactic quinidine in suppressing arrhythmias in patients with acute coronary heart disease it seems reasonable to suggest that prophylactic quinidine should be evaluated in a clinical trial to determine its effect on morbidity and mortality in ambulatory patients with coronary artery disease, who are at high risk of sudden death.

References

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