Time-Dependent Risk of and Predictors for Cardiac Arrest Recurrence in Survivors of Out-of-Hospital Cardiac Arrest With Chronic Coronary Artery Disease

Tetsushi Furukawa, MD, John J. Rozanski, MD, Akihiko Nogami, MD, Kazuo Moroe, MD, Arthur J. Gosselin, MD, and John W. Lister, MD

One hundred one consecutive patients with chronic coronary artery disease who had survived out-of-hospital cardiac arrest in the absence of acute myocardial infarction underwent electrophysiologic evaluation and were followed prospectively. Ventricular tachyarrhythmias were inducible in 76 patients (75%) in the control state and were suppressed by antiarrhythmic drugs or surgery in 32 of the 76 patients (42%). During a mean follow-up of 27 months, cardiac arrest recurred in 21 patients: in two of the 25 patients in whom ventricular tachyarrhythmias were not inducible in the control state, three of the 32 in whom inducible ventricular tachyarrhythmias were suppressed after treatment, and 16 of the 44 in whom inducible ventricular tachyarrhythmias could not be suppressed after treatment. Actuarial rate of cardiac arrest recurrence was 11.2% during the first 6 months of follow-up ("high-risk early phase") and then decreased to less than 4% in each subsequent 6-month period. Multivariate Cox proportional hazards analysis identified an ejection fraction less than 35% (p=0.0013) and persistent inducibility of ventricular tachyarrhythmias (p=0.0025) as independent predictors of cardiac arrest recurrence for the entire follow-up period. Separate analysis of variables within and after the first 6 months showed that an ejection fraction less than 35% was the strongest predictor for early phase recurrence (p=0.0078) but had only marginally significant predictive value for late phase recurrence (p=0.0516). Persistent inducibility of ventricular tachyarrhythmias had no significant predictive value for early phase recurrence (p=0.1382) but was the strongest predictor for late phase recurrence (p=0.0061). These data suggest that, in patients with chronic coronary artery disease who survive out-of-hospital cardiac arrest, poor ejection fraction and persistent inducibility of ventricular tachyarrhythmias have a different predictive influence on early and late phase recurrence. Time-dependent risk factor analysis may have great clinical relevance in assessing an individual's changing risk over time. (Circulation 1989;80:599–608)

Patients who have survived out-of-hospital cardiac arrest unassociated with acute myocardial infarction are at high risk of subsequent life-threatening ventricular tachyarrhythmias.1–8 Previous studies have indicated that the risk of subsequent arrhythmic events may change with time and is particularly high during the early phase of clinical follow-up.1–4,9–11 In this study, we examined the changing risk of cardiac arrest recurrence with time and changing influence of various clinical, angiographic, and electrophysiologic parameters on subsequent cardiac arrest recurrence with time in a cohort of patients with chronic coronary artery disease who have survived an out-of-hospital cardiac arrest. A better understanding of these factors may be helpful in selecting the most appropriate therapy.

Methods

Patients

One hundred forty-two consecutive patients who had survived out-of-hospital cardiac arrest unassociated with a myocardial infarction within the three weeks preceding the arrest underwent electrophysiologic evaluation between October 1980 and June 1987 and were prospectively followed up to June

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TABLE 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>66±10</td>
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<tr>
<td>Sex (male/female)</td>
<td>84/17</td>
</tr>
<tr>
<td>Presented arrhythmia</td>
<td></td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>82 (81%)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>19 (19%)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>82 (81%)</td>
</tr>
<tr>
<td>More than one MI</td>
<td>21 (21%)</td>
</tr>
<tr>
<td>Time duration from MI to CA</td>
<td></td>
</tr>
<tr>
<td>≥4 mo</td>
<td>27 (33%)</td>
</tr>
<tr>
<td>&lt;4 mo</td>
<td>55 (67%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>36 (36%)</td>
</tr>
<tr>
<td>Involved coronary vessels (n)</td>
<td></td>
</tr>
<tr>
<td>One vessel</td>
<td>28 (29%)</td>
</tr>
<tr>
<td>Two vessels</td>
<td>35 (37%)</td>
</tr>
<tr>
<td>Three vessels</td>
<td>32 (34%)</td>
</tr>
<tr>
<td>Left ventricular aneurysm</td>
<td>33 (33%)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>38±10</td>
</tr>
<tr>
<td>≥35%</td>
<td>45 (45%)</td>
</tr>
<tr>
<td>&lt;35%</td>
<td>56 (55%)</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; CA, cardiac arrest.

1988. For purposes of this study, only patients with coronary artery disease were included (101 patients). All patients required cardiopulmonary resuscitation including external direct-current countershock for restoration of stable cardiac rhythm.

Clinical characteristics of the patients are summarized in Table 1. The mean age of the patients was 66±10 years. The rhythm present at the time of cardiac arrest was ventricular fibrillation in 82 patients (81%) and ventricular tachycardia in 19 (19%). Previous myocardial infarction had occurred in 82 patients (81%) with 21 (21%) having had more than one infarction. Cardiac catheterization was performed in 95 patients. Six patients with a history of previous myocardial infarction were not catheterized because of advanced age. Significant coronary lesions were defined as greater than 70% reduction of the luminal diameter. One-vessel disease was detected in 28 patients (29%), two-vessel disease in 35 (37%), and three-vessel disease in 32 (34%). Segmental left ventricular wall motion abnormalities and ejection fraction were determined angiographically in 95 patients and by radionuclide-gated scan in six. Thirty-three patients had a left ventricular aneurysm. The mean ejection fraction was 38±10%; 56 patients (55%) had an ejection fraction <35%.

Electrophysiologic Study

After informed consent, electrophysiologic study was carried out in the fasting nonsedated state, at least five half-lives after antiarrhythmic medication had been discontinued. None of the patients received amiodarone before baseline electrophysiologic study. The electrophysiologic study was performed at a mean of 20.8 (range, 3–58) days after the episode of cardiac arrest. For stimulation, rectangular pulses of 1-msec duration were delivered at twice diastolic threshold. In all patients, we followed a strict stimulation protocol until a sustained ventricular tachyarrhythmia was initiated or the protocol was completed. One to four extrastimuli were delivered at drive cycle lengths of 600 and 400 msec. For each extrastimulus, diastole was scanned at 10-msec decrements to the point of ventricular refractoriness by the standard technique.12 The protocol was first performed at the right ventricular apex. If stimulation at the right ventricular apex did not result in a sustained ventricular tachyarrhythmia, the stimulation protocol was repeated at the second right ventricular site (outflow tract or septum), and one to four extrastimuli were delivered at drive cycle lengths of 600 and 400 msec. Induced ventricular tachyarrhythmias were defined as 1) sustained ventricular tachycardia: ventricular tachycardia lasting 30 seconds or more or having to be terminated before 30 seconds because of hemodynamic decompensation, 2) nonsustained ventricular tachycardia: ventricular tachycardia lasting 10 beats or more and self-terminating in less than 30 seconds, and 3) ventricular fibrillation: initiated arrhythmia if within 3 seconds after initiation of a sustained ventricular tachyarrhythmia, ventricular fibrillation characterized by completely disorganized electrical activity and no identifiable QRS complexes was present in any of the surface electrocardiographic leads.

Therapy was assessed by electrophysiologic testing in all patients in whom ventricular tachyarrhythmias were induced in the control state. Evaluated therapies included antiarrhythmic drugs and surgery (endocardial resection, endocardial cryoablation, or aneurysmectomy) guided by electrical mapping of activation sequence. Selection of drug regimens was based on each patient’s history of drug tolerance and clinical response. The following drugs were tested after intravenous administration: 10–15 mg/kg (50 mg/min) procainamide, 10 mg/kg (20 mg/min) quinidine, 0.2 mg/kg (1 mg/min) propranolol, and lidocaine, bolus infusion of 225 mg during 20 minutes, followed by a 2-mg/min continuous infusion. The following oral agents were tested at trough blood levels after administration of a sufficient number of doses to attain a steady-state serum drug level: 3–8 g/day procainamide, 1.2–1.6 g/day quinidine, 400–600 mg/day disopyramide, 0.8–1.2 g/day tocainide, 300–600 mg/day mexiletine, 200–400 mg/day encainide, 140–200 mg/day enacainide, and amiodarone 1,200–1,600 mg/day for 10 days, then 600–800 mg/day. Plasma drug concentrations, if available, were measured at the end of each drug study. In four patients, treatment with an oral antiarrhythmic drug was prematurely terminated before electrophysiologic testing because of development of spontaneous sustained ventricular tachycardia (two patients) or incessant ventricular tachycardia (two patients); two with 400 mg/day flecainide, one with procainamide 6 g/day, and one with 140 mg/day enacainide. Recommendations for surgical treatment were based on the presence of an apparent discrete left ventricular aneurysm, reproducible induction of sustained monomorphic ven-
tricular tachycardia that allowed endocardial mapping, failure of suppression of ventricular tachyarrhythmia induction by multiple drug trials, and the patient’s clinical course. Treatment with coronary artery bypass grafting was offered to patients on the basis of coronary artery anatomy, exercise stress testings, and the patient’s clinical course. Those patients (nine patients) with an inducible ventricular tachyarrhythmia who underwent coronary artery bypass grafting in addition to other treatment modalities had electrophysiologic testing after bypass grafting. Antiarrhythmic drugs or surgery were considered effective if neither sustained nor nonsustained ventricular tachyarrhythmias were inducible after treatment.

**Long-term Therapy and Follow-up**

Patients in whom induction of ventricular tachyarrhythmia was suppressed by antiarrhythmic drugs or surgery were discharged on the regimen that successfully suppressed induction of ventricular tachyarrhythmia. Drug dose was adjusted to yield serum levels matching levels found to be successful in suppressing ventricular tachyarrhythmia induction in the laboratory. In patients in whom induction of ventricular tachyarrhythmias was suppressed by amiodarone, the dose of amiodarone was reduced to 400 mg/day after 3–4 weeks.

Those in whom induction of ventricular tachyarrhythmia could not be suppressed before June 1986 were treated with antiarrhythmic drugs. The regimen was carefully determined based on the rate of induced ventricular tachyarrhythmia and hemodynamic stability during tachyarrhythmia. Those after June 1986 were treated with the automatic implantable cardioverter-defibrillator with no additional antiarrhythmic drug therapy.

Of the patients in whom ventricular tachyarrhythmia was not inducible in the control state, those in whom baseline 24-hour Holter recording showed a mean frequency of premature ventricular beats of 30 beats/hr or more were treated with antiarrhythmic drugs guided by Holter recording. Effective therapy was defined as that suppressing more than 80% of isolated premature ventricular beats, more than 90% of ventricular couplets, and 100% of ventricular triplets and longer repetitive forms on the Holter recording. In patients who had no inducible ventricular tachyarrhythmia in the control state and who were treated with antiarrhythmic drugs guided by Holter monitoring, coronary artery bypass grafting, or β-blocking agents, programmed electrical stimulation to assess potential “proarrhythmic” effects was not performed.

Follow-up data were obtained in all patients at 3–6 month intervals. The mean follow-up period was 27±17 months (range, 6 days to 63 months). Recurrent cardiac arrest was defined as sudden and unexpected circulatory collapse in a patient with previously stable circulatory function, resulting in death or requiring defibrillation for restoration of stable cardiac rhythm. For purposes of this study, internal defibrillator discharges were considered to represent recurrent cardiac arrest only if they were preceded by syncope or presyncope.

**Statistical Analysis**

Continuous data are expressed as mean±SD. Comparisons of the clinical characteristics between the subgroups were made by Student’s unpaired t test or χ² test with Yates’ correction as appropriate. Predictive values (p values) less than 0.05 were considered significant.

Actuarial curves and actuarial rates for cardiac arrest recurrence were calculated with the Kaplan-Meier method. Actuarial recurrence rates were expressed as mean±SEM and were compared between the groups with the Mantel-Cox statistic. Nineteen variables (see Table 2) were screened by univariate statistical methods to identify those associated with cardiac arrest recurrence. Multivariate Cox proportional hazards analysis was applied to all variables that had at least marginal univariate predictive value (p<0.10). This analysis was used to identify variables with significant independent predictive value (p<0.05).

**Results**

**Electrophysiologic Testing**

In the control state, 76 patients (75%) had inducible ventricular tachyarrhythmias. Sustained mono-

<table>
<thead>
<tr>
<th>TABLE 2. Nineteen Variables Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical variables</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Sex (male vs. female)</td>
</tr>
<tr>
<td>VF as a presenting arrhythmia at the time of CA</td>
</tr>
<tr>
<td>Previous MI</td>
</tr>
<tr>
<td>More than one MI</td>
</tr>
<tr>
<td>Anterior wall MI</td>
</tr>
<tr>
<td>Q wave MI</td>
</tr>
<tr>
<td>Time from remote MI to episode of CA (&lt;4 vs. ≥4 mo)</td>
</tr>
<tr>
<td>Angina</td>
</tr>
<tr>
<td>Congestive heart failure requiring treatment with digitalis or diuretics</td>
</tr>
<tr>
<td>BBB or IVCD</td>
</tr>
<tr>
<td>Lown grade IV B at baseline Holter recording</td>
</tr>
<tr>
<td>Lown grade IV B at predischarge Holter recording</td>
</tr>
<tr>
<td>Angiographic variables</td>
</tr>
<tr>
<td>Number of involved coronary vessels (one vessel, two vessels vs. three vessels)</td>
</tr>
<tr>
<td>Significant stenosis in LAD</td>
</tr>
<tr>
<td>Left ventricular aneurysm</td>
</tr>
<tr>
<td>Ejection fraction (≥55% vs. &lt;35%)</td>
</tr>
<tr>
<td>Results of electrophysiologic study</td>
</tr>
<tr>
<td>Inducibility of VTA in the control state</td>
</tr>
<tr>
<td>Persistent inducibility of VTA</td>
</tr>
</tbody>
</table>

VF, ventricular fibrillation; CA, cardiac arrest; MI, myocardial infarction; BBB, bundle branch block; IVCD, intraventricular conduction defect; LAD, left anterior descending coronary artery; VTA, ventricular tachyarrhythmia.
TABLE 3. Final Treatment of the Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Noninducible VTA (n=25)</th>
<th>Inducible VTA/VTSA suppressed (n=32)</th>
<th>Inducible VTA/VTSA persisted (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmic drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type IA*</td>
<td>11 (44%)</td>
<td>25 (78%)</td>
<td>39 (86%)</td>
</tr>
<tr>
<td>Type IB†</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Type IC†</td>
<td>6</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>0</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>Antiarrhythmic surgery</td>
<td>0 (0%)</td>
<td>6 (19%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>and drugs</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>AICD</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Additional treatment</td>
<td>11 (44%)</td>
<td>12 (38%)</td>
<td>12 (43%)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>7 (28%)</td>
<td>4 (13%)†</td>
<td>5 (11%)†</td>
</tr>
</tbody>
</table>

VTA, ventricular tachycardia; AICD, automatic implantable cardioverter-defibrillator; CABG, coronary artery bypass grafting.

*Procainamide, quinidine, or disopyramide.
†Mexiletine or tocainide.
‡Flecainide or encainide.
§Endocardial resection, endocardial cryoablation, or aneurysmectomy.
¶All four patients underwent coronary artery bypass grafting in addition to antiarrhythmic surgery.
||Two patients underwent coronary artery bypass grafting in addition to antiarrhythmic surgery, and three underwent coronary artery bypass grafting in addition to implantation of an automatic implantable cardioverter-defibrillator.

Morphogenic ventricular tachycardia occurred in 45, sustained polymorphic ventricular tachycardia in nine, nonsustained monomorphic ventricular tachycardia in nine, nonsustained polymorphic ventricular tachycardia in eight, and ventricular fibrillation in five. Twenty-five patients had no inducible ventricular tachyarrhythmias. The mean cycle length of induced sustained ventricular tachycardia was 268 msec (range, 200–430 msec), and that of nonsustained ventricular tachycardia was 246 msec (range, 190–310 msec). The mean duration of induced nonsustained ventricular tachycardia was 16 beats (range, 10–39 beats).

Treatment

Serial electrophysiologic testing was performed in all 76 patients who had inducible ventricular tachyarrhythmias in the control state (mean, 3.1±1.0 therapeutic trials/patient). Inducible ventricular tachyarrhythmias were suppressed after treatment in 32 patients (42%); 25 patients with antiarrhythmic drugs alone, six with antiarrhythmia surgery alone, and one with antiarrhythmic surgery and drugs (Table 3). Four patients underwent coronary artery bypass grafting in addition to antiarrhythmic surgery. These 32 patients were discharged on the regimen that successfully suppressed induction of ventricular tachyarrhythmias.

Forty patients in whom inducible ventricular tachyarrhythmias persisted after treatment before June 1986 were discharged on a drug regimen in which the induced ventricular tachyarrhythmia was slowed and was associated with hemodynamic stability: five patients with conventional antiarrhythmic drugs, 33 with amiodarone, and two with antiarrhythmic surgery and drugs. Four patients with persistent inducibility of ventricular tachyarrhythmias after June 1986 were treated with the automatic implantable cardioverter-defibrillator with no additional antiarrhythmic drug therapy. Two patients underwent coronary artery bypass grafting in addition to antiarrhythmic surgery, and three underwent coronary artery bypass grafting in addition to implantation of an automatic implantable cardioverter-defibrillator.

The 24 patients without inducible ventricular tachyarrhythmias in the control state were treated as follows: six with conventional antiarrhythmic drugs, five with coronary artery bypass grafting, eight with β-blocking agents, two with antiarrhythmic drugs and coronary bypass grafting, and three with antiarrhythmic drugs and β-blocking agents.

The clinical characteristics of each of the three subgroups of ventricular tachyarrhythmia inducibility are presented in Table 4. The subgroup with inducible ventricular tachyarrhythmias that were suppressed after treatment was more likely to have presented with ventricular tachycardia at the time of cardiac arrest than the subgroup without inducible ventricular tachyarrhythmias. Both of the two subgroups with inducible ventricular tachyarrhythmias were significantly more likely to have previous myocardial infarction, left ventricular aneurysm, and lower left ventricular ejection fraction than the subgroup without inducible ventricular tachyarrhythmias. There was no significant difference in any of the clinical characteristics between the two subgroups with inducible ventricular tachyarrhythmias.

Recurrent Cardiac Arrest for the Entire Follow-up Period

During a mean follow-up of 27 months, cardiac arrest occurred in 21 of the 101 patients. In 18 patients resuscitation was not performed or was not successful. Two patients were successfully resuscitated from cardiac arrest, and one had syncope followed by discharge of an implanted cardioverter-defibrillator. The cumulative actuarial rate of cardiac arrest recurrence at 4 years was 24.4±4.8% (Figure 1). Recurrent cardiac arrest occurred in two of the 25 without inducible ventricular tachyarrhythmias in the control state, in three of the 32 with inducible ventricular tachyarrhythmias in the control state that were suppressed after treatment, and in 16 of the 44 with inducible ventricular tachyarrhythmias in the control state that could not be suppressed after treatment. Patients with inducible ventricular tachyarrhythmias in the control state that could not be suppressed after treatment had a 40.9±8.0% cumulative cardiac arrest recurrence rate at 4 years. This was significantly higher than the recurrence rate for patients without induc-
Table 4. Comparisons of Clinical Characteristics Between Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Noninducible VTA (n=25)</th>
<th>Inducible VTA/VT suppressed (n=32)</th>
<th>Inducible VTA/VT persisted (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>67±11</td>
<td>64±11</td>
<td>66±8</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>23/2</td>
<td>23/9</td>
<td>38/6</td>
</tr>
<tr>
<td>Presenting arrhythmia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VF</td>
<td>24 (96%)</td>
<td>23 (72%)</td>
<td>35 (78%)</td>
</tr>
<tr>
<td>VT</td>
<td>1 (4%)</td>
<td>9 (28%)</td>
<td>9 (20%)</td>
</tr>
<tr>
<td>Previous MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 (60%)</td>
<td>30 (94%)</td>
<td>37 (84%)</td>
</tr>
<tr>
<td>Time duration from MI to CA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4 mo</td>
<td>5 (33%)</td>
<td>7 (23%)</td>
<td>15 (41%)</td>
</tr>
<tr>
<td>&lt;4 mo</td>
<td>10 (67%)</td>
<td>23 (77%)</td>
<td>22 (59%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (20%)</td>
<td>11 (34%)</td>
<td>20 (45%)</td>
</tr>
<tr>
<td>Involved coronary vessels (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One vessel</td>
<td>10 (43%)</td>
<td>7 (23%)</td>
<td>11 (27%)</td>
</tr>
<tr>
<td>Two vessels</td>
<td>4 (17%)</td>
<td>13 (42%)</td>
<td>18 (44%)</td>
</tr>
<tr>
<td>Three vessels</td>
<td>9 (39%)</td>
<td>11 (35%)</td>
<td>12 (29%)</td>
</tr>
<tr>
<td>LV aneurysm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (8%)</td>
<td>15 (47%)</td>
<td>16 (36%)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥35%</td>
<td>46±18</td>
<td>37±14</td>
<td>35±12</td>
</tr>
<tr>
<td>&lt;35%</td>
<td>14 (56%)</td>
<td>12 (37%)</td>
<td>19 (43%)</td>
</tr>
</tbody>
</table>

VTA, ventricular tachyarrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia; MI, myocardial infarction; CA, cardiac arrest; LV, left ventricle.

*p<0.05; †p<0.01.

Table contents:

- Age (yr): 67±11 (Noninducible), 64±11 (Inducible suppressed), 66±8 (Inducible persisted)
- Sex (male/female): 23/2, 23/9, 38/6
- Presenting arrhythmia:
  - VF: 24 (96%), 23 (72%), 35 (78%)
  - VT: 1 (4%), 9 (28%), 9 (20%)
- Previous MI: 15 (60%), 30 (94%), 37 (84%)
- Time duration from MI to CA:
  - ≥4 mo: 5 (33%), 7 (23%), 15 (41%)
  - <4 mo: 10 (67%), 23 (77%), 22 (59%)
- Congestive heart failure: 5 (20%), 11 (34%), 20 (45%)
- Involved coronary vessels (n):
  - One vessel: 10 (43%), 7 (23%), 11 (27%)
  - Two vessels: 4 (17%), 13 (42%), 18 (44%)
  - Three vessels: 9 (39%), 11 (35%), 12 (29%)
- LV aneurysm: 2 (8%), 15 (47%), 16 (36%)
- Ejection fraction (%):
  - ≥35%: 46±18, 37±14, 35±12
  - <35%: 14 (56%), 12 (37%), 19 (43%)

**Figure 1.** Cumulative actuarial curve of cardiac arrest recurrence. Actuarial recurrence rate in each 6-month period is shown along the top of the figure. Actuarial recurrence rate was 11.2% during the first 6 months ("high risk early phase") and decreased to less than 4% after 6 months. Numbers adjacent to the curve represent patients remaining.

**Figure 2.** Recurrence rate of cardiac arrest was not significantly different between patients without inducible ventricular tachyarrhythmias in the control state (9.0±6.1%, p=0.0154) and the recurrence rate for patients with inducible ventricular tachyarrhythmias in the control state that were suppressed after treatment (9.5±5.2%, p=0.0191). Recurrence rate of cardiac arrest was not significantly different between patients without inducible ventricular tachyarrhythmias in the control state that were suppressed after treatment (p=0.8652) (Figure 2).

**Figure 3.** Congestive heart failure (p=0.0313), greater number of involved coronary vessels (p=0.0329), an ejection fraction less than 35% (p=0.0012), and persistent inducibility of ventricular tachyarrhythmias (p=0.0029) were each significantly related to cardiac arrest recurrence according to univariate analysis (Table 5). Multivariate Cox proportional hazards analysis identified the following two variables as significant independent predictors of cardiac arrest recurrence: an ejection fraction less than 35% (p=0.0013) and persistent inducibility of ventricular tachyarrhythmias (p=0.0025) (Table 5).

**Figure 3.** Actuarial curves for cardiac arrest recurrence were constructed for the following four groups based on the two multivariate predictors above (Figure 2): group 1, an ejection fraction 35% or more and no persistent inducibility; group 2, an ejection fraction 35% or more and persistent inducibility; group 3, an ejection fraction less than 35% and no persistent inducibility; group 4, an ejection fraction less than 35% and persistent inducibility. The cumulative actuarial rate of cardiac arrest recurrence at 4 years was 3.9±3.8% for group 1, 13.4±9.0% for group 2, 14.1±6.6% for group 3, and 58.7±10.4% for group 4 (Figure 3). Cardiac arrest recurrence rate was significantly higher in
Time-Dependent Analysis of Cardiac Arrest Recurrence

Actuarial rate for cardiac arrest recurrence was calculated in each 6-month period up to 4 years (Figure 1). The actuarial recurrence rate was 11.2% during the first 6 months ("high risk early phase") and then decreased to less than 4% for each subsequent 6-month period. Multivariate Cox proportional hazards analysis was separately applied to the high risk early phase (≤6 months) and the lower risk subsequent phase (>6 months) (Table 6). During the first 6 months, an ejection fraction less than 35% was the only significant predictor for cardiac arrest recurrence (p=0.0078). After 6 months, the following three variables were identified as univariate predictors for cardiac arrest recurrence: congestive heart failure (p=0.0179), a greater number of involved coronary vessels (p=0.0245), and persistent inducibility of ventricular tachyarrhythmias (p=0.0043). The following two variables were identified as multivariate predictors: congestive heart failure (p=0.0173) and persistent inducibility (p=0.0061). An ejection fraction less than 35% had only marginal predictive value (p=0.0516).

Actuarial recurrence rates during the first 6 months and after 6 months were compared among the four groups. During the first 6 months, group 4 had a 28.8±9.2% recurrence rate, and this was significantly higher than the recurrence rate of group 1 (3.9±3.8%, p=0.0175) and that of group 2 (0.0±0.0%, p=0.0163). Group 3 had a 10.0±5.5% recurrence rate that was not significantly different from the recurrence rate of groups 1, 2, or 4. After 6 months, group 4 still had a high recurrence rate (47.5±13.3%), which was significantly greater than the recurrence rate of group 1 (0.0±0.0%, p=0.0047), group 2 (15.6±10.4%, p=0.0414), and group 3 (4.9±4.8%, p=0.0149).

Discussion

We studied survivors of out-of-hospital cardiac arrest who had coronary artery disease unassociated with a recent myocardial infarction. The main purposes of this study were to assess 1) the changing risk of cardiac arrest recurrence with time and 2) the changing predictive value of clinical, angiographic, and electrophysiologic parameters for cardiac arrest recurrence with time. Coronary artery disease is the most common cause of out-of-hospital cardiac arrest, accounting for approximately 80% of the cases.1-4 Survivors of out-of-hospital cardiac arrest with coronary artery disease may be quite different from those with other types of cardiac disease in terms of risk of cardiac arrest recurrence and its predictors.18-20 For example, a recent study by Trappe et al20 showed a much higher incidence of subsequent sudden cardiac death in survivors of out-of-hospital cardiac arrest with chronic coronary artery disease than those without. To minimize the influence of such uncontrollable variables, we chose a relatively homogeneous cohort of survivors of out-of-hospital cardiac arrest: those with chronic coronary artery disease in whom the cardiac arrest was unrelated to acute myocardial infarction so that the effects of time on the risk of and predictors for cardiac arrest recurrence could be studied.

In general, the risk of cardiac arrest recurrence is particularly high during the early phase of clinical follow-up. Studies from the early 1970s1-4 reflecting the best approximation of natural history available,19 in which a large fraction of patients were not on long-term antiarrhythmic therapy or received ther-
apy not considered appropriate by current standards, revealed a recurrence rate of 30% to 36% in the first year, decreasing to 10% to 15% in the second year. More recent studies, in which most patients were on long-term antiarrhythmic therapy guided by drug blood levels or electrophysiologic testing, indicated an improved cardiac arrest recurrence rate. \(^{10,11}\) Nevertheless, the recurrence rate for cardiac arrest continued to show two phases: a high risk early phase and a lower risk subsequent phase. The cumulative recurrence rate was 10% to 15% in the first year, decreasing to 5% in the following year. \(^{10,11}\) In our study of cardiac arrest survivors with chronic coronary artery disease, the actuarial curves for cardiac arrest recurrence also showed a similar biphasic change. Recurrence was high during the first 6 months (11.2%) and then decreased to less than 4% for each subsequent 6-month period.

A reduced ejection fraction and inducibility of ventricular tachyarrhythmias either in the control state or after treatment were identified as powerful predictors of outcome in previous studies. \(^{8,11,21-28}\) In our study, when multivariate Cox proportional hazards analysis was applied to the entire follow-up period, a reduced ejection fraction and persistent inducibility of ventricular tachyarrhythmias were also the only two significant independent predictors of subsequent cardiac arrest recurrence. These two predictors were found to have different influences during the early versus late phase of follow-up. Within the phases themselves, a reduced ejection fraction was the only predictor for early phase (≤6 months) recurrence, whereas persistent inducibility of ventricular tachyarrhythmia was the strongest predictor for late phase (>6 months) recurrence.

The predictive value of a reduced ejection fraction for early phase recurrence was very strong. Of the 11 cardiac arrest recurrences that occurred within the first 6 months, 10 occurred in patients with an ejection fraction less than 35%, and only one occurred in patients with an ejection fraction of 35% or more. The predictive value of a reduced ejection fraction for late phase recurrence decreased to a marginally significant level \(p=0.0516\). Bigger et al\(^{29}\) studied patients after myocardial infarction and showed a similar finding that a low ejection fraction predicted early (<6 months) mortality better than late (>6 months) mortality. It is reasonable

### Table 5. Predictors of Cardiac Arrest Recurrence: Entire Follow-up Period

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Recurrence of CA</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes ((n=21))</td>
<td>No ((n=80))</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>64±9</td>
<td>66±10</td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>18/3</td>
<td>66/14</td>
<td>0.4167</td>
</tr>
<tr>
<td>VF as presenting arrhythmia</td>
<td>17 (81%)</td>
<td>65 (81%)</td>
<td>0.9551</td>
</tr>
<tr>
<td>Previous MI</td>
<td>18 (86%)</td>
<td>64 (80%)</td>
<td>0.5510</td>
</tr>
<tr>
<td>More than one MI</td>
<td>6 (29%)</td>
<td>15 (19%)</td>
<td>0.2320</td>
</tr>
<tr>
<td>Anterior wall MI</td>
<td>12 (57%)</td>
<td>44 (55%)</td>
<td>0.7921</td>
</tr>
<tr>
<td>Presence of Q wave MI</td>
<td>15 (71%)</td>
<td>56 (70%)</td>
<td>0.7882</td>
</tr>
<tr>
<td>Time duration from MI to CA                   &lt;4 mo</td>
<td>13 (72%)</td>
<td>42 (66%)</td>
<td>0.4702</td>
</tr>
<tr>
<td>Angina</td>
<td>12 (57%)</td>
<td>35 (44%)</td>
<td>0.4261</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>12 (57%)</td>
<td>24 (30%)</td>
<td>0.0313</td>
</tr>
<tr>
<td>BBB or IVCD</td>
<td>14 (67%)</td>
<td>34 (43%)</td>
<td>0.0803</td>
</tr>
<tr>
<td>Lown grade IV B at baseline Holter</td>
<td>12 (57%)</td>
<td>33 (41%)</td>
<td>0.4553</td>
</tr>
<tr>
<td>Lown grade IV B at predischarge Holter</td>
<td>8 (38%)</td>
<td>10 (13%)</td>
<td>0.2882</td>
</tr>
<tr>
<td>Involved coronary vessels ((n))</td>
<td></td>
<td></td>
<td>0.0329</td>
</tr>
<tr>
<td>One vessel</td>
<td>2 (11%)</td>
<td>26 (34%)</td>
<td></td>
</tr>
<tr>
<td>Two vessels</td>
<td>8 (44%)</td>
<td>27 (35%)</td>
<td></td>
</tr>
<tr>
<td>Three vessels</td>
<td>8 (44%)</td>
<td>24 (31%)</td>
<td></td>
</tr>
<tr>
<td>LAD involvement</td>
<td>19 (90%)</td>
<td>67 (84%)</td>
<td>0.4300</td>
</tr>
<tr>
<td>LV aneurysm</td>
<td>12 (57%)</td>
<td>21 (26%)</td>
<td>0.3721</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>30±7</td>
<td>40±15</td>
<td>0.0012</td>
</tr>
<tr>
<td>&lt;35%</td>
<td>18 (86%)</td>
<td>38 (47%)</td>
<td></td>
</tr>
<tr>
<td>Inducibility of VTA in the control state</td>
<td>19 (90%)</td>
<td>57 (71%)</td>
<td>0.0871</td>
</tr>
<tr>
<td>Persistent inducibility of VTA</td>
<td>16 (76%)</td>
<td>28 (35%)</td>
<td>0.0029</td>
</tr>
</tbody>
</table>

CA, cardiac arrest; Uni, univariate analysis; Multi, multivariate analysis; VF, ventricular fibrillation; MI, myocardial infarction; BBB, bundle branch block; IVCD, intraventricular conduction defect; LAD, left anterior descending coronary artery; LV, left ventricle; VTA, ventricular tachyarrhythmia.
to assume that patients with a poor ejection fraction might tend to succumb during the first 6 months, whereas those with a fairly good ejection fraction might have a survival advantage during the early follow-up period. Congestive heart failure was found to be an independent predictor of late phase recurrence. Even though ejection fraction decreased, its predictive value for late phase cardiac arrest recurrence (p value changing from 0.0078 to 0.0516), ventricular function remained important as indicated by a history of antecedent congestive heart failure being significant (p=0.0173). Also, of note, the number of remaining patients, especially those with left ventricular dysfunction, became smaller after 6 months, which may affect the statistical analysis.

Persistent inducibility of ventricular tachyarrhythmias was the strongest predictor of cardiac arrest recurrence after 6 months but statistically had no significant predictive value during the first 6 months. In the electrophysiology laboratory, the influences of contributing factors, such as ischemia, autonomic nervous tone, electrolyte balance, and so on, could not be adequately assessed. In patients in whom ventricular tachyarrhythmias occurred clinically because of the contributions of these intangible factors, cardiac arrest may recur during the early phase of follow-up. These possible explanations, however, are not supported by any data, and further investigation is required before any definitive comment can be made.

The inducibility of ventricular tachyarrhythmias in this study (75%) was consistent with other studies (69–81%), whereas the rate of inducing ventricular fibrillation (5%) was relatively low compared with previous reports (8–15%). Inducible nonsustained ventricular tachycardia has been considered a potentially important finding by

![Graph](https://circ.ahajournals.org/)

**FIGURE 3.** Cumulative actuarial curve of cardiac arrest recurrence for each of the four groups based on two multivariate predictors: an ejection fraction less than 35% and persistent inducibility of ventricular tachyarrhythmias. Group 1, an ejection fraction of 35% or more and no persistent inducibility; group 2, an ejection fraction of 35% or more and persistent inducibility; group 3, an ejection fraction less than 35% and no persistent inducibility; group 4, an ejection fraction less than 35% and persistent inducibility. At the top of the panel, the cumulative recurrence rates during the entire period, the early phase, and the late phase of follow-up were compared. RCA, recurrence of cardiac arrest.

| Group 1 vs 4 | P=0.0003 | P=0.0175 | P=0.0047 |
| Group 2 vs 4 | P=0.0033 | P=0.0163 | P=0.0414 |
| Group 3 vs 4 | NS | P=0.0149 |

**TABLE 6.** Predictors of Cardiac Arrest Recurrence: Early and Late Phase of Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Early phase (&lt;6 mo)</th>
<th>Late phase (&gt;6 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.5151</td>
<td>0.8254</td>
</tr>
<tr>
<td>Sex</td>
<td>0.3893</td>
<td>0.9778</td>
</tr>
<tr>
<td>VF as presenting arrhythmia</td>
<td>0.7918</td>
<td>0.9022</td>
</tr>
<tr>
<td>Presence of MI</td>
<td>0.4755</td>
<td>0.9240</td>
</tr>
<tr>
<td>More than one MI</td>
<td>0.9320</td>
<td>0.0778</td>
</tr>
<tr>
<td>Anterior wall MI</td>
<td>0.4518</td>
<td>0.4109</td>
</tr>
<tr>
<td>Presence of Q wave</td>
<td>0.5611</td>
<td>0.8771</td>
</tr>
<tr>
<td>Time duration from MI to CA &lt;4 mo</td>
<td>0.5533</td>
<td>0.3996</td>
</tr>
<tr>
<td>Angina</td>
<td>0.3133</td>
<td>0.4173</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.4688</td>
<td>0.0179</td>
</tr>
<tr>
<td>BBB or IVCD</td>
<td>0.2639</td>
<td>0.1719</td>
</tr>
<tr>
<td>Lown grade IV B at baseline Holter</td>
<td>0.6027</td>
<td>0.5613</td>
</tr>
<tr>
<td>Lown grade IV B at predischarge Holter</td>
<td>0.4684</td>
<td>0.2822</td>
</tr>
<tr>
<td>Involved coronary vessels (n)</td>
<td>0.2584</td>
<td>0.0245</td>
</tr>
<tr>
<td>LAD involvement</td>
<td>0.7201</td>
<td>0.5013</td>
</tr>
<tr>
<td>LV aneurysm</td>
<td>0.1908</td>
<td>0.9558</td>
</tr>
<tr>
<td>Ejection fraction &lt;35%</td>
<td>0.0078</td>
<td>0.0078</td>
</tr>
<tr>
<td>Inducibility of VTA in the control state</td>
<td>0.3571</td>
<td>0.1417</td>
</tr>
<tr>
<td>Persistent inducibility of VTA</td>
<td>0.1382</td>
<td>0.0043</td>
</tr>
</tbody>
</table>

Uni, univariate analysis; Multi, multivariate analysis; VF, ventricular fibrillation; MI, myocardial infarction; CA, cardiac arrest; BBB, bundle branch block; IVCD, intraventricular conduction defect; LAD, left anterior descending coronary artery; LV, left ventricle; VTA, ventricular tachyarrhythmia.
some,23,26–28 but not all,22,24,25,30 investigators. Our study could possibly yield some false-positive responses by using nonsustained ventricular tachycardia as a positive response to programmed ventricular stimulation. Further controlled studies may be required to answer this issue. The percentage of patients in whom inducible ventricular tachyarrhythmia was suppressed after treatment (42%) was relatively low compared with some,8,11,22,24,25,27 but not all,23,26,28 of the previous reports. This may be due to the relatively small number of patients or differences in treatment modalities. Some of the previous studies indicate that inducibility of ventricular tachyarrhythmias in the control state instead of inducibility after treatment had a predictive value for clinical outcome.8,23–27 However, in our study, inducibility of ventricular tachyarrhythmias in the control state had only a marginal predictive value (p = 0.0871), which is in agreement with the recent study by Wilber et al.11 The actuarial rate of cardiac arrest recurrence was about the same between patients with no inducible ventricular tachyarrhythmias in the control state (9.0 ± 6.1%) and those in whom inducible ventricular tachyarrhythmias were suppressed after treatment (9.5 ± 5.2%).

The group with both a reduced ejection fraction and persistent inducibility of ventricular tachyarrhythmias had a very high recurrence rate over the entire follow-up period irrespective of treatment with antiarrhythmic drugs or surgery. The group with a reduced ejection fraction and no persistent inducibility also had a high recurrence rate during the first 6 months. It is important to identify patients at high risk for recurrence of cardiac arrest in whom aggressive treatment, including the automatic implantable cardioverter-defibrillator, is clearly indicated. Study of the changing time dependence of various predictors for cardiac arrest recurrence can allow an ongoing assessment of risk on an individual basis.

Limitations

Because of the high recurrence of out-of-hospital cardiac arrest, we used a relatively aggressive stimulation protocol of up to four extrastimuli to minimize false-negative responses. This could have yielded some false-positive responses.30,31 Long-term therapy was not completely uniform in patients with persistent inducibility of ventricular tachyarrhythmias and in those without inducible ventricular tachyarrhythmias in the control state. These therapeutic biases may limit rigorous interpretation of our results.

The small sample size of various subgroups might have substantially influenced statistical analysis of various predictors, especially those with borderline predictive value.

Acknowledgment

We greatly appreciate the statistical analyses performed by Robert W. Chen, PhD.

KEY WORDS • electrophysiology • ventricular fibrillation • ventricular tachycardia • antiarrhythmia • coronary artery disease • cardiac arrest
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