Arrhythmic Cardiac Arrest Due to Isolated Coronary Artery Spasm: Long-Term Outcome of Seven Resuscitated Patients

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Objectives. Our aim was to look at the clinical features and long-term follow-up of seven patients without coronary artery disease, who had a history of life-threatening ventricular arrhythmias due to coronary spasm.

Background. Arrhythmic cardiac arrest due to isolated coronary spasm is rare, and there is limited information on the patients affected by this entity alone.

Methods. The seven patients were recruited retrospectively from a cohort of survivors of cardiac arrest. None had a history of angina pectoris, structural heart disease or significantly narrowed coronary segments. All had a positive ergonovine provocation test result.

Results. The patients' mean age was 44 years; three were male and four female. All were habitual cigarette smokers. No arrhythmias were induced on programmed ventricular stimulation; corrected QT interval (QTc) and corrected JT interval (JTc) dispersion were within normal ranges. After the ergonovine provocation test, treatment with calcium channel blocking agents (diltiazem, verapamil, nifedipine or amlodipine) was initiated at a dose determined by titration until a negative test result was obtained. At a mean follow-up interval of 58 months for the total group, six patients remained free of symptoms, whereas the one patient who did not stop smoking had a new cardiac arrest despite treatment for coronary spasm.

Conclusions. A favorable long-term outcome may be expected in survivors of cardiac arrest due to coronary spasm, in the absence of significant coronary artery disease. Calcium channel blockers are the most appropriate therapy in these patients. These observations provide further evidence for the role of silent ischemia in cardiovascular death.

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Rarely, isolated coronary artery spasm that is not associated with coronary artery obstruction may trigger lethal ventricular arrhythmias (1–6). It has therefore been recommended that the ergonovine test should be performed in any patient who is resuscitated from cardiac arrest in whom no structural heart disease can be found. Few reports (1,5–10) have described the clinical characteristics and the long-term outcome of these patients. Treatment with calcium channel antagonists, with or without nitrates, seems to confer a good prognosis. However, because the number of patients reported on is small and the length of the follow-up period has usually been short, it is difficult to draw firm conclusions about this treatment.

The mechanism for the abnormalities in vasomotor tone of the coronary arteries is gradually being deciphered (11). The endothelium, a target of cigarette smoking, plays a key role in vasomotor regulation, and its dysfunction may be the first detectable sign of the early stages of atherosclerosis (12). However, there are no data to support the view that minor coronary atherosclerosis may be revealed by arrhythmic cardiac death.

It has been suggested (1,13,14) that silent ischemia due to coronary artery spasm may be capable of inducing ventricular arrhythmias in patients without flow-limiting structural coronary artery lesions. Nonetheless, the presence of an occult arrhythmogenic substrate cannot be completely ruled out in this context (15). Finally, in the era of automatic cardioverter defibrillators, there is still a lack of information regarding the optimal management of such patients.

In this study, we review our experience with seven patients who had arrhythmic cardiac arrest due to coronary artery spasm that was not associated with significant coronary artery narrowing. We place special emphasis on the characteristics and evolution of this unusual syndrome.

Methods

Study patients who were referred to three French hospital centers (Lyon, Grenoble and Saint-Etienne) for evaluation and treatment of documented malignant ventricular tachyarrhythmias requiring emergency cardiopulmonary resuscitation and defibrillation were retrospectively collected from a cohort of survivors of cardiac arrest. The inclusion criteria were those described by Myerburg et al. (1) and were: 1) cardiac arrest...
with documented ventricular fibrillation or sustained rapid ventricular tachycardia; 2) the absence of angina pectoris or acute myocardial infarction; 3) normal angiographic left ventricular ejection fraction and wall motion; 4) the absence of significant coronary artery narrowing (50%) or of any structural cardiac abnormalities; 5) a positive maleate ergonovine test result, defined as the occurrence of severe (>75% reduction in lumen diameter) coronary spasm, together with chest pain and electrocardiographic (ECG) evidence of ischemia; 6) the absence of identifiable or correctable causes of ventricular arrhythmia, such as pre-excitation syndromes, long QT interval, metabolic or electrolyte disturbances or drug toxicity. Other patients with possible spasm who were not suitable for the protocol were excluded. These were mostly patients with angina pectoris or coronary spasm occurring on introduction of the catheter into the coronary artery or patients with no repeat ergonovine test. Patients who had no documentation of the cardiac rhythm during resuscitation were also excluded from the study.

A medical history was taken from all patients, followed by a physical examination, chest X-ray, 12-lead ECG recorded at a paper speed of 25 mm/s, M-mode and two-dimensional echocardiography and measurement of cardiac enzymes. The length of the precordial QT interval, corrected QT interval (QTC, measured according to the Bazett formula [16]), QTC dispersion and corrected QT interval (JTC) dispersion were measured and compared with values in a control group of seven age-matched normal subjects. The QT interval was measured from the beginning of the QRS complex to the end of the T wave. The JT interval was defined as the time between the J point and the end of the T wave. Coronary angiography was performed by standard Judkins technique (6F, Softip, Schneider) with a biplane cineangiographic device; all patients were fasting and receiving 2,000 U of heparin intravenously before the procedure. The examination was completed by left and right ventricular angiography.

An electrophysiologic examination was performed without antiarrhythmic medication. Three electrode catheters (Bard laboratories) were introduced percutaneously through the femoral vein and positioned in the heart under fluoroscopic guidance. A 7F quadrupolar catheter was placed in the right atrium and two others were placed at the right ventricular apex and the atrioventricular junction (to record the bundle of His). During ventricular pacing (basic cycle length 600, 500 and 400 ms), single, double or triple ventricular extrastimuli were delivered every 8 beats. Pacing was performed at twice diastolic threshold with use of a 2-ms pulse width. If tachycardia was not induced, the same protocol was repeated after isoproterenol infusion.

The spasm provocation test was performed ≥1 week after the initial cardiac arrest. Methylergometrine solution was injected into a peripheral vein in four patients and into either the left main or the right coronary artery through the catheter in three patients. Doses of 0.4 mg were administered to trigger vasospasm. A standard 2-lead ECG was monitored continuously. Once the ability of ergonovine to induce spasm was established, the patients received a calcium channel blocker (diltiazem, verapamil, amlodipine or nifedipine). Then, the ergonovine test was repeated after a time interval of at least 5 drug half-lives. If a persistent positive test result was obtained, another calcium channel blocker was used and the methylergometrine test repeated. In this way, appropriate treatment, proved by a negative provocation test result was found for each patient.

Follow-up. Each patient was followed up in the outpatient clinic, by one of us (P.C., A.D., P.D.) or by the referring physician, after discharge, at 1 month and then every year. Patient compliance in taking the prescribed medications was evaluated by the medical history. Local ethical guidelines were followed in each center. The history was taken and a physical examination and 12-lead ECG were performed at each visit. Special attention was paid to any recurrence of symptomatic arrhythmia, as well as to the development of features of underlying structural heart disease that might previously have been latent. The length of follow-up was measured from initial documentation of the ventricular arrhythmia.

### Statistical analysis. Differences between groups were compared by analysis of variance and Fisher exact test. A p value <0.05 was considered statistically significant.

### Results

**Patient characteristics.** The clinical and paraclinical data are shown in Tables 1 and 2. All patients were found to have a combination of coronary artery spasm provoked by a maleate ergonovine test and documented ventricular arrhythmias. There were seven patients, three men and four women. Their mean age was 44 ± 16 years. None had a family history of cardiac disease or had previously had angina pectoris or any other prodrome. For each patient, the initial cardiac arrest had

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**Table 1. Demographic and Clinical Characteristics of the Seven Study Patients**

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Age (yr)/Gender</th>
<th>Date (mo/yr)</th>
<th>Rhythm at Time of Cardiac Arrest</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22/F</td>
<td>02/1986</td>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>2</td>
<td>46/M</td>
<td>05/1990</td>
<td>Ventricular tachycardia (230/min)</td>
</tr>
<tr>
<td>3</td>
<td>53/F</td>
<td>06/1990</td>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>4</td>
<td>50/F</td>
<td>02/1993</td>
<td>Ventricular tachycardia (230/min)</td>
</tr>
<tr>
<td>5</td>
<td>44/M</td>
<td>11/1993</td>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>6</td>
<td>52/M</td>
<td>06/1994</td>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>7</td>
<td>45/F</td>
<td>12/1995</td>
<td>Ventricular fibrillation</td>
</tr>
</tbody>
</table>

*All seven patients presented clinically with cardiac arrest and all were habitual cigarette smokers at the time of the arrest. F = female; M = male; Pt = patient.*
been sudden and unexpected, and it had required resuscitation and electric defibrillation. Five patients had had ventricular fibrillation and the other two had had rapid sustained ventricular tachycardia. No obvious triggering factors, such as stress or an emotional disorder, could be found. All patients were habitual smokers. There was no past history of alcohol or drug abuse.

Results of the physical examination were normal in all patients. No structural heart disease or known causes of ventricular arrhythmia were apparent. No patient was taking medication at the time of the cardiac arrest. Signal-averaged electrocardiography and electrophysiologic testing yielded negative results. Values for left ventricular ejection fraction were within normal range. Although no patient had significant coronary lesions, minimal diameter narrowing, judged to be \( \leq 30\% \), was found in four patients at the site of spasm. No ECG or angiographic evidence of a prior myocardial infarction was apparent.

The QTc interval was normal in the seven patients \((340 \pm 60\, \text{ms})\), and there were no significant differences in either QTc \((34 \pm 12\, \text{vs.} \, 40 \pm 16\, \text{ms})\) or JTc \((28 \pm 8\, \text{vs.} \, 30 \pm 11\, \text{ms})\) dispersion between the patient and control groups. During the ergonovine test, only Patient 2 had nonsustained ventricular tachycardia. In each patient, the triggered spasm was promptly relieved by intracoronary nitroglycerin. Long-term pharmacologic treatment was determined by means of a maleate ergonovine test during coronary arteriography. Testing was repeated, after the addition of different calcium channel blockers, until spasm could no longer be induced. With this method, three patients were given a single calcium channel blocker, while the others were treated using two calcium channel antagonists.

**Long-term follow-up.** The follow-up period after the documented episode of ventricular arrhythmia ranged between 12 and 129 months (mean 58). At the final consultation, all seven patients were still alive and six were symptom-free. The remaining patient (Patient 1, a 22-year old woman), was resuscitated from a new cardiac arrest 10 years after the first one. Angina pectoris had developed 1 year after the initial cardiac arrest, despite optimal medical therapy and good compliance. Repeat angiography demonstrated the unexpected appearance of a fixed proximal stenosis in the left anterior descending coronary artery and the right coronary artery, exactly at the site of the previous coronary spasms. This young patient was the only one who had not given up smoking. She underwent insertion of an automatic implantable cardioverter defibrillator. Coronary bypass surgery was temporarily postponed because of the cerebral sequelae of the cardiac arrest, but it was later undertaken. In the other six patients, calcium channel blockers appeared to give long-lasting protection.

**Discussion**

The seven study patients with coronary spasm–induced cardiac arrest were from three different hospital centers that are close to each other. The main investigators have long been working in a close relation, benefiting from the geographic proximity of the three centers. The same methods for evalua-
tion and medical management were therefore used for all of the patients selected for the study. This represents a unique series in terms of the number of patients included, the common protocol and the length of follow-up.

**Follow-up data.** Previous studies of survivors of arrhythmic cardiac arrest due to isolated coronary spasm have been scarce and limited in size and in duration of follow-up. In 1980, MacAlpin (9) documented ergonovine-induced isolated coronary spasm in nine patients with angina pectoris who had been resuscitated from cardiac arrest. Only one patient had a recurrent cardiac arrest; it occurred 3 months after the initial event despite treatment with a combination of nitrates and calcium channel blockers. The length of follow-up of the remaining patients was not stated. Some years later, Morady et al. (7), described 2 similar patients, recruited from 19 survivors of cardiac arrest, who had no apparent heart disease. They were treated with calcium channel blockers alone and had no recurrence of cardiac events during a follow-up period of 36 and 16 months, respectively. Soon afterward, Fellows et al. (5) followed up 3 patients with isolated coronary spasm who were identified from a cohort of 260 survivors of cardiac arrest. All were treated with nitrates and calcium channel blockers and remained symptom-free at 3, 6 and 19 months of follow-up, respectively. In 1992, Myerburg et al. (1) described five patients who were resuscitated from coronary spasm–related sudden death. Four of them received calcium channel antagonists and had no recurrence during a mean follow-up period of 36 ± 18 months; the fifth patient was treated with beta-blockers and also remained event-free. Weston et al. (8) described a 37-year-old woman who experienced a cardiac arrest due to coronary artery spasm. Treatment with calcium antagonists was sufficient to prevent a recurrence of the cardiac arrest, but the follow-up interval was not specified. Igarashi et al. (6) found 1 patient, among 25 survivors of sudden cardiac arrest, with ergonovine-induced coronary spasm and no coronary stenosis. He was treated by calcium channel blockers and nitrates and was asymptomatic during the 13-month follow-up period. Among 11 patients with cardiac arrest and no overt heart disease, Wever et al. (10) found only 1 with a positive ergonovine test result. This patient, treated with an automatic implantable cardioverter defibrillator alone, experienced an appropriate electric shock (i.e., for true ventricular tachycardia) during the follow-up period, which lasted 43 months for the whole cohort.

**Predisposing factors.** In our series, more women than men were affected. A male predominance has been suggested by other studies (5–7), although a female predominance is seen in patients with Prinzmetal angina and normal coronary arteries (17). The mean age of our patients was slightly lower than that reported in the study of Myerburg et al. (1) (44 ± 16 vs. 53 ± 9 years), but it is similar to that noted in other studies (5,8). Overall, these patients seem to be younger than those affected by other causes of cardiac arrest (18).

Negative findings on programmed ventricular stimulation appears to be a common observation in such patients (1,7,9). Unlike other investigators (1), we did not observe atrial fibrillation in any of our patients. Moreover, we found no basal abnormality of ventricular repolarization, expressed by the QTc duration and QTc and JTc dispersion. It is possible that dynamic studies, with or without pharmacologic testing, are more likely to detect susceptibility to ventricular arrhythmias in this kind of patient. None of the few reported studies were able to identify a predisposing factor for the occurrence of ventricular arrhythmias in these patients.

**Role of cigarette smoking.** Although all our patients were addicted to smoking, there was only one such patient in the report by Myerburg et al. (1). Other studies (5,7,9,10) did not mention cardiovascular risk factors. A single case report (8) dealt with a 32-year-old woman who was a cigarette smoker. There is strong evidence supporting the role of smoking as a risk factor for coronary spasm (19). In our study, angina pectoris and recurrent cardiac arrest were observed only in the patient who continued smoking. However, this recurrent cardiac arrest was probably due to progression of the coronary artery disease rather than to recurrent coronary spasm. Indeed, in this patient, fixed stenotic lesions were documented as subsequently developing at the previous sites of spasm. It might be speculated that failure to control spasm, due to persistent smoking, may lead to progressive damage to the arterial wall. In this context, Nobuyoshi et al. (20) suggested that minimal coronary lesions were more likely to progress when abnormal spasticity was present.

**Conclusions.** As suggested by this retrospective uncontrolled study in patients with coronary spasm associated with cardiac arrest, guided medical treatment with calcium channel antagonists is usually associated with an event-free clinical course. This observation further stresses the usefulness of the ergonovine test in patients resuscitated from cardiac arrest. Stopping smoking is a necessary complementary measure. Implantable cardioverter defibrillators are not required in most cases. However, recourse to implantable devices remains an alternative in patients who can not benefit from optimal management because of a lack of proved effective therapy or poor compliance.

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