Low prevalence of coronary artery spasm in patients with normal coronary angiograms and unexplained ventricular fibrillation

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Aims The aetiology of ventricular fibrillation in patients without identifiable structural heart disease is unknown. Recently, a high prevalence of silent ischaemia due to coronary artery spasm has been reported in such patients. However, in at least one report, all patients had non-critical coronary artery lesions. Identification of coronary artery spasm as the underlying aetiology of ventricular fibrillation has important therapeutic implications.

Methods and Results We performed ergonovine provocation tests in 18 patients (14 males, and four females; mean age, 36 years) with documented ventricular fibrillation in the absence of identifiable structural heart disease who had undergone aborted sudden death. In group I (n=7) ergonovine provocation tests were performed at a mean interval of 31 months (range 21–42 months) after the index episode. These patients had already received an implantable cardioverter defibrillator, after failed electrophysiologically guided antiarrhythmic therapy. In group II (n=11) the ergonovine provocation test was performed prospectively as part of the diagnostic evaluation. All patients were off antiarrhythmic drugs, calcium entry or beta-adrenoceptor blockers at the time of the ergonovine provocation test. Ergonovine was administered intravenously as a bolus injection, beginning with 0·05 mg followed every 3 min by incremental doses up to a cumulative maximum dose of 0·45 mg. Predefined end-points were: (1) recording of ischaemic ST segment shifts of $\geq 1$ mm in at least two corresponding leads of the 12-lead electrocardiogram; (2) induction of ventricular tachycardia or ventricular fibrillation; and (3) administration of a cumulative dose of 0·45 mg. A positive response to ergonovine was seen in only one patient (5%) in group I in whom there developed ST segment elevation without angina and a short burst of rapid ventricular tachycardia.

Conclusions This study found a low prevalence of coronary artery spasm in patients with aborted sudden death resulting from documented ventricular fibrillation and non-apparent underlying heart disease. All patients had normal coronary angiograms and a negative history for spontaneous episodes of chest pain. The mechanism of arrhythmogenesis in such patients remains largely unknown.

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See page 977 for the Editorial comment on this article.

Introduction

The most frequent cause of unexpected cardiac arrest is ventricular fibrillation, a condition often secondary to ventricular tachycardia. In most survivors, an underlying aetiology is associated with this life-threatening event. This is often advanced coronary artery disease, particularly previous myocardial infarction. However, ventricular fibrillation is unrelated to any identifiable cardiac or non-cardiac disease and is referred to as idiopathic ventricular fibrillation in 1 to 8% of the overall group of survivors of out-of-hospital cardiac arrest, and in up to 14% of the patients younger than 40 years. A high risk of recurrence of major arrhythmic events, ranging from 33% during 19 months follow-up to 37% during 43 months follow-up in patients surviving episodes of idiopathic ventricular fibrillation, has been reported. The implantable cardioverter-defibrillator has been advocated as an important therapeutic tool in the majority of these patients.
The underlying arrhythmogenic mechanism in this patient category is still unknown. However, in most previous studies [6–8], ergonovine testing for coronary artery spasm was not routinely performed in patients without a history of angina and without any electrocardiographic or other evidence of myocardial ischaemia. Recent reports [12–14] suggested a high prevalence of silent ischaemia due to coronary artery spasm as a cause of idiopathic ventricular fibrillation. In one report [12], all patients with coronary artery spasm had ‘non-critical’ coronary artery lesions, while in the study by Igarashi et al. [13,14] the number of patients with no or minor coronary artery disease was not indicated. Identification of coronary artery spasm in patients with ventricular fibrillation would have important therapeutic implications, because monotherapy with a calcium channel blocker might provide adequate protection [12,15].

The objective of the present study was to define the prevalence of coronary artery spasm in patients with documented idiopathic ventricular fibrillation and normal coronary angiograms.

**Methods**

**Patients**

Patient characteristics

Between January 1988 and January 1997, 215 consecutive patients who had survived an episode of documented ventricular fibrillation were referred to the Cardiac Arrhythmia Unit of our hospital. Eighteen of these patients (8%) who had recovered good general health and in whom thorough clinical evaluation did not provide any evidence for structural heart disease or other known causes of ventricular fibrillation were included in the study. None of the patients had a history of chest pain or other symptoms suggestive of angina and none had acute or chronic-stage myocardial infarction. None of the patients had hypertension, diabetes or any medication at the time of the index episode. Substance abuse was excluded. The arrhythmic event was unrelated to metabolic or electrolyte disturbances and drug toxicity.

During hospitalization, all patients were kept in the telemetry monitoring area and were evaluated according to a predefined protocol. This included the patient’s history, routine physical examination, 12-lead electrocardiogram, 24-h (2-channel) Holter monitoring, exercise testing (Bruce protocol) and Valsalva manoeuvre [16], laboratory tests including serum potassium and magnesium concentrations, chest roentgenograms, echocardiography with wall motion analysis and Doppler screening, cardiac catheterization with cineangiography of both the left and right ventricle, coronary angiography, scintigraphic assessment of left ventricular ejection fraction and multiple right ventricular endomyocardial biopsies. In patients undergoing transthoracic implantation of a cardioverter defibrillator, additional transmural biopsies were taken from the right and left ventricular walls. Ventricular preexcitation and long QT patterns, either persistent or transient, were excluded. The aforementioned clinical evaluation comprised the necessary investigations to make the diagnosis of idiopathic ventricular fibrillation according to a recently published consensus statement [16]. We performed a baseline electrophysiological study while off drugs in all patients according to a standard protocol, described previously [17].

Ergonovine provocation test

An ergonovine provocation test was performed as a late additional test after implantation of a cardioverter defibrillator (group I, n=7 patients) or as a part of the baseline evaluation (group II, n=11 patients) in patients without antiarrhythmic drugs, calcium entry or beta-adrenoceptor blockers. The mean time lag between the index episode and the ergonovine provocation test in group I patients was 31 months (range 21–42 months) and in group II patients 2 months (range 1–4 months). All tested patients were in a fasting state and because silent ischaemia and coronary artery spasm occur more often during the morning hours, the tests were performed before 12 noon [17]. Because coronary angiography had already been carried out in the referring centre and was known to be normal, the test was performed at the bedside under continuous five lead (I, II, III, V1, V2) electrocardiographic monitoring and with intravenous access to immediate nitroglycerin injection if necessary. Ergonovine was administered intravenously at 3-min intervals, beginning at 0·05 mg with incremental doses up to a cumulative maximum dose of 0.45 mg. Before each subsequent injection, the patient was questioned about chest pain or other symptoms and a 12-lead electrocardiogram was recorded. Predefined end-points were: (1) recording of ischaemic ST segment shifts of \( \geq 1 \) mm in at least two corresponding leads of the 12-lead electrocardiogram; (2) occurrence of ventricular tachycardia or ventricular fibrillation; or (3) administration of the cumulative dose of 0.45 mg of ergonovine. After the test, the patients were kept in the telemetry monitoring area for at least 3 h.

**Results**

**Patients**

Patient characteristics

Eighteen patients (14 men and four women) meeting the criteria for idiopathic ventricular fibrillation were enrolled in the present study. Mean age of the patients was 36 years; median 32 years; range 17 to 67 years. Eleven of the 18 patients (61%) were younger than 40 years. In five of the 18 patients cardiac arrest had occurred in the morning. Rapid ventricular tachyarrhythmias were inducible by programmed electrical stimulation in six patients (33%); 12 patients were
non-inducible. In one patient non-sustained monomorphic ventricular tachycardia was induced, in one patient non-sustained polymorphic ventricular tachycardia, in one sustained polymorphic ventricular tachycardia and in three ventricular fibrillation. Mean follow-up in group I was 87 months; median 86 months; range 76 to 98 months and in group II 41 months; median 41 months; range 9 to 58 months. During follow-up, major arrhythmic events recurred in four group I patients (57%) and in three group II patients (27%).

Ergonovine provocation test
During the ergonovine provocation test, six patients in group I and 11 in group II were asymptomatic, and the electrocardiogram revealed no ST-T segment changes or ventricular arrhythmias. In one patient in group I, a 54-year-old male, ST-segment elevations occurred in leads II and III of the 12-lead electrocardiogram after administration of 0·45 mg of ergonovine, followed by non-sustained rapid ventricular tachycardia (Fig. 1). After administration of 0·4 mg nitroglycerin, the ST-segment elevation disappeared within 15 s and ventricular arrhythmias did not recur (Fig. 1). Complications did not occur in any of the patients.

Figure 1 Electrocardiogram recording (leads I, II, III, V 1, and V 5) of a 54-year old male with unexplained ventricular fibrillation. Leads II and III show ST segment elevations followed by nonsustained rapid ventricular tachycardia after infusion of 0.45 mg ergonovine. Fifteen seconds after infusion of 0·4 mg nitroglycerin, ST segment elevations have almost disappeared. Negative T waves in leads II and III due to recent ischaemia are still present.

Discussion
In this study a low prevalence of ergonovine-induced coronary artery spasm was found in patients with cardiac arrest due to idiopathic ventricular fibrillation. The patients satisfied the recently published diagnostic criteria for idiopathic ventricular fibrillation[4], and only one of 18 patients (5%) showed a positive response to ergonovine. Our findings are in contrast with recently published studies, suggesting a relatively high prevalence of silent ischaemia due to coronary artery spasm in such patients[12–14]. However, several differences may be noted. First, and probably most significant, is the observation that our patients had normal coronary angiograms. In the study of Myerburg et al.[12] all patients with spasm had some form of coronary artery disease manifested by ‘non-critical’ coronary artery lesions (<50% luminal narrowing). Igarashi et al.[13–14] reported an absence of coronary stenoses of 50% or more, but did not indicate how many patients had normal angiograms. Thus, it is possible that some form of coronary artery disease may have predisposed the study patients to the higher prevalence of coronary artery spasm in those studies. Ventricular fibrillation due to coronary artery spasm has been described, especially in patients with coronary artery disease[19–21].

Second, the mean age of the patients in our study and in those of Myerburg et al.[12] and Igarashi et al.[13,14] were different, 36, and 53 and 50 years, respectively. It is of interest that the one patient in our study who had a positive response to ergonovine was also older, 54 years. Although this patient too had angiographically normal coronary arteries, some form of local atherosclerotic involvement of the epicardial vessels, invisible in the coronary angiogram, cannot be excluded.
Third, it is possible that the long time lag (mean 31 months, range 21-42 months) between the index arrhythmia and the ergonovine provocation test in group I patients may have negatively influenced the outcome of the test in our study. Spontaneous remissions with a decrease or loss of sensitivity to ergonovine are well known in patients with variant angina\textsuperscript{21}. However, this interpretation to explain the low number of positive responses is not quite satisfactory, since four of the seven patients in group I still had appropriate defibrillator shocks during the few weeks preceding the ergonovine provocation test. Moreover, patients in group II were tested at a mean interval of 2 months (range 1 to 4 months) following the index arrhythmia as part of the diagnostic work-up. In this group, no patient had a positive ergonovine provocation test, despite the fact that they were tested during the morning hours, when sensitivity to coronary spasm is known to be the highest\textsuperscript{17,21}. All patients (in group I and group II) were off drugs at the time of ergonovine testing.

We therefore feel that the conclusions of M. yerburg et al.\textsuperscript{12} and Igarashi et al.\textsuperscript{13,14} should not be extrapolated to the group of patients with idiopathic ventricular fibrillation, who are young and have normal coronary angiograms. Recent observations suggest that patients with idiopathic ventricular fibrillation are a heterogeneous group in which both abnormalities of ventricular repolarization and depolarization, alone or in combination, can be identified\textsuperscript{22}, patients with transient right bundle branch block and ST elevation in leads V\textsubscript{1} through V\textsubscript{3} have been described\textsuperscript{23}, and the autonomic nervous system may be a trigger for arrhythmias\textsuperscript{24,25}. Although there is ample evidence that autonomic nervous system imbalance contributes to the development of ventricular arrhythmias in both acute ischaemia and substrate-related sudden death\textsuperscript{26,27}, data on its role in idiopathic ventricular fibrillation are still limited.

It is of interest to note that the one patient in group I, who had a positive response to ergonovine with ST elevation in the inferior leads of the electrocardiogram, had several defibrillator shocks preceded by syncope. However, previous spontaneous episodes of non-sustained polymorphic ventricular tachycardia recorded during telemetry monitoring were not preceded by ST- or T-wave changes. Nonetheless, after prescription of a calcium entry blocker, defibrillator shocks were no longer recorded and the patient remained asymptomatic subsequently. It seems likely that in this patient the choice of the monitoring lead of the electrocardiogram was inappropriate and did not represent the positive site of spasm-associated ischaemia. Therefore, in such patients multiple electrocardiographic leads, representing both the anterior and inferior/posterior wall of the heart, are necessary\textsuperscript{28}.

Despite the low prevalence of coronary artery spasm in our study, we believe that for optimal diagnostic work-up, an ergonovine provocation test should be performed in all patients with ventricular fibrillation and non-apparent cardiac disease. In experienced hands and with the necessary precaution, the ergonovine provocation test has a very low complication rate in patients with normal coronary angiograms or insignificant coronary artery disease\textsuperscript{29,30}. A positive test would have important therapeutic implications. The patient with a positive ergonovine test in our series who had experienced frequent appropriate defibrillator shocks, remained free of shocks during 50 months of follow-up after treatment with a calcium channel blocker. In patients with aborted sudden death due to coronary artery spasm, a negative repeated ergonovine test during calcium channel blocker treatment was associated with a low recurrence rate of sudden death\textsuperscript{12,15}.

**Limitations of the study**

Although the specificity and sensitivity of the ergonovine provocation test have been described as very good for patients with frequent symptomatic attacks of variant angina pectoris (up to 98% for both sensitivity and specificity)\textsuperscript{31}, sensitivity in patients with sporadic attacks has been reported to be much lower (77%)\textsuperscript{32}. The prevalence of coronary artery spasm provoked by an ergonovine provocation test may therefore be underestimated in the studied patient population. However, ST-T segment deviations were never seen to precede documented arrhythmia episodes. Although reproducibility in ergonovine provocation tests show good results\textsuperscript{31}, more positive results may have resulted if repeated tests had been performed, or if we had performed other provocation tests, such as hyperventilation, cold pressor or methacholine provocation tests.

Only patients who survived an episode of cardiac arrest and who recovered without major neurological complications were tested. The incidence of coronary artery spasm in patients who could not be tested remains unknown.

**Conclusions**

This study found a low prevalence of coronary artery spasm in patients with cardiac arrest due to documented ventricular fibrillation and non-apparent cardiac disease. All patients had normal coronary angiograms. The cause of arrhythmias in these patients remains unknown. More studies are needed to elucidate the role of spasm in these patients.

**References**


