Clinical characteristics, aetiological factors and long-term prognosis of myocardial infarction with an absolutely normal coronary angiogram

A 3-year follow-up study of 91 patients

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Objectives The purpose of this study was to evaluate the clinical outcome of a large cohort of patients who suffered an acute myocardial infarction with absolutely normal epicardial coronary arteries at the post-myocardial infarction coronary angiogram. The aetiological and prognostic factors in this population were also analysed.

Background Few data exist concerning the outcome, and aetiological and prognostic factors, of patients with myocardial infarction and angiographically absolutely normal coronary arteries.

Methods Ninety-one patients (34 females/57 males; mean age 50 ± 13 years, range 24–78 years) admitted with an acute myocardial infarction had absolutely normal coronary arteries at the angiogram performed 6.2 ± 4 days (range 1–15 days) after the myocardial infarction, defined by smooth contours and no focal reduction (NC). Of the 91 NC patients, 71 were evaluated prospectively, alongside a systematic search of all aetiological factors reported in the literature. The NC patients were matched for age, sex, and the same period of myocardial infarction onset with a group of 91 patients with coronary artery stenosis (>50% diameter stenosis) at the angiogram performed 7.3 ± 4 days (range 1–15 days) after the myocardial infarction (SC).

Results The percent of smokers was similar between the two groups; higher prevalence rates of coronary heart disease family history, obesity, hypertension, hypercholesterolaemia and diabetes mellitus were found in SC (P=0.043 to 0.0001). In NC, coronary spasm was found in 15.5%, congenital coagulation disorders in 12.8%, collagen tissue disorders in 2.2%, embolization in 2.2%, and oral contraceptive use in 1.1%. Left ventricular ejection fraction at hospital discharge was higher in NC (60% ± 13%) than in SC (55% ± 13%, P=0.04). The mean follow-up was 35 months (range 1–100 months). Kaplan–Meier event-free survival, with the combined end-point defined as death, reinfarction, heart failure and stroke was 75% in NC vs 50% in SC (P<0.0001). Survival rate was 94.5% in NC compared to 92% in SC (ns). Univariate predictors of events in NC were left ventricular ejection fraction (P=0.03), age (P=0.02), diabetes (P=0.01), and smoking (P=0.03). Using Cox multivariate analysis, independent predictors of long-term outcome in NC patients were left ventricular ejection fraction (P=0.003) and diabetes (P=0.004).

Conclusion Aetiological factors, predominantly coronary spasm and inherited coagulation disorder, can be detected in only one third of the patients with myocardial infarction and absolutely normal coronary angiograms despite a systematic search in a prospective population. Mortality rates are similar but morbidity is lower in myocardial infarction patients with absolutely normal coronary angiography compared with those with coronary artery stenosis. The only two independent factors predictive of poor outcome in myocardial infarction patients with normal coronary arteries are left ventricular function and diabetes.

Key Words: Myocardial infarction, prognosis, angiographically normal coronaries.

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Introduction

Although acute myocardial infarction is generally associated with obstructive coronary artery disease, myocardial infarction with normal epicardial coronary arteries have also been documented\(^1\)–\(^{22}\). The overall prevalence rate of myocardial infarction with a normal coronary angiogram is low, approximately 3%, but appears to vary with age, with higher rates in young patients\(^{33}–^{41}\). Various mechanisms have been hypothesized\(^{42}\) including coronary spasm\(^{43}–^{45}\), acquired or inherited coagulation disorders\(^{31}–^{37}\), toxic conditions\(^{38}–^{41}\), embolization\(^{42}\). There are limited data in the published literature regarding the long-term follow-up of large series of patients who suffered an acute myocardial infarction with an absolutely normal coronary arteriogram. In addition, to our knowledge, a systematic search of the most frequently reported aetiological factors has not been done prospectively in a large cohort of patients. The aim of the present study was: (1) to compare the long-term prognosis of a large cohort of myocardial infarction patients with an absolutely normal coronary angiogram with that of myocardial infarction patients with coronary artery obstructive disease; 71 patients (78%) out of our total cohort of patients were studied prospectively and constituted a prospective arm; (2) to systematically seek aetiological factors in the prospective arm of the study and (3) to test whether prognostic factors may be identified within the group of myocardial infarction patients with an absolutely normal coronary angiogram.

Methods

Patient population

Patients who were admitted with acute myocardial infarction to our institution were screened retrospectively from January 1990 to September 1994 and then prospectively from October 1994 to December 1998. The diagnosis of myocardial infarction was based on the triad of chest pain, ECG changes, and raised plasma enzyme activity. Ninety-one patients (34 females/57 males; mean age 50 ± 13 years, range 24–78 years) were identified as having angiographically absolutely normal coronary arteries, defined by epicardial vessels, smooth contours and no focal reduction on the coronary angiogram, which was performed 6–2 ± 4 days (range 1–15 days) after myocardial infarction onset (NC). Among these 91 patients, 20 were retrospectively included and 71 (78%) were prospectively studied. Patients in the NC group were matched for age and gender with a group of 91 patients who presented with an acute myocardial infarction during the same period but who had coronary artery stenosis defined by >50% diameter reduction of at least one major epicardial coronary vessel at the angiogram performed 7.3 ± 4 days (range 1 to 15 days) after the myocardial infarction (SC).

Classification of the patients into the two groups, based on the analysis of the coronary angiogram, was made by three independent experienced angiographers. Age, gender, angiographic left ventricular ejection fraction, myocardial infarction location, number of vessels diseased in the SC group and risk factors including family history of coronary artery disease, diabetes, cigarette smoking, hypertension, obesity, hypercholesterolaemia were entered into the analysis. Clinical conditions known to be associated with hypercoagulation, such as pregnancy, carcinoma, polycythaemia, collagen tissue disorder, oral contraceptive use were sought systematically.

Detection of inherited coagulation disorders

Inherited coagulation disorders were sought in only two of the 20 patients of the retrospective arm and in all the 71 patients of the prospective arm. Blood samples were taken 4 weeks after myocardial infarction. The absence of an inflammatory syndrome was documented by a normal fibrinogen level. Quantitative measurements of protein C, antithrombin III (ATIII), and plasminogen were performed by colorimetric assay using, respectively, coamatic protein C from chromogenix (Möln达尔, Sweden), Stachom ATIII automated, and Stachrom PLG (Diagnostica Stago, Asnières, France). Quantitative determination of functional protein S, based on the inhibition of factor Va, was established using a clotting assay of protein S (Staclot protein S, Diagnostica Stago). A clotting assay was used for quantitative determination of factor XII. The activated protein C (APC) resistance test was performed as previously described with an ST 888 instrument (Diagnostica Stago) using the coatest activated protein C resistance (APCR, factor V Leiden) test kit from Biogenic. Patients with a ratio <2.9 were then subjected to factor V genotyping using a polymerase chain reaction technique.

Provocative testing for coronary spasm

From September 1994 a provoking test using intravenous ergonovine maleate 0.4 mg within 2 min, was performed prospectively and systematically in all 71 patients with a normal coronary angiogram to identify coronary artery spasm. The test was considered positive when at least 70% focal reduction of luminal diameter was present.

Follow-up

Clinical events were defined as follows: (1) heart failure; (2) myocardial infarction recurrence; (3) stroke; and (4) cardiovascular mortality. Clinical evaluation was made with a combined end-point, defined by at least one clinical event. Follow-up (by telephone and interviewing the patients and their family medical doctor) was carried out in December 1998 by three observers blinded to the initial status of the patient. Follow-up was accomplished...
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Table 2 Aetiological factors in the group of patients with myocardial infarction and absolutely normal coronary arteries (in each column, the denominator represents the number of patients in whom the abnormality has been actually sought)

<table>
<thead>
<tr>
<th></th>
<th>Retrospective arm (n=20)</th>
<th>Prospective arm (n=71)</th>
<th>Overall cohort (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary spasm</td>
<td>ND</td>
<td>11/71 (15.5%)</td>
<td>11/71 (15.5%)</td>
</tr>
<tr>
<td>Inherited coagulation disorder</td>
<td>1/2</td>
<td>8/71 (11.26%)</td>
<td>9/73 (12.2%)</td>
</tr>
<tr>
<td>Embolization</td>
<td>1/20 (5%)</td>
<td>1/71 (1.4%)</td>
<td>2/91 (2.2%)</td>
</tr>
<tr>
<td>Collagen tissue disorder</td>
<td>1/20 (5%)</td>
<td>1/71 (1.4%)</td>
<td>2/91 (2.2%)</td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td>0/20</td>
<td>1/71 (1.4%)</td>
<td>1/91 (1.1%)</td>
</tr>
</tbody>
</table>

ND=no data.

Results

Baseline characteristics of the two groups

Comparison between NC and SC patients regarding baseline clinical data, risk factors, location of myocardial infarction and left ventricular dysfunction are presented in Table 1. NC patients did not differ from SC patients regarding age, gender and smoking. Statistically significant higher prevalence rates of coronary heart disease family history, obesity, hypertension, hypercholesterolaemia and diabetes mellitus were found in SC. Angiographic left ventricular ejection fraction at hospital discharge was higher in NC (60% ± 14%) than in SC (55% ± 13%, P=0.04). No difference was found between NC and SC regarding myocardial infarction location.

Aetiological factors in patients with myocardial infarction and absolutely normal coronary arteries

Aetiological factors of myocardial infarction in NC patients are summarized in Table 2. In the 71 NC patients studied prospectively, a coronary spasm was documented in 15.5%. Congenital coagulation disorders were found in nine of 73 patients (12.3%), with eight cases observed in the 71 patients (11.3%) of the prospective arm. Congenital coagulation disorders were APC resistance in seven patients, factor XII in one patient and protein C deficiency in one patient. In the total cohort of the 91 NC patients, we found a collagen tissue disorder in two patients (2.2%), one patient with systemic lupus erythematosus and one patient with sarcoidosis, embolization in two patients (2.2%) and oral contraceptive use in one (1.1%).

Follow-up

The mean follow-up was 35 months (range 1–100 months). Table 3 shows the events observed during the follow-up in each group. Twenty-two events occurred in the 91 NC patients: heart failure (n=8), myocardial reinfarction (n=5), stroke (n=5) and cardiovascular mortality (n=4). Forty four events occurred in the 91 SC patients (P<0.0001 vs NC): heart failure (n=19; P=0.04 vs NC), myocardial reinfarction (n=15; P=0.02 vs NC), stroke (n=3, P=0.9) and cardiovascular mortality (n=7, P=0.38). Although the cardiovascular mortality rate was 76% higher in SC than in NC (8% vs 4.5%), the difference did not reach statistical significance. Kaplan–Meier event-free survival, with combined end-point defined by the association of death, reinfarction, heart...
failure and stroke was 75% in NC vs 61% in SC (P=0.01). Among 11 variables tested including age, gender, smoking, hypertension, diabetes, obesity, cholesterol level, family history of ischaemic heart disease, left ventricular ejection fraction, myocardial infarction location, presence of at least one aetiological factor, univariate analysis found that predictors of cardiovascular events in NC were left ventricular ejection fraction (P=0.03), age (P=0.02), diabetes (P=0.01), and smoking (P=0.03). Using Cox multivariate analysis, independent predictors of long-term outcome were left ventricular ejection fraction (P=0.003) and diabetes (P=0.004).

In the SC group, among 11 variables tested including age, gender, smoking, hypertension, diabetes, obesity, cholesterol level, family history of ischaemic heart disease, left ventricular ejection fraction, myocardial infarction location, number of vessels diseased, univariate analysis found that predictors of cardiovascular events were left ventricular ejection fraction (P=0.009) and hypertension (P=0.04). Cox multivariate analysis in SC patients showed that only left ventricular ejection fraction (P=0.02) was an independent predictor of long-term outcome.

**Discussion**

Our study suggests that aetiological factors, predominantly coronary spasm and inherited coagulation disorder, can be detected in only one third of patients with myocardial infarction and an absolutely normal coronary angiogram, despite a systematic search in a prospective population. Although morbidity in these patients is lower than in myocardial infarction patients with coronary artery stenosis, the mortality rate is similar. In myocardial infarction patients with an absolutely normal coronary angiogram, the only two independent prognostic factors are left ventricular function and diabetes.

There are limited data in the published literature regarding the long-term follow-up of large series of patients who suffered an acute myocardial infarction with an absolutely normal coronary arteriogram. In addition, to our knowledge, a systematic search of the most frequently reported aetiological factors has not been done prospectively in a large cohort of patients. The first largest cohort, with a long-term follow-up, was reported by Raymond et al.[15] who suggested a 10 year survival rate in 74 patients with myocardial infarction and normal coronary arteries. In the retrospective work by Raymond et al.[15], only 40 of the 74 studied patients had absolutely normal coronary arteries and, aetiological factors were not systematically sought. In terms of factors predictive of clinical outcome, Raymond et al.[15] did not analyse statistics comparing survivors and non-survivors in the group of patients with a normal coronary angiogram. More recently, out of a total of 8839 patients who had had a history of myocardial infarction, Zimmerman et al.[21] reported a better survival rate at 7 years in the 720 patients with either angiographically normal coronary arteries or minimal to moderate disease, including stenosis with a diameter reduction up to 69%, than in the remaining patients with obstructive coronary artery disease. Zimmerman et al. did not, however, perform an analysis of either prognostic factors or aetiological mechanisms within the subgroup of patients with absolutely normal coronary arteries[21].

**Pathophysiology of myocardial infarction with normal epicardial coronary arteries**

Various mechanisms have been suggested to explain the occurrence of myocardial infarction despite normal epicardial coronary arteries including coronary spasm, acquired or inherited coagulation disorders, toxic agents, embolization, connective tissue disease. Coronary artery spasm has been proposed as a classic aetiological factor of myocardial infarction with normal coronary arteries[24–30], but the actual prevalence rate has remained ill-defined due to the lack of ergonovine tests in large series of patients. In their study, Raymond et al. found that coronary artery spasm was present in five of the 16 patients (31%) in whom an ergonovine maleate test was performed[15]. The same prevalence was found by Legrand et al.[17] and Lindsay and Pichard[9] who evaluated, respectively, 18 and nine patients. According to our results with a systematically performed ergonovine maleate test in a larger population of myocardial infarction patients with normal coronary arteries, the prevalence rate of coronary artery spasm appears to be lower than that previously reported in small sample size populations, since we documented a spasm in only 11 of the tested 71 patients (15.5%).

Congenital coagulation abnormalities have also been hypothesized as possible mechanisms of myocardial infarction with angiographically normal coronary arteries[31–37]. Owing to the small size of the population sample in previous studies, there was no conclusive answer[33–36]. Recently, a multicentre study has found a higher prevalence rate of factor V Leiden, a newly described congenital coagulation disorder, in patients with myocardial infarction and normal

**Table 3  Comparison of outcome at long-term follow-up between patients with absolutely normal coronary arteries and those with obstructive coronary arteries**

<table>
<thead>
<tr>
<th>Follow-up (months)</th>
<th>NC</th>
<th>SC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>8/88 (9-1%)</td>
<td>19/88 (22%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Stroke</td>
<td>5/88 (5-7%)</td>
<td>3/88 (3-4%)</td>
<td>ns</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>5/88 (5-7%)</td>
<td>15/88 (17%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>4/88 (4-5%)</td>
<td>7/88 (8%)</td>
<td>ns</td>
</tr>
<tr>
<td>Combined end-point</td>
<td>22/88 (25%)</td>
<td>44/88 (50%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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coronary arteries, compared with myocardial infarction patients and coronary artery stenosis or healthy subjects [15]. In our study, congenital disorders of coagulation, including activated protein C resistance, Factor XII and deficiency in protein C, were found in only eight of the 71 patients (11.3%) in whom such abnormalities were systematically and prospectively sought. This prevalence rate of congenital coagulation abnormalities is lower than that of 18.2% we reported previously in a much smaller cohort of younger patients [36].

Our data show that aetiological factors of myocardial infarction, with angiographically absolutely normal coronary arteries, are detected in only one third of patients, even when a systematic search of all causal factors reported in the published literature is performed. These results may be partially explained by limitations of the angiography technique per se, a normal coronary angiogram being not necessarily synonymous with structurally normal vessel. This calls for further prospective studies on the pathophysiological mechanisms of myocardial infarction.

**Long-term prognosis of myocardial infarction patients with normal coronary angiogram: is it so good as believed?**

Only two large trials have previously been published on the long-term survival rate of patients with myocardial infarction and a normal coronary angiogram. The first large cohort studied with a long-term follow-up was reported by Raymond et al. [15], who described findings in 74 patients with myocardial infarction and normal coronary arteries over a mean follow-up period of 10.5 years. In the retrospective work by Raymond et al. [15], only 40 of the 74 studied patients had absolutely normal coronary arteries. In their study, Raymond et al. [15] found an 85% survival rate at follow-up in patients with a normal coronary angiogram vs 73% in 74 patients with coronary occlusive disease. More recently, in a total of 8839 patients who had had a history of myocardial infarction, Zimmerman et al. [21] reported an excellent survival rate of 91% at 7 years in the 720 patients with zero-vessel disease compared with that of 75% (P<0.0001) in the remaining patients with obstructive coronary artery disease. Zero-vessel disease was defined in the study by Zimmerman et al. [21] as either angiographically normal coronary arteries or minimal to moderate disease, including stenosis with a diameter reduction of up to 69%. When patients with zero-vessel disease were further stratified, there was no significant difference in survival rates among patients with normal arteries, and minimal or moderate disease, but the re-infarction rate was higher in those with minimal and moderate disease (11% and 16% respectively) than in patients with angiographically normal arteries (5%, P=0.0002).

In agreement with these two previous studies [15,21], we have found a high survival rate of 95.5% at 3 years in our 91 patients with myocardial infarction and absolutely normal coronary arteries. However, despite this excellent survival rate, the morbidity of these patients seems to be significant since the combined end-points, including the other major cardiac events (heart failure, stroke, re-infarction), were observed in 20%. Our results regarding overall complications are in agreement with the findings of Maggi et al. [20] who showed, in a smaller group of 41 patients with myocardial infarction and completely normal coronary arteries, that the incidence of complications including angina, re-infarction and death was 19% after 12 years of follow-up.

**Prognostic factors in myocardial infarction with normal coronary angiogram**

By univariate analysis we identified four factors associated with a poor prognosis in our patients with myocardial infarction and normal coronary arteries: left ventricular ejection fraction, age, smoking and diabetes. Multivariate analysis showed that the only two independent predictive factors were left ventricular ejection fraction and diabetes. These two variables have been demonstrated as major long-term prognostic factors in patients with myocardial infarction and coronary artery stenosis [43,44]. To our knowledge, our study is the first to demonstrate the independent prognostic role of left ventricular ejection fraction and diabetes in myocardial infarction patients with absolutely angiographically normal coronary arteries. Diabetes may play a role in the prognosis of these patients through its related microvascular dysfunction which may enhance left ventricular remodelling [45].

**Study limitations**

Twenty of our 91 studied patients have been evaluated retrospectively and our study has therefore the inherent limitations of this design. In particular, several aetiological factors, such as coronary artery spasm and coagulation disorders, have been evaluated prospectively in only 71 patients. However, our study provides the largest prospective series of patients with myocardial infarction and absolutely normal coronary arteries in whom aetiological factors reported in the literature have been systematically sought. A larger prospective and multicentre study would have been better suited to the objectives. The other significant limitation is probably due to the absence of endovascular analysis with recent technologies such as coronary angioscopy and intravascular ultrasound, which would allow a better analysis of the vessel structure and have enabled the limitations of the angiographic technique to be circumvented.

**Conclusions**

Patients with myocardial infarction and an absolutely normal coronary angiogram have a better long-term
prognosis than those with coronary artery stenosis, but the combined morbidity and mortality are not negligible in this subset of patients. The only two independent predictive factors of poor outcome in patients with myocardial infarction and absolutely normal coronary arteries are left ventricular function and diabetes. Despite a systematic search, aetiological factors are found in only one third of patients and further prospective studies are needed to improve our understanding of the pathophysiology of myocardial infarction with normal coronary arteries.

Table 4 Prognosis factors in the group of patients with myocardial infarction and normal coronary arteries

<table>
<thead>
<tr>
<th>Aetiological factor</th>
<th>Patients with events (n=22)</th>
<th>Patients without events (n=66)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 ± 13</td>
<td>49 ± 13</td>
<td>0.025</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>41%</td>
<td>20%</td>
<td>ns</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>64%</td>
<td>56%</td>
<td>0.026</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>23%</td>
<td>15%</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>15%</td>
<td>5%</td>
<td>0.01</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>23%</td>
<td>9%</td>
<td>ns</td>
</tr>
<tr>
<td>Cholesterol (%)</td>
<td>18%</td>
<td>21%</td>
<td>ns</td>
</tr>
<tr>
<td>Family history of CAD (%)</td>
<td>5%</td>
<td>20%</td>
<td>ns</td>
</tr>
<tr>
<td>% anterior MI</td>
<td>36-3%</td>
<td>18-2%</td>
<td>ns</td>
</tr>
<tr>
<td>Aetiological factor</td>
<td>53 ± 14</td>
<td>61 ± 13</td>
<td>0.03</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; MI = myocardial infarction; LVEF = left ventricular ejection fraction.

References


