Long term prognosis of patients with myocardial infarction and normal coronary angiography: impact of inherited coagulation disorders

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Summary
The prognosis of patients with myocardial infarction (MI) and normal coronary arteries (NCA) in the presence of an inherited coagulation disorder is unknown. The purpose of this study was to compare the clinical thrombosis outcome of patients with (GpI) or without (GpII), inherited coagulation disorders, who suffered from an acute MI with NCA. Eighty two consecutive patients (mean age 49 ± 15 years; 39 females) with MI, but NCA, were recruited. Twelve patients (15%) had an inherited coagulation disorder. GpI and GpII were statistically similar regarding age (45 ± 11 vs. 50 ± 16 years-old), gender (33 vs. 36% female), tobacco consumption (50 vs. 53%), diabetes mellitus (8 vs. 10%), hypertension (25 vs. 17%), obesity (8.3 vs. 14%), family history of coronary heart disease (33 vs. 19%), hypercholesterolemia (50 vs. 21%; p = .08), left ventricular ejection fraction (58 ± 13 vs. 61 ± 13%) and spasm (8.3% vs. 17%). All patients were initially treated with antiplatelet agents with the exception of one (8%) in GpI and 6 (9%) in GpII who were taking oral anticoagulant therapy (ns). The mean follow-up was 57 ± 26 (range from 2-91 months). During the outcome, 12/78 (15.4%) thrombosis events occurred, including venous thrombosis or pulmonary embolism (1/12 vs. 1/66), reinfarction (2/12 vs. 4/66), and stroke (2/12 vs. 2/66), with two events in one patient (GpI). Kaplan-Meier event-free survival, with combined end-point, defined as venous thrombo-embolic event, reinfarction, or stroke differed between the two groups: 4/12 (33.3%) in GpI and 7/66 (10.6%) in GpII (p < .02). Patients with MI, NCA and congenital coagulation disorder present a high risk of thrombosis recurrence under antiplatelet agent.

Keywords
Myocardial infarction, prognosis, angiographically normal coronaries, inherited coagulation disorders

Introduction
Although acute myocardial infarction (MI) is generally associated with obstructive coronary artery disease, MI with normal epicardial coronary arteries (NCA) have also been documented (1-22). The overall prevalence rate of MI with normal coronary angiogram is low, approximately 3%, but appears to vary with age with higher rates in young patients (5-7, 21). Various mechanisms have been hypothesized (23-43) including coronary spasm (24-30), toxic conditions (38-41), embolization (42) and acquired or inherited coagulation disorders (31-37, 44). There are limited data in the published literature regarding long-term follow-up of large series of patients who suffered an acute MI with NCA (43). As well, to our knowledge, the impact of inherited coagulation disorders on the long-term prognosis has not been studied in a large cohort of patients with NCA. The purpose of this study was to compare the clinical thrombosis outcome of patients, who suffered from an acute MI with NCA, with (GpI) or without (GpII) on inherited coagulation disorders.
Methods

Patient population
Patients who were admitted for acute MI at our institution were consecutively screened from September 1994 to November 2000. Ninety-eight patients were identified as having angiographically NCA with a coronary angiogram performed within 7 days after the MI onset. The following criteria were used for inclusion: 1) recent MI with localized akinesia, dyskinesia or severe hypokinesia on left ventricular angiography. 2) normal coronary angiography with smooth contours to the epicardial vessels and no significant focal diameter reduction. 3) Informed consent was required for genetic analysis. MI was diagnosed according to all of the four following criteria: 1) acute onset of chest pain, 2) ST segment elevation > 0.1 mV on at least 2 adjacent electrocardiographic leads with appearance of deep Q waves followed by T waves inversion in the same leads on subsequent electrocardiograms, 3) rise in creatine kinase to peak level of at least 3-fold the upper limit of normal values, 4) concordance between the site of angiographic contraction abnormalities and Q waves. Among the 98 patients, a coagulation disorder research was performed in 82 patients (84%), and 16 patients were excluded because they failed to give informed consent for genetic analysis or did not come for coagulation analysis 4 weeks after the MI. The final study group consisted of 82 patients (mean age 49 ± 15 years; 29 females). Patients with normal coronary were divided into two groups, based on presence (GpI) and absence (GpII) of an inherited coagulation disorder. Age, gender, angiographic left ventricular ejection fraction (LVEF), MI location, and risk factors including family history of coronary artery disease, diabetes, cigarette smoking, hypertension, obesity, hypercholesterolemia were all entered into the analysis.

Cardiac catheterization
Coronary angiography was performed using a percutaneous femoral approach and the Judkins technique. Left ventriculogram was obtained in the 30° right anterior oblique and 60° left anterior oblique positions. Luminal narrowing was determined by consensus decision between 2 experienced angiographers. Only patients with normal (smooth contours) and no significant focal reduction were included. Regional left ventricular function was analyzed by the usual method.

A provocation test for coronary spasm
A provocation test with intravenous ergonovine maleate 0.4 mg within 2 minutes, was performed prospectively and systematically in all the 82 patients with NCA to identify coronary artery spasm. The test was considered as positive when at least 70% focal reduction of luminal diameter was present.

Detection of inherited coagulation disorders
Screening for inherited coagulation disorders was conducted in all patients in a prospective fashion. Blood samples were taken four weeks after MI. The absence of an inflammatory syndrome was documented by normal C reactive protein and fibrinogen levels. Quantitative measurements of protein C, antithrombin III (ATIII), and plasminogen were performed by colorimetric assay using respectively, coamatic protein C from chromogenix (Mölndal, 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 by chronometric technique was used for quantitative determination of factor XII. The 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 (44). Patients with a ratio < 2.9 were then subjected to factor V genotyping using polymerase chain reaction (PCR) technique (44).

Follow-up
Clinical events were defined as follows: (1) venous thrombosis event (pulmonary embolism or venous thrombosis); (2) myocardial infarction recurrence; (3) stroke. Clinical evaluation was made with a combined end point defined by at least one clinical event. Follow-up was obtained during October 2002 by one observer (KH) blinded to the patient’s initial status by interviewing the patients and their medical doctor (medical practitioner and cardiologist). Follow-up was accomplished in 78/82 patients (95%), and four patients were lost at follow-up, 0% in GpI and 5.7% in GpII (ns).

Statistical analysis
All continuous variables were reported as mean value ± SD. Differences among the two groups were assessed by one-way ANOVA. Follow-up of event-free survival, with combined end-point defined as venous thrombo-embolic event, reinfarction, or stroke was performed by Log rank test and Kaplan Meier analysis to assess whether clinical variables (age, gender, risk factors including family history of coronary artery disease, diabetes, cigarette smoking, hypertension, obesity, hypercholesterolemia), left ventricular function, spasm and coagulation disorders are predictors of cardiac events. A p value < 0.05 was considered as significant. Multivariate Cox analysis incorporating all variables with p value < 0.05 in the univariate model was performed to search for independent predictive factors of cardiac events.
Results

Baseline characteristics
Baseline clinical data, risk factors, location of MI and left ventricular function are presented on Table 1. The mean LVEF was of 60 ± 13% but thirty-one patients (37.8%) had a LVEF under 60% (mean LVEF of 46 ± 9%).

Comparison of the two groups (Table 2)
Twelve patients (15%) had an inherited coagulation disorder: APC resistance in 8 pts, factor XII deficiency in 3 pts and protein C deficiency in 1 pt. GpI and GpII were statistically similar regarding age (45 ± 11 vs 50 ± 16 years-old), gender (33 vs. 36% female), tobacco consumption (50 vs. 53%), diabetes mellitus (8 vs. 10%), hypertension (25 vs. 17%), obesity (8.3 vs. 14%), coronary heart disease family history (33 vs. 19%), hypercholesterolemia (50 vs. 21%; p = .08), and left ventricular ejection fraction (58 ± 13 vs. 61 ± 13%). Prevalence of coronary spasm did not differ significantly (8.3% vs. 17%) between the two groups. All patients were initially treated with antiplatelet agents with the exception of one (8%) in GpI and 6 (9%) in GpII, who were taking oral anticoagulant therapy (ns).

Follow-up
The mean follow-up was 57 ± 26 (range from 2-91 months). Four patients were lost at follow-up, 0% in GpI and 5.7% in GpII (ns). During the follow-up period, 12/78 (15.4%) thrombosis events occurred, including venous thrombosis or pulmonary embolism (1/12 vs. 1/66), reinfarction (2/12 vs. 4/66), and stroke (2/12 vs. 2/66), with two events in one patient (GpI). Kaplan-Meier event-free survival, with combined end-point defined as venous thrombo-embolic event, reinfarction, or stroke differed between the two groups: 4/12 (33.3%) in GpI and 7/66 (10.6%) in Gp II (p < .02). Event-free survival rate with combined end point defined as reinfarction or stroke was 3/12 (25%) in GpI and 6/66 (9.1%) in GpII (p = 0.062). Two deaths occurred, one in each group due to non cardiac disease.

In the overall population of patients with MI and NCA all variables were tested including age, gender, smoking, hypertension, diabetes, obesity, cholesterol level, family history of ischemic heart disease, LVEF, MI location, spasm, presence of inherited coagulation disorders). Univariate analysis found that predictors of cardiovascular events in this overall population were LV EF (p = 0.035) and presence of an inherited coagulation disorders (0.02). Using Cox multivariate analysis, these two factors remained independent predictors of long-term out-

<table>
<thead>
<tr>
<th>Table 1: General population characteristics.</th>
<th>Study Population (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr.)</td>
<td>49±15</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>29/82 (35%)</td>
</tr>
<tr>
<td>Tobacco consumption</td>
<td>43/82 (52%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8/82 (10%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15/82 (18%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>11/82 (13.4%)</td>
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<tr>
<td>Coronary disease familial history</td>
<td>17/82 (21%)</td>
</tr>
<tr>
<td>Hyperlipemia</td>
<td>21/82 (26%)</td>
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<tr>
<td>MI localisation:</td>
<td></td>
</tr>
<tr>
<td>- anterior</td>
<td>39</td>
</tr>
<tr>
<td>- inferior or posterior</td>
<td>28</td>
</tr>
<tr>
<td>- inferior</td>
<td>15</td>
</tr>
<tr>
<td>- lateral</td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>60±13</td>
</tr>
<tr>
<td>Coronary spasm</td>
<td>13/82 (16%)</td>
</tr>
<tr>
<td>Inherited coagulation disorder</td>
<td>12/82 (15%)</td>
</tr>
</tbody>
</table>

| Table 2: Patient comparison: Group I and Group II. |
|---------------------------------------------|------------------------|
| Group I (n=12)                              | Group II (n=70)        | P value |
| Age (yr.)                                   | 45±11                  | 50±16   | .22     |
| Gender (% female)                           | 33%                    | 36%     | .87     |
| Tobacco consumption                         | 50%                    | 53%     | .85     |
| Diabetes mellitus                           | 8%                     | 10%     | .85     |
| Hypertension                               | 25%                    | 17%     | .80     |
| Obesity                                    | 8.3%                   | 14%     | .36     |
| Coronary disease familial history           | 33%                    | 19%     | .44     |
| Hypercholesterolemia                        | 50%                    | 21%     | .08     |
| Coronary artery spasm                       | 8.3%                   | 17%     | .68     |
| LV ejection fraction (%)                    | 58±13                  | 61±13   | .46     |
| Anticoagulant agents                        | 1 (8%)                 | 6 (9%)  | .79     |
| Long term thrombotic events                 | 4/12 (33.3%)           | 7/66 (10.6%) | .02* |

Significant P value by univariate analysis: <.05; * significant by multivariate analysis.
come: LVEF (p = 0.03) and presence of inherited coagulation disorders (p = 0.01).

Discussion

Normal coronary angiography is found in 1 to 3% of patients with acute myocardial infarction (5-7, 21). Generally, it occurs in “young” patients with risk factors for coronary artery disease. The pathophysiology of acute MI and NCA remains controversial. Two explanations have been proposed in the literature: a long-lasting vasospasm leading to complete occlusion of a NCA or, an occlusive thrombus totally lysed after a few hours or days resulting in angiographically normal coronary vessel (24-30, 31-37). It has also been demonstrated that, the prevalence of inherited coagulation is higher in patients with MI and NCA than in patients with MI and coronary stenosis (36, 37, 45), but data concerning the impact of coagulation disorders on the long term prognosis are lacking. In a prospective follow-up of 82 patients who survived after a first MI with NCA, the presence of an inherited coagulation disorder was associated with a statistically significant threefold increase in the risk of a recurrent thrombosis event. Thus, our study highlights the impact of coagulation disorders on the long-term prognosis of patients with MI and NCA under antithrombotic agents, and our findings support the hypothesis that anticoagulation therapy should be recommended in this selected situation.

Pathophysiology of myocardial infarction with NCA

Various mechanisms have been suggested to explain the occurrence of MI despite NCA, frequent ones include coronary spasm (24-30), and acquired or inherited coagulation disorders (31, 33-37, 45). The actual prevalence rate of coronary spasm remains difficult to define depending on the systematic performance of the ergonovine test. High rates of prevalence up to 31% have been reported by other investigators in small series of patients (7, 9, 15), whereas we only found a 16% rate in our large series of 82 patients systematically tested.

Although several studies have documented congenital coagulation abnormalities as a possible mechanism of MI with NCA (31, 33-37, 45), important variations in the prevalence rate can be observed. A large multicenter study has found a 12% prevalence rate of factor V Leiden in 107 patients with MI and NCA compared with MI patients and coronary artery stenosis or healthy subjects (37). A higher prevalence (19.5%) has been reported more recently in 41 patients age < 50 years with normal or near NCA (stenosis < 50%) (45). In our study, congenital disorders of coagulation including activated protein C resistance, Factor XII and deficiency in protein C, were found in 12 of the 82 patients (15%) in whom such abnormalities were systematically and prospectively searched.

Prognosis of patients with MI and normal coronary arteries

There are limited data in the published literature regarding long-term follow-up of a large series of patients, who suffered an acute MI with absolutely NCA. The first large cohort study over a long-term follow-up was reported by Raymond et al, who found an 85% survival rate at 10 years follow-up in 74 patients with NCA versus 73% in 74 patients with coronary occlusive disease (15). In 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 NCA or minimal to moderate disease including stenosis up to 69% diameter reduction than in the remaining patients with obstructive coronary artery disease. In agreement with these two previous studies (15, 21), we have found a high survival rate of 95.5% at 3 years in 91 patients with MI and NCA (43). In this later study, the only two independent factors predictive of poor outcome in MI patients with NCA were left ventricular function and diabetes (43). Our results emphasized the role of left ventricular ejection fraction and identified the prognostic value of inherited coagulation disorders, the only two independent predictors of thrombosis events.

Impact of coagulation disorders on the long-term prognosis of patients with MI and NCA

Despite the recognized role of congenital coagulation disorders in the occurrence of MI and NCA, their impact on the long-term prognosis has not been evaluated yet. Inherited coagulation abnormalities have been shown to be predictive factors of recurrent venous thrombosis after a first idiopathic venous thromboembolism (46), but no data have been reported regarding the role of inherited coagulation abnormalities on vascular thrombosis recurrence after a first MI and NCA. To our knowledge, the present study reports for the first time the long-term prognosis impact of inherited coagulation disorders in a population with NCA and MI. We found that, the risk of vascular (venous or arterial) thrombosis new event is three-fold greater in patients with inherited coagulation abnormalities than in patients without these coagulation defects after the onset of a first MI with NCA. In our study, there was also a trend towards increased arterial thrombosis recurrence (stroke and reinfarction) due to inherited coagulation abnormalities in our patients after a first MI and NCA.

Therapeutic implications

In patients with MI and NCA, the antithrombotic strategy remains to be clarified. Whether those patients should be treated with long-term oral anticoagulation agents or antiplatelet agents remains to be prospectively evaluated. As our findings suggest that patients with inherited coagulation disorders and NCA are prone to recurrent thrombosis despite antiplatelet agents, it seems reasonable to recommend long term oral anticoagulation therapy in this subset of patients.
Study limitations
Among 98 patients who fulfilled all the inclusion criteria, a coagulation disorder research was performed in only 82 patients (84%), not in all patients. However, our study provides the largest prospective series of patients with MI and normal or near NCA, in whom long-term prognosis was compared between patients with and without coagulation disorders. Furthermore, the impact of anticoagulation treatment was not studied in a prospective fashion and a larger prospective and multicenter study would have been better suited to meet those objectives. Thus, although it could not be totally excluded that some patients in the study group had myocarditis we feel that using very strict criteria, their number is, at the most, very limited and has little influence on the results. The other significant limitation is probably due to the absence of endovascular analysis with recent technologies such as coronary angiography and intravascular ultrasound, which would allow a better analysis of the vessel structure and would allow to circumvent the limitations of angiographic technique. Despite a clear MI definition, patients had a mean LVEF of 60%, which seems to be high for this selected group, but the good long-term prognosis and LVEF preservation has been previously demonstrated in this subset (19-21; 43). In addition, the analysis of our population found thirty-one patients (=38%) with a LVEF under 60% (mean LVEF of 46 ± 9%) and the expected preserved LVEF is in part due to the absence of prolonged occlusion: spasm, acute thrombosis, normal vessels and therapies used, mainly thrombolytic agents. At last, carriers of factor V Leiden or other inherited coagulation disorder (heterozygous status) raise important issues concerning their family genetic status. Future studies are needed to define the role of prophylactic anticoagulation therapy in symptom-free individuals identified after screening of families.

Conclusions
Patients with MI, NCA and congenital coagulation disorder present a high risk of thrombosis recurrence under antiplalet agent. Anticoagulation therapy should be recommended in this situation.

References
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