

# Prevalence of factor V Leiden (APCR) and other inherited thrombophilias in young patients with myocardial infarction and normal coronary arteries

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## Abstract

**Objective**—To investigate the role of activated protein C resistance (APCR, factor V Leiden) in coronary artery thrombosis. **Methods**—The prevalence of APCR and of congenital deficiencies of antithrombin III, protein C, protein S, plasminogen, and factor XII was investigated in adult patients under 45 years of age with acute myocardial infarction. The results were compared with those of a group of 53 age and sex matched control subjects.

**Results**—Among 75 patients under the age of 45 years who were admitted from November 1994 to April 1996 for acute myocardial infarction, 22 (29.3%) had normal coronary arteriography (group I) and 53 (70.7%) had significant coronary artery disease (group II). Inherited thrombophilia was more often found in group I (4/22, 18.2%) than in group II (4/53, 7.5%) but the difference was not significant (*F* test:  $p = 0.22$ ). The prevalence of APCR was 9.1% (2/22) in group I, 3.8% (2/53) in group 2 ( $p = 0.57$ ), and 3.8% (2/53) in the normal control group ( $p = 0.57$ ).

**Conclusions**—The prevalence of congenital thrombophilias, including APCR, does not seem to be increased in young patients with myocardial infarction and normal coronary angiograms, compared with young patients with coronary atherosclerosis and with normal control subjects. However, the statistical power of the study is too low to detect a significant difference and these results are published to allow a meta-analysis of this problem in the future.

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Keywords: myocardial infarction; factor V Leiden; coagulation factors; inherited thrombophilia

Numerous pathophysiological mechanisms have been proposed to explain the occurrence of myocardial infarction in young patients with angiographically normal coronary arteries, but the role of inherited thrombophilia remains unknown in this group.<sup>1</sup> Resistance to activated protein C (APCR) has emerged as the most common cause of inherited thrombophilia.<sup>2-15</sup> Recently Ridker *et al* and Emmerich *et al* reported a similar prevalence of the factor V

mutation between patients with myocardial infarction and an age matched control group.<sup>16,17</sup> However, in these two studies, patients had either significant coronary artery atherosclerosis or coronary angiographic data were not available. Little has been published on myocardial infarction in patients with angiographically normal coronary arteries and congenital coagulation disorders.<sup>18-21</sup> We therefore investigated the prevalence of congenital coagulation disorders, including APCR, in a prospective study of a group of patients with normal coronary arteries who had suffered myocardial infarction. Assuming that genetic factors are likely to have their strongest influence in younger people, we only evaluated patients under 45 years of age. Data were compared with those obtained in a group of young patients with myocardial infarction and coronary atherosclerosis, and a group of healthy age and sex matched controls.

## Methods

### PATIENT POPULATION

All patients under 45 years of age who were admitted for acute myocardial infarction at our institution were prospectively screened between November 1994 and April 1996. The diagnosis of myocardial infarction was based on the triad of chest pain, ECG changes, and raised plasma enzyme activity.

Patients on anticoagulant treatment before their infarction were excluded. Fifty three healthy age and sex matched subjects living in the same geographical area as the study patients and without a personal or family history of ischaemic heart disease, stroke, or thromboembolic disease served as a control group. All patients gave informed consent, and the study was approved by the human studies ethics committee of Rhône-Alpes.

### CARDIAC CATHETERISATION

Coronary arteriography and left ventriculography were performed by the Judkins technique five to eight days after the onset of myocardial infarction. Patients were divided into two groups. In the first group, coronary arteries were angiographically normal with smooth contours to the epicardial vessels and no focal diameter reduction; in the second group, coronary artery disease was present and was angiographically defined by the presence of either significant stenosis (> 50% obstruction) or epicardial vessels with irregular contours.

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## ANALYSIS OF HAEMATOLOGICAL PROFILE

Blood samples were taken four weeks after myocardial infarction. The absence of an inflammatory syndrome was documented by a normal fibrinogen level. Quantitative measurements of protein C, ATIII, and plasminogen were performed by colorimetric assay using, respectively, coamatic protein C from Chromogenix (Möln dal, Sweden), Stachrom ATIII automated, and Stachrom PLG (Dianostica 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 (Sta clot protein S, Diagnostica Stago). A clotting assay was used for quantitative determination of factor XII. The APC resistance test was performed as previously described<sup>22</sup> with an ST 888 instrument (Diagnostica Stago) using the Coatest APC resistance kit from Biogenic. Patients with a ratio of < 2.9 were then subjected to factor V genotyping using a polymerase chain reaction (PCR) technique.

## STATISTICAL ANALYSIS

Quantitative values are expressed as mean (SD) and were compared using unpaired Student *t* test. The  $\chi^2$  test and Fisher's exact test were used for analysis of categorical data. A Bonferroni correction was used for multiple comparison between the three groups, and a probability (*p*) value < 0.025 was considered significant.

## Results

The clinical characteristics and haematological profiles of the three groups are shown in table 1. No patient had an inflammatory syndrome at the time of blood sampling. Among the 75 patients with myocardial infarction, there were 22 (29.3%) with normal coronary arteries (group I) and 53 (70.6%) with coronary atherosclerosis (group II). The sex ratio was similar in the two groups (20 male and two female in group I; 46 male and seven female in group II; NS). Patients in group I were slightly younger than patients in group II (36.7 (5.8) *v* 39.2 (4.7) years, *p* = 0.056). Groups I and II were identical with regard to risk factors (smoking, family history, hypertension, hyperlipidaemia, diabetes mellitus, and obesity) and location of the myocardial infarct, but patients in group I had a greater ejection fraction than those in group II (0.65 (10.5) *v* 0.543 (1.4); *p* = 0.0015). Inherited thrombophilia was found in four of the 22 patients in group I (18.2%) and in four of the 53 patients in group II (7.5%) (Fisher test, *p* = 0.22). The coagulation disorders in group I were: APCR (2), pro-

tein C deficiency (1), and factor XII deficiency (1). In group I the disorders were: APCR (2), protein C deficiency (1), and factor XII deficiency (1). Resistance to APC was observed in two of the 22 patients (9.1%) in group I, in two of the 53 patients (3.8%) in group II, and in two of the 53 normal control subjects (3.8%) (Bonferroni test, *p* > 0.025).

## Discussion

Coronary spasm, coronary embolism, hypercoagulable state, platelet dysfunction, and connective tissue disease with or without anticardiolipin antibodies have been postulated as possible causes of myocardial infarction in a few reported cases and retrospective studies, but these mechanisms remain debated.<sup>1, 21</sup> Although congenital coagulation abnormalities have also been hypothesised as possible mechanisms, the prevalence of these disorders in patients who have had a myocardial infarct with normal epicardial coronary arteries remains unknown.<sup>1</sup>

Only two previously published retrospective studies have addressed this issue, but owing to the small size of the population sample, no conclusive answer was given.<sup>19, 20</sup> Furthermore, a new congenital coagulation disorder associated with thrombus formation has been recently described as APCR or factor V Leiden.<sup>1-14</sup> This factor V Leiden is present in 4% to 6% of the general population.<sup>3, 15-17, 23</sup> In our normal population, we found a prevalence of 3.8%, which is similar to the reported values. The role of factor V mutation in patients with myocardial infarction has not been fully investigated; in particular, the prevalence of this congenital disorder in young patients with myocardial infarction and normal coronary arteries remains unknown.<sup>23-26</sup> Ridker *et al* found that the prevalence of heterozygosity for this mutation among 374 patients of mean age 59.5 years who had had a myocardial infarct was similar to that of 704 age matched control subjects (6.1% *v* 6.0%, *p* = 0.9).<sup>16</sup> Emmerich *et al* also found similar prevalence of the factor V mutation between 609 men who had had a myocardial infarct and 692 controls (5.1% *v* 4.6%; NS) (17). Kontula *et al* compared 51 young survivors of myocardial infarction (under 45 years of age) with 50 controls without cardiovascular disease and found similar results (6% *v* 2%; NS).<sup>26</sup> On the other hand, Marz *et al* found that mutant factor V was more common (9%) in 89 patients under 55 years of age with myocardial infarction than in controls (4%, *p* = 0.032).<sup>25</sup> In the studies by Ridker *et al*,<sup>16</sup> Emmerich *et al*,<sup>17</sup> Kontula *et al*,<sup>26</sup> and Marz *et al*,<sup>25</sup> coronary angiography data were not available. The populations studied by Ridker *et al* and Marz *et al* were older than in our study, and in the study by Emmerich *et al* the age of the population was not given.<sup>17</sup> To our knowledge, APCR in young patients with myocardial infarction and normal epicardial coronary arteries documented by a coronary arteriogram has been studied in only six cases.<sup>18, 24</sup> Thus it remains unknown whether the heterozygous mutation in the factor V gene creates a

Table 1 Clinical characteristics and haematological profiles of the three groups

	Group I	Group II	Group III
Number of patients	22	53	53
Age (years) (mean (SD))	36.7 (5.8)	39.2 (4.7)	36.5 (5.6)
Sex (F/M)	2/22 (9.1%)	7/53 (13.2%)	7/53 (13.2%)
Resistance to APC	9.1%	3.8%	3.8%
Combined congenital coagulation disorders	18.2%	7.5%	ND

Group I, MI with normal coronary angiogram; Group II, MI with stenosed or occluded arteries; Group III, age and sex matched healthy subjects.  
APC, activated protein C; ND, no data.

predisposition to myocardial infarction in young patients with normal coronary angiograms.

In our study, the prevalence of APCR was higher (9.1%) in the group of patients without coronary artery atherosclerosis than in the group of patients with significant coronary atherosclerosis (3.8%) and the normal control group (3.8%), but the difference was not significant. When all congenital coagulation disorders were pooled, the prevalence of a coagulation abnormality was also higher in patients with normal coronary arteries (18.2%) than in patients with significant atherosclerosis (7.5%), but the difference was again not significant (Fisher test,  $p = 0.22$ ; odds ratio method, 95% confidence interval 0.61 to 12; NS).

#### CONCLUSIONS

There appears to be no significant difference between the prevalence of congenital thrombophilic disorders, including APCR, in young patients who have had a myocardial infarction with normal coronary angiography compared with young patients with coronary atherosclerosis and normal control subjects. However, the statistical power of our prospective study was too low to detect a significant difference and these results are published to allow a meta-analysis of this problem in the future.

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