Premature ischaemic heart disease and the gene for coagulation factor V

To the editor — Myocardial infarction and unstable angina are commonly precipitated by thrombotic occlusion of a coronary artery complicating atheromatous obstruction[1]. Although a relationship between ischaemic heart disease and elevated levels of coagulation factors such as fibrinogen and factor VII or deficiencies of the natural anticoagulants, protein C and S, have been described[2,3], discrete prothrombotic conditions are uncommonly implicated in myocardial infarction. However, resistance to activated protein C (APC) has been found to be the most frequent predisposition associated with unexplained venous thrombosis[4,5]. A strong association between resistance to APC and a single point mutation in the gene for coagulation factor V (factor V Leiden) has been subsequently described[6-8]. There is evidence that factor V is consumed in thrombus formation during acute myocardial infarction and that activated platelets release factor V from their α-granules[2,3]. We proposed that factor V Leiden might be a candidate gene for ischaemic heart disease, particularly for myocardial infarction, and report a study of relatively young patients with ischaemic heart disease and a normal control population.

Heterozygous factor V Leiden was found in 5 of 126 (4.0%) control subjects, in 11 of 222 (5.0%) patients overall and in 7 of 149 (4.7%) with myocardial infarction. Most of the patients, both with and without factor V Leiden, had conventional risk factors for ischaemic heart disease, listed in the Table, with current or previous cigarette smoking outstanding (83% of patients, 42% of controls). Five of the 11 patients with the mutation had a family history of ischaemic heart disease or sudden unexpected death in a first degree relative aged <60 years, but so did 44% of patients without the mutation. Of the 211 patients without the mutation, 169 were Caucasian, 23 Australian aboriginal or part aboriginal and 19 were of other ethnic background whereas 9 of the 11 with the mutation were Caucasian and one of aboriginal descent.

The patient group consisted of 222 patients less than 50 years, presenting to one hospital for admission or for coronary angiography, with symptomatic ischaemic heart disease, over an 18-month period. They were prospectively documented for risk factors and genetic studies. To qualify for inclusion they had either unequivocal acute myocardial infarction with historical, electrocardiographic and enzyme documentation or symptomatic coronary artery disease with at least one obstruction of a major coronary artery >50% diameter at angiography. The control group were 126 subjects less than 50 years of age, randomly selected from the electoral roll and who did not have a history of angina or myocardial infarction. Genomic DNA was extracted from EDTA blood by standard procedures and the factor V Leiden mutation was detected by a modification of the method of Bertina *et al*[6].

Factor V genotype and coronary risk factors in patient groups

	Normal Factor V genotype			Factor V Leiden genotype		
	MI	no MI	total	MI	no MI	Total
Number	142	69	211	7	4	11
Males	124	60	184	7	2	9
Cigarette smoking (current or ex)	121	57	178	5	2	7
Plasma total cholesterol of >6.5 mmol l^{-1}	28	13	41	3	2	5
History						
Hyperlipidaemia	52	24	76	3	2	5
Hypertension	41	26	67	0	2	2
Diabetes	23	10	33	0	0	0
Family*	62	31	93	2	3	5

*First-degree relative with known ischaemic heart disease or sudden unexpected death, aged <60years; MI, myocardial infarction.

At a population level, there was no substantial impact of factor V Leiden on either myocardial infarction or coronary artery disease without infarction in this study. While thrombotic coronary occlusion usually precedes myocardial infarction, it is also usually secondary to rupture or dissection of an atheromatous plaque, albeit often only a previously mildly occlusive soft plaque, with release of multiple activators of platelets and coagulation factors[1]. This may be why the mutation of factor V, which is associated with resistance to APC and a high frequency of venous thrombosis[4-8], does not appear to be particularly associated with myocardial infarction. Alternatively, the mutation might be less relevant to thrombosis in the coronary circulation. It has been suggested that thrombin generation and platelet activation may contribute to the pathogenesis of atherosclerosis by promoting smooth muscle and fibroblast proliferation but we did not find the factor V Leiden mutation associated with angiographically defined obstructive disease.

We studied a relatively young population with ischaemic heart disease, in whom a genetic and prothrombotic influence might be expected to be most clearly evident. However, the results cannot necessarily be extrapolated to older patients, nor to patient groups recruited differently. For example, long-term survivors of myocardial infarction may have an enriched frequency of the mutation if they had infarction on the basis of thrombotic coronary occlusion with minimal or no atheromatous obstructive disease. Two such young female patients with myocardial infarction who were homozygous for the mutation have recently been reported[9]. We did not encounter the homozygous condition, although the frequency of heterozygotes for factor V Leiden in the control population (4.0%) was similar to that found in previous reports.

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