Activated protein C resistance and myocardial infarction

Our understanding of coagulation and thus the mechanisms causing thrombosis has grown enormously in recent years. A crucial part of this development has been an understanding of the anticoagulant systems that normally limit and regulate coagulation. Particular advances have been made in relation to the protein C-protein S system, which is one of the three natural anticoagulant systems. Together with antithrombin-heparin and tissue factor pathway inhibitor (TFPI), the protein C-protein S system acts to limit the extent and magnitude of thrombin generation and thus to prevent inappropriate thrombosis. A deficient response to this system, activated protein C resistance (APCR), is the subject of this review.

Regulation of coagulation

The physiological initiator of coagulation is tissue factor (TF), which is expressed ubiquitously in extravascular tissues and is an important constituent of atheromatous plaques. When plasma is exposed to TF, either as a result of injury or plaque rupture, factor VII is bound from plasma and activated to form a TF–VIIa complex. This then initiates coagulation by activating factor X and factor IX leading to generation of thrombin. A crucial step in this process is neutralisation of free thrombin by antithrombin-heparin and tissue factor pathway inhibitor (TFPI), the protein C-protein S system acts to limit the extent and magnitude of thrombin generation and thus to prevent inappropriate thrombosis. A deficient response to this system, activated protein C resistance (APCR), is the subject of this review.

Activated protein C resistance

Addition of APC to an in vitro plasma clotting test, such as the activated partial thromboplastin time, causes a prolongation of the time to clot formation as a result of the accelerated degradation of factor Va and factor VIIIa. In 1993 Dahlback reported that in a family affected by a hereditary tendency to thrombosis, the plasma from affected members demonstrated an abnormally low response to APC in this type of test. This phenomenon was termed activated protein C resistance (APCR) and was later shown in ~90% of cases to arise from a mutation in the factor V molecule. The mutation was later shown to replace Arg by Gln at residue 506 in the factor V molecule thus destroying one of the important APC cleavage sites and rendering it resistant to the action of APC.

The APC resistant factor V molecule is now frequently called factor V Leiden or F506Q. It is easy to imagine how the prolonged activity of factor Va that results may cause an increased tendency to thrombosis. Indeed, approximately 30% of patients with factor V Leiden have evidence of increased thrombin generation as measured by concentrations of the thrombin activation peptide, F1+2, although this is not in itself a good predictor of thrombosis.

One of the most important aspects of APCR and factor V Leiden to emerge is their very high prevalence in the populations first studied. In most of Europe, the factor V Leiden heterozygote frequency is 5–10% (being particularly high in Scandinavia and Greece) but it is virtually absent in other populations such as in the Japanese and Chinese.

Figure 1. (Left) The coagulation network showing pro and anticoagulant mechanisms. Coagulation in vivo is initiated by the exposure of tissue factor (TF), which binds factor VIIa and greatly increases its activity against factor X and factor IX. The small amount of thrombin generated is able greatly to amplify further thrombin production by activating the cofactors factor V and factor VIII. When activated, factor VIII is released from its carrier protein, von Willebrand’s factor (vWF). Thrombin then cleaves fibrinogen to form fibrin. The hatched boxes indicate that the complex is formed on a phospholipid surface. This surface is provided by the cell membrane for VIIa–TF and by platelets for VIIIa–IXa and Va–Xa. The procoagulant proteases including thrombin are neutralised by formation of complexes with antithrombin (AT). Factor VIIa–TF is neutralised by tissue factor pathway inhibitor (not shown). (Right) Thrombin is also able to bind to thrombomodulin (TM) after which it activates protein C (PC) to its activated form (APC). In conjunction with its cofactor protein S (PS) APC degrades the active forms of factor VIII and factor V (VIIIa and Va) into inactive forms (VIIIi and Vi).
Associated with APCR was approximately 7.6. Subsequent studies showed that the relative risk of DVT associated with their first DVT and that the relative risk of DVT as assessed by the original test and these patients do not seem to develop thrombosis.12 This in turn suggests that the effect of factor V Leiden can be ameliorated by a combination of other plasma factors. Doubtless many factors and combinations of factors can give rise to changes in the measured response or resistance to APC and to the individual's net risk of thrombosis. Several methods have been devised to make a plasma test more specific for factor V Leiden and circumvent the effect of oral anticoagulants.13

**APCR, factor V Leiden, and risk of thrombosis**

After Dahlback's original report a flurry of papers attested to the importance of APCR in the pathogenesis of deep venous thrombosis (DVT). The Leiden thrombophilia study (a large case controlled study) determined that the phenomenon was present in 20% of patients presenting with their first DVT and that the relative risk of DVT associated with APCR was approximately 7.7. Subsequent studies have generally used the genetic test for factor V Leiden rather than the original clotting based APCR, and the relative risk values obtained have varied somewhat although the groups studied have been different.7 The relative risk of venous thrombosis for homozygotes (or occasional hemizygotes) is, not surprisingly, greater and probably in the region of 80-fold.1

Factor V Leiden has been associated with thrombosis in a large number of patient groups including those on renal dialysis, pregnant women, women with recurrent miscarriage, and patients with Budd-Chiari syndrome. It has also been shown to interact synergistically with the combined contraceptive pill in increasing the risk of thrombosis. Although in most of these studies the associated risk of factor V Leiden is not large, its high prevalence makes it of great clinical importance and it has rapidly proved to be the most common and prevalent genetic factor predisposing to venous thrombosis. However, the role of APCR in arterial disease has been more difficult to determine.

**APCR and factor V Leiden**

Most patients with APCR as estimated by the original test of Dahlback also have the FVRS06Q mutation. However, there is not complete overlap between these two groups and approximately 10% of patients with APCR do not have the mutation. This phenomenon is more common in patients with thrombosis suggesting that APCR from whatever cause is in itself a risk factor for thrombosis. Clearly, a poor anticoagulant response to APC may arise from other factors or combinations of factors in the patient's plasma. Some possibilities are theoretically attractive, such as mutations elsewhere in the factor V molecule or a mutation at an APC cleavage site in factor VIII. Very recently, a mutation at another APC cleavage site in factor V was reported but it appears to be extremely rare.9,10 No similar mutations in factor VIII have been identified so far. It has been noted that some plasmas containing a lupus-like anticoagulant have a reduced response to APC. The physiological significance of this phenomenon is uncertain but interference with the protein C-protein S pathway is one postulated mechanism for the prothrombotic effect of lupus-like anticoagulant. Some patients with APCR but not factor V Leiden have a high concentration of factor VIII and reproduction of this in vitro causes a striking reduction in the response to APC.11 This is probably one of the mechanisms contributing to APCR in pregnancy and in women taking the oral contraceptive pill. It is of note that all these circumstances, which produce phenotypic APCR, are themselves well recognised prothrombotic states.

Conversely, some patients with factor V Leiden do not have APCR as assessed by the original test and these patients do not seem to develop thrombosis.12 This in turn suggests that the effect of factor V Leiden can be ameliorated by a combination of other plasma factors. Doubtless many factors and combinations of factors can give rise to changes in the measured response or resistance to APC and to the individual's net risk of thrombosis. Several methods have been devised to make a plasma test more specific for factor V Leiden and circumvent the effect of oral anticoagulants.13

**Coagulation factors and myocardial infarction**

In recent years there has been increasing interest in the role of coagulation factors in myocardial infarction and there is little doubt that in the vast majority of cases the final stages of coronary occlusion are via activation of the coagulation system. Large cohort studies, beginning with the Northwick Park heart study,14 established that procoagulant factors such as factor VIIc, fibrinogen, and factor VIIIc, as well as reduced fibrinolytic activity conferred an increased risk of subsequent ischaemic heart events. These effects have been confirmed subsequently by numerous studies such as the PROCAM (prospective cardiovascular Münster) study.15 It seems quite likely that the recently established predictive effect of C reactive protein for myocardial infarction may be operating at least in part via an increase in procoagulant activity.16 It is interesting that the most recent factor to be added to this list is trombomodulin,17,18 and recent reports suggest that mutations in this gene may be associated with myocardial infarction. This gene is crucial to the protein C-protein S pathway, and deficiency would impair the ability of the body to generate APC as a result of thrombin generation—that is, it would result in APC deficiency rather than resistance.

Meade et al observed that coagulation factors are most powerful at predicting ischaemic events in the short term.19 However, they also suggested that the coagulation system, particularly fibrinogen, could also have a longer term effect (16 years) and may therefore play a role in the development of atherosclerosis itself. Whether this is achieved by increased thrombin generation, blood viscosity, platelet aggregation, or some other mechanism is not clear.

In the short term it is likely that these factors would have their greatest impact on thrombosis in the absence of severe coronary artery disease. Siscovick and colleagues10 point out that the contribution of thrombosis to atherothrombotic disease may be particularly important in the young where multiple risk factors such as smoking, diabetes, and obesity are frequently also present. It is in this group that we are most likely to see the effects of coagulation factors. These factors become less important in the elderly where atherosclerosis is just another aspect of aging. This greatly affects the interpretation of trials looking for
the effect of factors such as factor V Leiden and APCR, because the age of entry to the study and the likely health of the entrants (that is, the presence of a censoring effect) may influence the results.

**Myocardial infarction and APCR**

In view of the role of haemostatic factors in both generating atherosclerosis and vaso-occlusive thrombus, factor V Leiden and APCR might reasonably be expected to play a role in myocardial infarction. However, early studies of sometimes large numbers of patients with myocardial infarction failed to show any increased risk associated with factor V Leiden.

One of the largest studies to look at the relation between factor V Leiden and myocardial infarction is the health physicians study in which no difference was found in the prevalence of factor V Leiden between those who did and did not develop myocardial infarction. It is important to note that the age of entry into the study was > 40 years so that those with myocardial infarction at a young age were excluded, there were very few smokers, and the study entrants were male. This study used the factor V Leiden genotype rather than the APCR plasma based test and so does not rule out a role for APCR resistance per se in this group. A significant effect did not emerge when the data were adjusted for other risk factors including age but the odds ratio and p value did increase and decrease respectively.

Rosendaal et al conducted a rather different study of young women (18–44 years and thus younger than the health physicians study entrants) with myocardial infarction. Although factor V Leiden had little effect on its own, (odds ratio 2.4; 95% confidence interval 1.0 to 5.9) it had a large effect on those who also smoked (odds ratio 3.6; 95% confidence interval 0.9 to 14.4). The combination of smoking and factor V Leiden was associated with an odds ratio of 32 (95% confidence interval 7.7 to 133) compared to non-smoking non-carriers.

Similarly, in a study from Holland, although the presence of factor V Leiden could not be demonstrated to have any effect on mortality overall, the data suggested an associated ninefold increase in dying from ischaemic heart disease before the age of 45 years. These studies require repetition with larger numbers of patients to establish their significance and eliminate possible confounding factors. It is likely that any excess risk associated with factor V Leiden will be more noticeable for smokers.

Finally, van der Boven et al found that APCR analysed as a continuous variable was associated with stroke but factor V Leiden was not, implying that the net degree of APCR present in plasma may be more important and predictive than the presence or absence of the factor V Leiden mutation alone. As is frequently quoted: “it is your phenotype that kills you, not your genotype.”

**Conclusions**

The role of coagulation in producing occlusive coronary episodes and the increased thrombin generation associated with APCR make it a likely candidate for increasing the risk of coronary events. Factor V Leiden appears to have a relatively weak effect in this regard, which is likely only to be evident in young patients with additional risk factors. It has already been effectively demonstrated in young women with the additional risk factor of smoking. Although factor V Leiden genotyping is convenient and definitive, the net degree of APCR may be the crucial phenotypic characteristic. This will reflect the effect of factor V status but will also be determined by other coagulation factors and factor VIIIc in particular.

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[1-20] References

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[21-24] Further information

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