Hemostatic markers and prognosis in ischemic heart disease

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Failure of traditional risk factors in identifying patients who develop a cardiac event, has led investigators to focus on other factors involved in precipitating cardiac events. As acute or subacute thrombosis is the major complication of atherosclerotic plaque rupture, attention has been dedicated to prothrombotic markers as possible risk factors. Recently, the role of new laboratory markers in predicting the risk of cardiac events has been evaluated in large epidemiological studies. The results of these studies as well as the value and applicability of new prothrombotic markers in the clinical practice are discussed.

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Various methods have been devised to assess the individual risk of coronary artery disease, but their sensitivity and specificity do not justify their widespread application. The distribution of values in those who develop an acute coronary syndrome and that in those who remain event free are so overlapping that no cut-off level discriminates them with an accuracy which is sufficient for practical purposes. However, as the events of concern are the thrombotic sequelae of coronary atherosclerosis, it is possible that risk assessment may be improved by evaluation of the hemostatic status.

The majority of patients with acute myocardial infarction and unstable angina have high plasma levels of fibrinopeptide A, prothrombin fragment 1+2 and thrombin antithrombin complex. These findings are consistent with the results of angiographic, angioscopic and pathologic studies clearly showing that intracoronary thromboses play a pivotal role in the pathogenesis of these coronary syndromes[1,2]. However, one of the aims of recent research has been to investigate their prognostic significance.

Some studies have evaluated their role in the formulation of an in-hospital prognosis in patients with acute coronary syndromes. Ardissino et al.[3] measured plasma and urinary fibrinopeptide A levels at hospital admission in patients with unstable angina, and found that high plasma levels were associated with a higher risk of developing primary (death or myocardial infarction) or secondary clinical endpoints (refractory angina requiring emergency coronary revascularization) during hospitalization; furthermore, Granger et al.[4] found that higher baseline levels of prothrombin fragment 1+2 were associated with an increased likelihood of death or myocardial reinfarction during the 30-day follow-up of patients with myocardial infarction receiving thrombolytic therapy. High plasma levels of these markers in patients with acute coronary syndromes therefore seem to be associated with a worse prognosis, but due to their overlapping values they are of little use in individual patients.

The serial measurement of coagulation activation peptides over time has provided interesting information concerning the pathophysiology of acute coronary syndromes. Merlini et al.[5] measured prothrombin fragment 1+2 and fibrinopeptide A plasma levels in patients with unstable angina or myocardial infarction during the acute phase and 6 months later. The levels of prothrombin fragment 1+2 and fibrinopeptide A were both high during the acute ischemic episode (thus reflecting the presence of intracoronary thrombosis) but, in the patients with an uneventful clinical course at 6 months, the fibrinopeptide A levels had returned to normal whereas the prothrombin fragment 1+2 levels remained high (Fig. 1). The observation of a decrease in plasma fibrinopeptide A levels without any substantial change in pro-

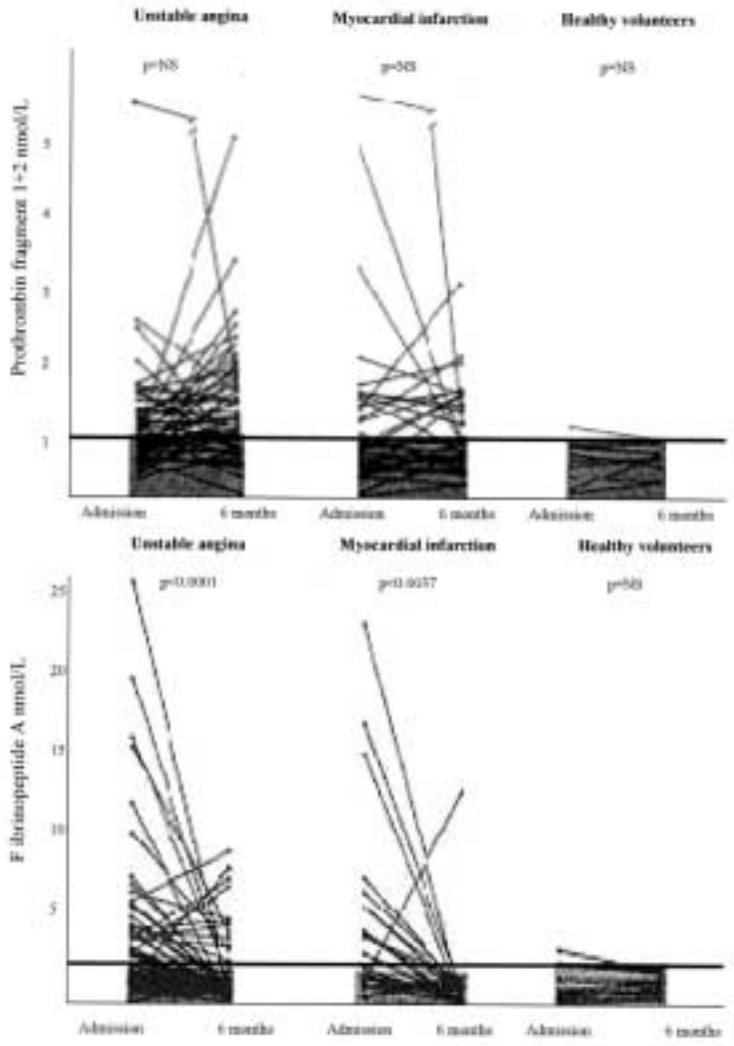

Figure 1. *Plots of plasma concentrations of prothrombin fragment 1+2* (panel A) *and plasma levels of fibrinopeptide A* (panel B) *in 57 patients with unstable angina and 23 patients with myocardial infarction at hospital admission. All patients had an uneventful clinical course, and follow-up determinations were obtained at 6 months. In 12 healthy blood donors, plasma concentrations of prothrombin fragment 1+2 and fibrinopeptide A were evaluated at baseline (admission) and after 6 months. The* top of the shaded area *indicates the upper limit of the normal range for each measurement (95th percentile of the distribution for the control group of 32 healthy individuals matched for age and sex with the study population). From Merlini et al.[5], modified.*

thrombin fragment 1+2 indicates that increased thrombin generation persists after initial coronary ischemic episodes. Miller et al.[6] showed that, in men who were clinically free from cardiovascular disease, factor IX activation peptide, prothrombin fragment 1+2, fibrinopeptide A, factor VII antigen, factor VII coagulant activity, and activated factor VII levels all positively and significantly correlated with higher risk scores for fatal coronary artery disease. Recently, the Second Northwick Park Heart Study[7] investigated the prognostic value of novel hemostatic markers in 4600 men aged 50-61 years who were followed up for 5 years. These markers were factor VII antigen, factor VII activity, activated factor VII, fibrinogen, prothrombin fragment 1+2, fibrinopeptide A, the activation peptides of factor IX and factor X, and activated factor XII. Table I[7] shows the independent association of baseline measurements with any cardiac event: a high level of activated factor XII was associated with an increased risk of coronary heart disease, but low levels were not protective; plasma factor VIIa and factor X activation peptide were independently and inversely related to risk; plasma factor IX and fibrinogen were positively associated with risk, but the relationships were no longer statistically significant after adjustment for other factors, including factor VIIa and apo A-I. These data show that the consideration of hemostatic activity markers in addition to conventional risk factors for coronary heart disease failed to improve the identification of men at high risk for a first event: the predictive accuracy of the novel hemostatic factors was broadly similar to that of a history of non-insulin-dependent diabetes mellitus, systolic blood pressure, smoking, alcohol intake, and serum cholesterol.

The inability of hemostatic factors to add any predictive power to that provided by conventional risk factors, and vice versa, may be due to technical factors such as sample size, laboratory measurement errors, and the

Table I. Independent associations of baseline measurements with any coronary heart disease endpoint.

	Without VIIa and apo A-I (n=1153)		With VIIa and apo A-I (n=643)*	
	OR (95% CI)**	p	OR (95% CI)	p
Diabetes***	8.50 (3.31-21.81)	< 0.0001	4.50 (1.03-19.60)	0.05
Smoking§	2.05 (1.30-3.23)	0.002	2.09 (1.13-3.84)	0.02
Alcohol§§	0.51 (0.31-0.83)	0.007	0.56 (0.30-1.03)	0.06
Systolic blood pressure	1.32 (1.05-1.66)	0.02	1.37 (1.02-1.83)	0.04
Cholesterol	1.34 (1.07-1.66)	0.01	1.39 (1.07-1.80)	0.02
Log_e fibrinogen	1.35 (1.08-1.68)	0.009	1.26 (0.92-1.74)	0.15
Log_e IX peptide	1.25 (0.95-1.63)	0.11	1.32 (0.96-1.82)	0.09
Log_e X peptide	0.66 (0.52-0.84)	0.001	0.74 (0.56-0.98)	0.04
XIIa				
Low	1.76 (0.97-3.19)	0.04	2.67 (1.21-5.89)	0.01
High	1.96 (1.12-3.42)	–	2.62 (1.24-5.54)	–

CI = confidence interval; OR = odds ratio. * 70 endpoints; ** OR (95% CI) for increase of 1 SD in continuous variables; *** non-insulin-dependent diabetes mellitus vs others; § current smoker vs others; §§ at least one alcoholic drink in the previous week vs others. From Cooper et al.[7], modified.

use of single measures to capture a long-standing disease. As things stand at the moment, the hemostatic status does not add any significant predictive power to that provided by conventional risk factors, but it is capable of substituting them effectively. The overall modest predictive value undoubtedly indicates that certain aspects of coronary heart disease are not measurable by current techniques.

Conclusions

The laboratory detection of a biochemical hypercoagulable state has been made possible by the development of new assays that allow the different steps of the coagulation cascade to be monitored. The information provided by coagulation activation markers has greatly contributed to the improvement in our understanding of the mechanisms of disease. Clinical studies using these markers indicate that a biochemical imbalance between procoagulant and anticoagulant mechanisms can be detected in the blood of individuals before the development of a thrombotic disorder. However, there is currently no evidence that screening for any of the above hemostatic markers in the general population or within subgroups would have any prognostic or therapeutic consequences.

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