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STUDIES OF HAEMOSTASIS IN ACUTE CORONARY SYNDROMES AND DIABETES MELLITUS

AKADEMISK AVHANDLING
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ABSTRACT

The pathophysiology of acute coronary syndromes (ACS) includes atherosclerotic plaque rupture and coronary thrombus formation. Antithrombotic treatment is effective but recurrent atherothrombotic or bleeding complications are not uncommon.

Aim: To study new markers and methods concerning haemostasis in ACS and conditions associated with high risk of this disease, in the search for laboratory tools that could help increase understanding of disease mechanisms and help to identify patients at risk.

Methods and Results: Eighty-seven patients suffering from ACS were investigated at admission (S1), after 24 h on standard antithrombotic treatment (S2), and six months after the acute event (S3). Sex- and age-matched healthy controls were also investigated. Thrombin generation *in vivo* was assessed by measurement of prothrombin fragment F1+2 in plasma and *in vitro* by using the calibrated automated thrombogram (CAT). Fibrinolysis was measured by assessment of PAI-1 and TAFI activity concentrations. The latter method was used as a result of a methods evaluation study. We also employed a global method developed by our group (Oh-index), to evaluate haemostasis. Oh-index gives a measure of fibrin formation and degradation capacity in plasma. Furthermore, a flow cytometric assay set up by our group was employed to measure platelet microparticles (PMP) in plasma formed upon platelet activation. In addition, we investigated ADAMTS13, an enzyme previously called von Willebrand factor (VWF)-degrading protease, and we also measured its substrate (i.e. VWF). The ACS patients, of whom more than half were high-risk patients (TIMI score $\geq$ 4), showed signs of inflammation and endothelial activation, as expected. Only the CAT method could detect hypercoagulability in the patients (increased peak thrombin concentration) and this finding was evident acutely and 6 months after the event. Thrombin generation *in vivo* (F1+2) or fibrin generation capacity in plasma did not indicate hypercoagulability at any time point. CAT, F1+2 and fibrin generation capacity were strongly reduced following initiation of antithrombotic treatment (S2), as expected. PAI-1 and TAFI levels were elevated, reflecting impaired fibrinolysis, but this was not observed with our method that assesses fibrin degradation capacity; rather, this method indicated increased fibrinolytic capacity at admission and this capacity was grossly increased after initiation of standard antithrombotic treatment (S2). ADAMTS13 activity and antigen concentrations were unchanged during and after ACS, but the VWF:ADAMTS13 ratio was significantly elevated in ACS patients and two different populations of patients with diabetes mellitus. The ACS patients had significantly elevated concentrations of PMP at admission, particularly PMP subpopulations with exposed P-selectin and tissue factor (TF). Concentrations of PMP decreased following initiation of antithrombotic treatment (S2), but in the subpopulations with exposed P-selectin and TF they remained significantly higher than in controls at 6 months (S3).

Conclusions: Our PMP data are in agreement with the concept of a dominating role of platelets in the pathophysiology of ACS, and PMP deserve to be studied in more detail in coronary artery disease, including their roles in the effects of treatment and relationships to coagulation, risk and prognosis. However, the data on coagulation and fibrinolysis obtained in this study indicate that there is not yet sufficient information to support the clinical use of markers to assess coagulation or fibrinolysis in individual patients.

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