STUDIES OF HAEMOSTASIS IN ACUTE CORONARY SYNDROMES AND DIABETES MELLITUS

From the DEPARTMENT OF CLINICAL SCIENCES
DANDERYD HOSPITAL
DIVISION OF CARDIOVASCULAR MEDICINE
Karolinska Institutet, Stockholm, Sweden

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet officiellt försvaras i Aulan, Danderyds sjukhus

Fredagen den 9 december 2011, kl 09.00
av
Mika Skeppholm
Leg läkare

Huvudhandledare:
Docent Håkan Wallén
Karolinska Institutet
Institutionen för kliniska vetenskaper,
Danderyds Sjukhus
Enheden för kardiovaskulär medicin

Bihandledare:
Med dr Karin Malmqvist
Karolinska Institutet
Institutionen för kliniska vetenskaper,
Danderyds Sjukhus

Prof em Margareta Blombäck
Karolinska Institutet
Institutionen för molekylär medicin och kirurgi

Docent Anders Kallner
Karolinska Institutet
Institutionen för molekylär medicin och kirurgi

Fakultetsopponent:
Professor Harald Arnesen
University of Oslo
Center for Clinical Heart Research
Dept of Cardiology
Oslo University Hospital

Betygsämnd:
Docent Jonas Oldgren
Uppsala Universitet
Institutionen för medicinska vetenskaper
Akademiska sjukhuset

Docent Gerd Lärfars
Karolinska Institutet
Institutionen för klinisk forskning och utbildning,
Södersjukhuset

Docent Andreas Hillarp
Lunds Universitet
Institutionen för laboratoriemedicin
Skånes Universitetssjukhus

Stockholm 2011
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 ≥ 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.

ISBN 978-91-7457-496-8