Activation Markers of Coagulation and Fibrinolysis: Alterations and Predictive Value in Acute Coronary Syndromes

Hans Martin Hoffmeister, Wolfgang Heller, Ludger Seipel

From the Medizinische Klinik, Abt. III, Eberhard-Karls-Universität, Tübingen, Germany

Key words

Fibrinolysis, coagulation, inflammation, activation marker, acute coronary syndromes

Summary

Several alterations of the coagulation, of the fibrinolysis and of inflammation are known in patients with acute coronary syndromes. To extend current knowledge of the pathophysiology and to optimize therapeutic strategies, the new molecular markers can be used in clinical studies. Furthermore, several studies were undertaken to assess the prognostic value of activation markers of these systems for patients with unstable angina pectoris and acute myocardial infarction with or without thrombolytic therapy. The majority of studies focussed on markers of thrombin activation, fibrinogen, fibrin degradation products and t-PA and its main inhibitor PAI-1. While there are stimulating results from larger studies, the value for prognosis for the individual patient still is limited by the overlap of patients with good versus a poor outcome.

Introduction

Acute coronary syndromes are characterized by a completely or incompletely occluding thrombus at the site of a coronary plaque rupture. Procoagulant, fibrinolytic and inflammatory pathways appear to be activated in most patients with acute coronary syndromes. The following text will mainly focus on markers of activation and their possible prognostic impact on acute thrombotic vessel (re)occlusion.

Markers of Activation of the Hemostatic and Fibrinolytic Systems

In general, activation of pathways can be assessed by functional tests measuring activity or by measurement of concentrations of a precursor, a substrate, an inhibitor or a reaction product. Functional measurements are sometimes disturbed by quick inhibition of activity in plasma, by activation of associated pathways or by medications like heparin given to a patient. Furthermore, in most instances functional tests need a prolonged time to be done, and they may be unspecific. Interpretation of concentrations of precursors and inhibitors is highly dependent on the plasma half-life/resynthesis rate as well as on the relative size of the plasma pool of the respective protein. Thus, when activated proteases cannot be directly measured, complexes of activated proteases with their natural inhibitors may serve as a means to assess the extent of activation of a specific pathway. Therefore, more direct measurements of markers, which are generated in association with activation of an pathway, is clinically useful today. The majority of such markers is determined using ELISA test systems. The next paragraphs will focus mainly on this type of activation markers.

Coagulation

Generation of thrombin thus increasing its plasma activity is the central step of the activation of coagulation. The prothrombin fragment F1+2 is a marker of thrombin generation. The thrombin/antithrombin III complexes (TAT) can be determined as a molecular marker of the thrombin activation. Fibrinopeptide A (FPA) can be measured as indicator of thrombin activity. It has a very short plasma half-life, but can also be measured in the urine. The urinary excretion is rapid, therefore measurement of fibrinopeptide A in the urine reflects the mean of activity over the collection. Antithrombin III concentration can be determined as the main inhibitor of thrombin. A considerable decrease would be indicative of an increased thrombin activation with a consecutive consumption of antithrombin III.

Fibrinolysis

The tissue-type plasminogen activator is the main activator of plasminogen in the vascular compartment and can be assessed both as concentration and activity. The measurement of the mass concentration of t-PA reflects both free t-PA antigen as well as t-PA in the t-PA-PAI-1 complex. Plasminogen activator inhibitor-1 (PAI-1) can also be measured as activity as well as mass concentration.

As a reaction product of plasmin activation the plasmin-antiplasmin complexes can be determined in order to assess the activation of this pathway. Measurements of precursor concentrations in the fibrinolytic system include plasminogen and fibrinogen. Determination of inhibitors like antiplasmin can be performed to assess its consumption due to formation of plasmin-antiplasmin complex. Degradation products of fibrinogen like FDP or of cross-linked fibrin like d-dimers provide information on fibrinolytic activation. The latter marker is more reflective for lysis of fibrin in thrombi, but some d-dimers may also stem from plasma (1). The determination would be valuable to assess, whether an activation of the fibrinolysis has occurred.

Coronary Syndromes

Coagulation

In patients with unstable angina pectoris or acute myocardial infarction a procoagulant activity is observed with an elevated thrombin activation and increased d-dimers for at least five days of follow-up.
Release of tissue factor either locally from the ruptured coronary plaque or from stimulated monocytes seems to be of key importance. Thrombin activation may also result from a stimulated kallikrein-kinin-factor XII system (i.e. the contact phase of the coagulation), as observed both in patients with acute myocardial infarction and with unstable angina pectoris (2, 3, 5). These two pathways result in thrombin activation.

Fibrinogen levels are higher than those of control persons and increase further during the first days of an acute coronary syndrome constituting an acute phase reaction (2, 6).

Preliminary reports provided evidence, that a relationship between the extent of activation of the coagulation (assessed as TAT complexes) and the occurrence of myocardial injury (judged as troponin release) in acute coronary syndromes can be assumed (7). It was recently discussed, that myocardial troponin can clinically be considered as a surrogate marker for coronary thrombi (8). Merlini and coworkers described, that the elevation of the prothrombin fragment F1+2 is persisting after acute coronary syndromes for up to 6 months while the activity of thrombin (fibrinopeptide A) is decreased during the follow-up in patients with an uncomplicated outcome (9). The reason for this observation is not understood completely. Another paper of the same group described a less favourable early outcome in patients with acute coronary syndrome if fibrinopeptide A in plasma was elevated, while the urinary excretion of fibrinopeptide A did not show any significant differences (10). Other authors described a persisting TAT activation after acute coronary syndrome to be associated with a more critical follow-up. The main problem of the use of thrombin markers for the individual prognosis of a patient is the large overlap between groups with different outcome. Therefore, these markers are not well suited for identification of individual patients there is some overlap between cases with favourable and unfavourable outcome after acute myocardial infarction similarly to the overlap in patients with acute coronary syndrome. Therefore TAT and other thrombin marker are not very well suited for monitoring the success of thrombolytic therapy.

Fibrinolytic System

High levels of t-PA mass concentration including t-PA bound to PAI-1 are present in these patients. Endothelial release of t-PA is reduced in the initial phase of acute myocardial infarction or unstable angina pectoris (16). Increased levels of plasminogen activator and its inhibitor PAI-1 have been observed in patients being at increased risk of complications in the setting of acute coronary syndromes or acute myocardial infarction (17, 18). Patients with high PAI-1 activity and acute myocardial infarction were found to be less responsive to acute thrombolytic therapy and those with chest pain and altered markers of the fibrinolytic system were prone to an increased risk of recurrent coronary events in the near future (17, 19). Recently it turned out that an increased t-PA mass concentration is predictive for future coronary events even in apparently healthy men (20).

Thrombus formation results from a shifted balance between procoagulant and fibrinolytic factors. In acute coronary syndromes the plasminogen activator system of the fibrinolysis is disturbed: plasminogen activator inhibitor activity (PAI-1) is enhanced and tissue-type plasminogen activator (t-PA) mass concentration is elevated (21, 17).

Increased levels of degradation products of fibrin together with increased activation levels of the coagulation indicate a procoagulant state, which has frequently been reported in a number of studies on patients with acute coronary syndromes and acute myocardial infarction with and without thrombolytic therapy (2, 3, 4, 22). The problem in the assessment of d-dimers is the fact, that in acute coronary syndromes most of the d-dimers have to be attributed to other sources like plasma fibrin and not to the very small intracoronary thrombus. Therefore, they indicate systemic alterations (1) more than being direct markers of the occurrence or size of a thrombus. A better correlation of increases of this marker to thrombus size is more likely to be found in extended thrombi like in deep vein thrombosis. As marker of plasmin activation an increase of the plasmin-antiplasmin complex can be used to assess stimulation of the plasmin system due to thrombolytic therapy in acute coronary syndromes. These complexes are already increased in patients with acute myocardial infarction (4) implying activation of plasmin to cope with the procoagulant situation. The determination of the plasmin-antiplasmin complexes by an ELISA technique seems to be more sensitive compared with the determination of the precursor plasminogen or of the concentration of the inhibitor antiplasmin in order to quantify plasmin activation caused by thrombolytic agents (3, 4, 23).

Besides the elevated PAI-1 the other plasma inhibitors are not markedly changed but still within their regulatory range in patients with acute coronary syndromes. Changes during early follow-up are caused by consumption e.g. the reduction of the C1-esterase inhibitor is caused both by consumption in the contact phase, in the fibrinolysis [as plasma inhibitor of t-PA (24)] and in the activated complement cascade (25). Smaller changes of other inhibitors during early follow-up in patients with acute coronary syndromes reflect consumption or acute phase reactions (23, 26) and are not the cause of the procoagulant state.

Hemostasis, Inflammation and Blood Cells

There are multiple interactions between the stimulated hemostatic and inflammatory systems in acute coronary syndromes (27). The complement system becomes activated (25). It has several interactions with the coagulation and fibrinolysis by consuming C1-esterase inhibitor, generation of bradykinin and positive feedback loops with factor XII and plasmin. Furthermore its involvement in endothelial lesion and in myocardial damage in acute myocardial infarction was proven (6, 28, 29). A large number of substances/mediators like kinins, interleukins, TNFα and others, which are involved e.g. in endothelial function, thrombus formation and interaction with blood cells, are released in patients with acute coronary syndromes.

These reactions propagate thrombus growth by activating platelets (also via thrombin) and the endothelium and by promoting cell adhesion as evidenced by the increase of soluble and cellular adhesion molecules (30, 31, 32). Similar as the hypothesis of a chronically mild activation of the coagulation in atherosclerosis with consecutive thrombus formation leading to “atherothrombotic” disease, a chronic inflammation in atherosclerosis has been observed by several authors (33, 34) and infectious agents were discussed to play a key role in this process (35-40). Basal inflammatory tone, endothelial and leukocyte activation, activation of complement and an acute phase reaction can be identified. Inflammatory reactions may have an impact on coagulation via fibrinogen and PAI-1, which both are involved in the pathogenesis of acute coronary syndromes. While the details and the quantitative meaning of the large number of such interactions is not completely known today, an
increasing number of reports confirms the presence of elevated levels of markers of inflammation in patients with acute coronary syndromes (including CRP, fibrinogen, soluble and cellular adhesion molecules) (41-44). The prognostic value of these markers (besides their accepted pathophysiological meaning) is still issue of ongoing debates, especially compared with the impact of measuring troponins.

**Conclusion**

Today a large number of markers is available to determine the pathophysiological alterations occurring in patients with acute coronary syndromes. These markers are used to characterize different pathways and to develop a better understanding of the ongoing processes in patients with acute coronary syndromes. However, since from the rupture of a plaque to the formation of an adherent thrombus a variety of systems is involved, determination of only one marker usually is of limited impact on the individual prognosis. Measurement of other markers, which represent the sum of the pathophysiological alterations for the myocardium, like determination of troponin T or I are today’s first choice clinically to assess the outcome of an individual patient. These markers include the integral of acute changes in the vessel lumen, of the collateral flow, and of the energetic deficit and determine thus the ischemic load and the resulting myocardial damage. In the future however, some markers of the fibrinolytic system or of the hemostasis may become of therapeutic importance by allowing to individualize the dosing and choice of a specific thrombolytic or anticoagulative treatment in acute myocardial infarction. Furthermore, patients with excessive thrombin generation may be candidates for an intensified and prolonged anticoagulation therapy to prevent reocclusion after initially successful reperfusion therapy.

**References**