Thrombosis Research 132 (2013) 138–142

Contents lists available at SciVerse ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Activation of the contact system in patients with a first acute myocardial infarction

Joke Konings [a,*], José W.P. Govers-Riemslag [a], Henri M.H. Spronk [a], Johannes L. Waltenberger [b,c], Hugo ten Cate [a]

[a] Laboratory for Clinical Thrombosis and Haemostasis, Department of Internal Medicine, Cardiovascular Research Institute Maastricht, Maastricht University Medical Centre, Maastricht, The Netherlands
[b] Department of Cardiology, Maastricht University Medical Centre, Maastricht, The Netherlands
[c] Department of Cardiovascular Medicine, University of Münster, Münster, Germany

ARTICLE INFO

Article history:
Received 7 February 2013
Received in revised form 12 April 2013
Accepted 21 May 2013
Available online 7 June 2013

Keywords:
Acute myocardial infarction
Coagulation factor XI
Contact system
Coagulation factor XII
Prekallikrein
C1 esterase inhibitor

ABSTRACT

Introduction: The contribution of the contact system to arterial thrombosis is unclear, results of clinical studies are conflicting. Particularly, little is known about the involvement of the contact system in the progression of arterial thrombosis. Therefore, we investigated the activation of the contact system during an acute myocardial infarction (AMI) and 3 and 6 months following the acute event.

Methods: Plasma of patients with a first AMI was collected on admission and 3 and 6 months after the AMI. The levels of complexes of activated factor XI (FXIa), FXIIa and kallikrein with C1 esterase inhibitor (C1INH) and the levels of complexes of FXIa with α_1-antitrypsin (AT) were measured in these plasmas. Recurrent cardiovascular events were recorded during a one year period after the AMI.

Results: We observed that the levels of FXIa-C1INH were elevated during the acute phase compared to the steady-phase 3 and 6 months after the AMI. The levels of FXIa-AT, FXIIa-C1INH and kallikrein-C1INH did not change over time. The levels of FXIa-C1INH, FXIa-AT, FXIIa-C1INH and kallikrein-C1INH were not predictive for a recurrent event.

Conclusion: We observed that during an AMI, the activation of FXI was increased. The levels of FXIIa-C1INH were not elevated, suggesting that activation of FXI during the acute phase did not result from contact activation. The levels of the enzyme inhibitor complexes were not predictive for a recurrent event one year after the first AMI.

© 2013 Elsevier Ltd. All rights reserved.

Introduction

Acute myocardial infarction (AMI) is a major cause of morbidity and mortality worldwide. It is the result of partial or complete occlusion of the coronary arteries due to coronary thrombus formation, impairing myocardial blood supply. A hypercoagulable state, characterized by activation of the coagulation system, is detectable in patients with AMI [1–3]. Furthermore, within atherosclerotic lesions, coagulation factors, including contact factor components, are abundantly present [4]. This way, hypercoagulability in blood and in atherosclerotic lesions may have impact on the course of atherosclerosis as well as the risk of atherothrombotic complications.

The role of the contact activation system of coagulation in the development and progression of coronary artery disease (CAD) is still unclear. In animal studies, deficiency in coagulation factor XI (FXI) or FXII is associated with a decreased risk for arterial thrombosis, however, the results from clinical studies are not straightforward. Several studies found that high levels of FXI or activated FXI (FXIa) are associated with an increased risk of CAD [2,5,6], however, in studies focussing only on women this association is less clear [7–9]. Furthermore, FXI deficiency does not protect against AMI [10]. The association between FXII and CAD is complex, with a different association depending on whether zymogen or enzyme levels were measured. Low levels of FXII were found to be a risk factor for AMI, coronary heart disease (CHD) and all-cause mortality [5,11,12], high levels of FXIIa and low levels of FXIIa in complex with its main natural inhibitor C1-esterase inhibitor (FXIIa-C1INH) were associated with an increased risk of CHD [13–18]. However, other studies that measured FXII, FXIIa or FXIIa-C1INH did not confirm an association with CHD [6,8,12,19,20]. In all these studies the levels of FXI or FXII were measured at one single time point. We set up a study to determine the activation of the contact system during the acute

Abbreviations: AMI, acute myocardial infarction; A.U, arbitrary units; C1INH, C1-esterase inhibitor; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHD, coronary heart disease; CI, confidence interval; CV, coefficient variation; ELISA, enzyme-linked immunosorbent assays; F, coagulation factor; F1.2, prothrombin fragment 1.2; IQR, interquartile range; LMWH, low-molecular-weight-heparin; OR, odds ratio; PCI, percutaneous coronary intervention; SD, standard deviation; STI, soybean trypsin inhibitor.

* Corresponding author at: Laboratory for Clinical Thrombosis and Haemostasis, Department of Internal Medicine, Cardiovascular Research Institute Maastricht, Maastricht University Medical Centre, P.O. Box 616, UNS50:Box8, The Netherlands. Tel.: +31 433881542; fax: +31 433884159.
E-mail address: J.Konings@maastrichtuniversity.nl (J. Konings).

0049-3848/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.thromres.2013.05.016

phase as well as during follow-up in patients with a first AMI and used these data to determine whether contact activation could be used as a marker for the occurrence of a recurrent thrombotic event.

Materials and Methods

Study Design

The study design has been described previously [21]. Consecutive patients with a first AMI were included. Patients were included if they met the following inclusion criteria: chest pain lasting longer than 30 min but not exceeding 24 h, ST-segment elevation > 1 mm on electrocardiography and biochemical evidence of myocardial necrosis. Exclusion criteria were a history of AMI or stroke and present use of oral anticoagulants. Blood samples were drawn on admission and before administration of low-molecular-weight-heparin (LMWH) or any other intervention and repeated after 3 months and 6 months. To rule out the use of LMWH before blood sampling, anti-Xa levels were determined in all baseline samples. Only samples with undetectable anti-Xa ($\leq$0.05 U ml^{-1}) were considered to be free of LMWH and only these samples were included in the analysis.

The clinical outcome was recorded 3 months, 6 months and 12 months after inclusion. The combined end point comprised cardiovascular death, recurrent MI, a second coronary intervention [percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)] and ischemic stroke. The study protocol was approved by the Medical Ethics Review Committee of the Maastricht University Medical Center, the Netherlands. All patients gave written informed consent. Venous blood was collected in 10 mM EDTA containing 100 μg ml^{-1} soybean trypsin inhibitor (STI) and 20 mM benzamidine for the measurement of enzyme inhibitory complexes and in 3.2% (w/v) citrated tubes for other measurements.

Assays

The levels of FXIa, FXIIa and kallikrein in complex with C1-esterase inhibitor (C1INH) and FXIa in complex with α_1-antitrypsin (FXIa-C1INH, FXIIa-C1INH, kallikrein-C1INH and FXIa-AT) were measured in plasma with enzyme-linked immunosorbent assays (ELISAs), as described previously [18]. The detection limits were 0.03 arbitrary units (A.U.) for all assays and values below the detection limit were set at 0.03 A.U. The inter- and intra-assay coefficient variations (CVs) of these assays have been published [18].

The levels of FXIc and FXIIc were determined by one-stage aPTT-based clotting assays, performed on a Sysmex CA-7000 Automated Coagulation Analyzer with reagents obtained from Dade Behring (Liederbach, Germany) and calibrated to WHO standards. D-dimer measurements in platelet-poor plasma were performed using the Ddimer Plus test (Dade Behring Inc., Liederbach, Germany) according to the manufacturer's instructions. Prothrombin fragment 1.2 (F1.2) was quantified by ELISA according to the manufacturer's instructions (Dade Behring Inc.). Anti-Xa activity was determined using the Coamatic Heparin test (Instrumentation Laboratory, Breda, the Netherlands).

Statistical Analysis

The data are expressed as median [interquartile range (IQR)] or as mean (standard deviation (SD)). Differences between two groups were analysed using the Mann–Whitney U test (levels of inhibitory complexes, D-dimer and F1.2) or the Student's t-test (levels of FXIc and FXIIc), depending on distribution characteristics. Correlations between the enzyme inhibitory complexes were determined using Spearman's rho correlation. The difference in the levels of the inhibitory complexes between the different time points was determined by the Friedman test, followed by the Dunn's multiple comparison test. The association between dichotomized levels of enzyme inhibitory complexes and outcome was assessed using Pearson chi-square test, and expressed as corresponding odds ratios (ORs) and 95% confidence intervals (CIs). Results were viewed to be statistically significantly different at $p < 0.05$. Statistical analyses were performed using IBM SPSS Statistics 20 for Windows (Armonk, New York: IBM Corp.) and Prism for Windows 5.00 (GraphPad Software Inc., San Diego, CA, USA).

Results

Of the 135 patients included in this clinical study, plasma samples of 89 patients on admission were available for the measurement of enzyme inhibitory complexes. In total, 16 patients were excluded because anti-Xa levels were > 0.05 U ml^{-1}. Of 30 patients, the availability of plasma was not sufficient to perform analyses. The baseline characteristics of these 89 patients are represented in Table 1. Of them 14 had a recurrent cardiovascular event during the follow-up period of 1 year. The levels of the enzyme inhibitory complexes on admission did not differ between patients stratified for gender, smoking or the presence of hypertension, diabetes mellitus or hypercholesterolemia and did not correlate with age.

Enzyme-inhibitory Complexes

From 70 patients, complete sets of plasma samples from the three time points (on admission and at 3 months and 6 months after the acute event) were available to measure the levels of the enzyme inhibitory complexes. Fig. 1 shows the levels of the enzyme inhibitory complexes on admission and during the follow-up period. For most patients, the levels of FXIa-C1INH were highest on admission and declined during follow-up. There was a statistically significant reduction in FXIa-C1INH complex levels with 55.7% of the patients at 3 months and 70% at 6 months showing a decline in this inhibitor complex compared with levels on admission. The median level of FXIa-C1INH declined by 7.2% [IQR: -19.9% - 25.9%] and 9.5% [IQR: -7.1% - 22.1%] at 3 and 6 months, respectively. The levels of FXIa-AT, FXIIa-C1INH and kallikrein-C1INH did not change significantly over time.

Because of the wide distribution of the data we were interested to determine the correlation for each enzyme-inhibitor complex, comparing different time points. The levels of FXIa-C1INH on admission, correlated well with the levels at 3 months and at 6 months (Spearman's rho: 0.84 and 0.88 $p < 0.001$, respectively). The same was true for the levels of FXIIa-C1INH (Spearman's rho: 0.77 and 0.87 $p < 0.001$, respectively) and FXIa-AT (Spearman's rho: 0.76 and 0.77 $p < 0.001$, respectively). Since only few samples had levels above the detection limit for kallikrein-C1INH, we did not perform correlation analyses for this enzyme inhibitor complex. These high correlations indicate that patients with relatively high or low level of an enzyme inhibitor complex at one time point, will most likely remain relatively high or low at a later time point.

Recurrent Events

Table 2 shows the differences in the levels of FXIc, FXIIc, D-dimer, F1.2 and the enzyme inhibitory complexes on admission between patients that developed a recurrent event during follow-up and those that did not. The levels of D-dimer and F1.2 were higher in the

Table 1
Baseline characteristics of the study population.

	Total group	Male	Female
N (%)	89 (100%)	66 (74%)	23 (26%)
Age, years (range)	61 (34 – 88)	60 (39 – 83)	66 (34 – 88)
Hypertension, n (%)	23 (25.8%)	18 (27.3%)	5 (21.7%)
Smoking, n (%)	5 (5.6%)	3 (4.5%)	2 (8.7%)
Type 2 diabetes, n (%)	47 (52.8%)	33 (50.0%)	14 (60.9%)
Hypercholesterolemia, n (%)	18 (20.2%)	14 (21.2%)	4 (17.4%)

Download English Version:

https://daneshyari.com/en/article/6002636

Download Persian Version:

https://daneshyari.com/article/6002636

Daneshyari.com