Primary research

Adhesion molecules in different treatments of acute myocardial infarction

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Abstract

Background: Tissue damage after ischemia and reperfusion involves leukocyte endothelial interactions mediated by cell adhesion molecules. This study was designed to determine the time course of soluble adhesion molecules in patients with acute myocardial infarction after attempted reperfusion by thrombolysis with tissue plasminogen activator (tPA) or streptokinase (SK), or percutaneous transluminal coronary angioplasty (PTCA).

Methods: In 3 × 10 randomly selected patients with acute myocardial infarction undergoing thrombolysis with tPA or SK, or treated with PTCA, plasma concentrations of soluble L-selectin, P-selectin, E-selectin, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and platelet endothelial cell adhesion molecule-1 (PECAM-1) were measured by enzyme-linked immunosorbent assay, 30 min and 1, 2, 4, 8, 12 and 24 hours after intervention.

Results: After thrombolysis with tPA, soluble L-selectin concentrations were persistently depressed and soluble PECAM-1 concentrations were elevated, compared with controls, SK and PTCA. While soluble VCAM-1 concentrations did not differ within the first hours after interventions between the three groups, soluble VCAM-1 rose by 24 hours after tPA thrombolysis but did not increase after SK and PTCA treatment. Soluble ICAM-1 concentrations were consistently elevated after PTCA compared with controls and thrombolysed patients. Soluble E-selectin was depressed after tPA thrombolysis and PTCA in comparison with controls, while the SK group showed an increase throughout the observation period. Soluble P-selectin was increased after PTCA and SK lysis up to 8 hours after treatment compared with controls, but no significant differences could be found between treatment groups.

Conclusion: Adhesion molecules mediating leukocyte endothelial interactions are altered subsequent to postischemic reperfusion and by treatment with thrombolytic agents and angioplasty. The clinical relevance of these biological changes remains to be determined.

Keywords: adhesion molecules, myocardial infarction, thrombolysis

Introduction

Coronary artery reperfusion is the only intervention that has been shown to reduce the size of myocardial infarction. Thrombolysis and PTCA are established methods to achieve reopening of an occluded vessel in patients with acute myocardial infarction [1–3]. Despite this observation,

ICAM-1 = intercellular adhesion molecule-1; PECAM-1 = platelet endothelial cell adhesion molecule-1; PTCA = percutaneous transluminal coronary angioplasty; SK = streptokinase; tPA = tissue plasminogen activator; VCAM-1 = vascular cell adhesion molecule-1.

there has been concern that reperfusion itself may have some deleterious effects on the myocardium by inducing an acute inflammatory response, leading to a secondary reperfusion injury in addition to the ischemia-related injury [4,5].

Reperfusion of occluded vessels leads to an activation of endothelial cells and an extravasation of leukocytes. This consecutive extravasation is regulated by the sequential interaction of adhesion molecules and their cognate ligands, expressed by leukocytes, platelets, and endothelial cells. The first contact between leukocytes and the vessel wall is established by members of the selectin family of adhesion molecules: L-selectin (CD62L), which is exclusively expressed by leukocytes; P-selectin (CD62P), which can be found in platelets and Weibel–Palade bodies of endothelial cells; and E-selectin (CD62E), a transcriptionally regulated glycoprotein exclusively expressed by endothelial cells. After selectin-mediated slowing down of the leukocytes, their firm adhesion to the vessel wall involves the interaction between leukocyte surface-expressed β2 or α4 integrins, and the members of the immunoglobulin superfamily, ICAM-1 (CD54) and VCAM-1 (CD106) [6–8]. Whereas ICAM-1 is expressed on a broad variety of cells, VCAM-1 expression is restricted to endothelial cells. After firm adhesion, leukocytes proceed to transendothelial migration, which involves homotypic adhesion mediated by PECAM-1 (CD31), that is expressed by endothelial cells, platelets, and various leukocytes.

Soluble forms of adhesion molecules, such as sICAM-1, sP-selectin and sE-selectin, have been the aim of several previous studies. Increased levels were found in patients with acute myocardial infarction or coronary artery disease [9–17]. It is, however, still unknown what effects different treatments aimed at the reopening of occluded coronary arteries, such as thrombolysis or PTCA, may have concerning these adhesion molecules.

The objective of this prospective controlled, non-randomized study was to investigate the early course of six different adhesion molecules after myocardial infarction and reopening therapy with thrombolysis or PTCA. Furthermore, the influence of singular thrombolytic agents should be evaluated by comparing SK and tPA.

Materials and methods

Patients and therapy

All patients were admitted to the general medical intensive care unit of a university hospital with the diagnosis of acute myocardial infarction, based on a history of typical chest pain and electrocardiographic changes according to the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-I) study [2]. In the following, diagnosis was confirmed by typical elevation of cardiac enzymes. The initial treatment consisted of three different strategies and was based on the decision of the initially attending emergency physician. The first strategy was an intravenous thrombolysis with SK, 1.5 million IU over 30 min. As a second protocol, patients received tPA as the thrombolytic agent, according to the accelerated regime [18] starting with a 15 mg bolus, followed by 0.75 mg/kg over 30 min, and then 0.50 mg/kg over the next 60 min (tPA group). Both thrombolysis regimes were started preclinically in the ambulance. For the third strategy, patients underwent percutaneous transluminal coronary angioplasty within 6 hours after the onset of chest pain (PTCA group).

Within a period of 2 years, 10 patients were randomly selected from each of the three treatment groups and included in the study. The 30 patients were aged from 33 to 85 years (mean, 60 ± 14 years; 26 male, 4 female), and concomitant treatment with acetylsalicylic acid and heparin was identical in all three groups, according to the GUSTO-I protocol [2]. Fourteen healthy individuals with a similar pattern of age, gender, and body weight served as control group for the assays. The protocol was approved by the Institutional Review Board for Ethics and included the informed consent of all patients.

Blood samples

Samples from all patients were taken immediately after thrombolysis or angioplasty, and then 1, 2, 4, 8, 12 and 24 hours after treatment. Plasma was obtained by centrifugation at 4°C, at 3000 rpm for 10 min. Samples were stored at −80°C before measurement of plasma levels of the soluble forms sE-selectin, sL-selectin, sP-selectin, sICAM-1, sVCAM-1, and sPECAM-1 using commercially available enzyme-linked immunosorbent assays (ELISAs) (R&D Systems Europe, Abingdon, UK). Blood samples of 14 healthy volunteers served as controls and were centrifuged, stored and measured in the same way as already described.

To investigate direct interactions of tPA or SK with the ELISA, additional measurements were performed after *in vitro* incubation of control samples with SK (250 U/ml) and tPA (1 μg/ml) at therapeutical concentrations [19,20] for 30 min.

Clinical data

On admission, the patients' clinical status was assessed, including age, sex, height, weight, and time from onset of clinical symptoms until start of treatment. Complications, especially postinfarctial angina pectoris, arrhythmia (ie ventricular tachycardia, ventricular fibrillation), hypotension (systolic blood pressure $<$90 mmHg), renal failure (urea $>$50 mg/dl, creatinine $>$2 mg/dl), and cerebral ischemia or hemorrhage were recorded at hospital discharge.

Statistics

Differences between the three treatment groups were tested with the Kruskal–Wallis test, and differences

between treatment groups and native controls were tested with the Mann–Whitney *U* test at each point of time. The significance of intra-individual changes during the observation period was examined using Friedman's test. Differences between native and supplemented (tPA, SK) control samples were explored by Wilcoxon rank sum test. Fisher's exact test was used to analyse nominal clinical data. $P < 0.05$ defined significance.

Results

Demography

The clinical characteristics of the 30 patients with acute myocardial infarction showed no significant differences between the groups concerning sex, age, height, weight, time until onset of therapy, and rate of complications (data not shown).

Measurements

Impact of in vitro incubation on soluble adhesion molecule measurements

Incubation with tPA or SK resulted in a small but significant decrease of sE-selectin concentrations, from 29.3 ± 2.2 to 28.1 ± 2.0 or 24.8 ± 2.4 ng/ml, respectively. The concentration of sL-selectin increased significantly (from 998.0 ± 64.7 to 1080.8 ± 79.3 or 1053.2 ± 67.7 ng/ml, respectively) and that of sICAM-1 decreased significantly (from 230.2 ± 15.9 to 183.6 ± 12.5 or 182.4 ± 12.2 ng/ml, respectively). *In vitro* incubation with tPA caused a significant decrease of sVCAM-1 concentrations (from 403.4 ± 22.4 to 367.8 ± 25.7 ng/ml), whereas SK did not affect sVCAM-1 concentrations. Both the sPECAM-1 and sP-selectin concentrations did not show significant changes after *in vitro* incubation with tPA or SK.

sE-selectin (Fig. 1a)

PTCA as well as tPA lysis led to lower sE-selectin levels in comparison with healthy controls. This decrease was, however, much more pronounced than the decrease after *in vitro* incubation, resulting in a significant difference between supplemented control samples and samples of patients treated with lytic agents. The declension of sE-selectin in the tPA patients remained significant during the whole observation period. No increasing or decreasing intra-individual trends could be observed, either in the tPA group or in the PTCA group. SK patients, in contrast, revealed increasing sE-selectin levels; significance, however, was failed. There were also no differences of sE-selectin levels between the three treatment groups.

sL-selectin (Fig. 1b)

Analysis of sL-selectin showed similar results. Plasma levels in the tPA group were significantly decreased in comparison with control samples as well as in comparison with the other treatment groups. In contrast, levels of the other treatment groups did not differ significantly from controls. No decreasing or increasing intra-individual changes could be found. Direct interactions of tPA or SK with the assays were not responsible for the observed phenomena, confirmed by the *in vitro* assays.

sP-selectin (Fig. 1c)

Plasma levels of all treatment groups were elevated compared with controls; elevation of sP-selectin in samples of patients undergoing SK lysis or PTCA reached a level of significance during the first 8 hours after treatment. Analysis of intra-individual changes indicated a significant decrease in both the SK and PTCA groups. No significant differences could be found between the three treatment groups.

sVCAM-1 (Fig. 2a)

The sVCAM-1 plasma concentrations were elevated in all treatment groups compared with healthy controls. Only the tPA group, however, reached a level of significance. The tPA patients also showed an intra-individual increase, which only just failed to be significant ($P = 0.06$) in Friedman analysis, but reached the level of significance in comparison with the other therapies 12 and 24 hours after treatment. Direct interactions of tPA or SK with the assays were not responsible for the observed phenomena; this was confirmed by the *in vitro* assays.

sPECAM-1 (Fig. 2b)

Plasma of patients undergoing tPA lysis showed significantly increased sPECAM-1 concentrations compared with controls, while SK lysis and PTCA did not cause any differences. Investigation of intra-individual changes and differences between the treatment groups did not produce any significant results.

sICAM-1 (Fig. 2c)

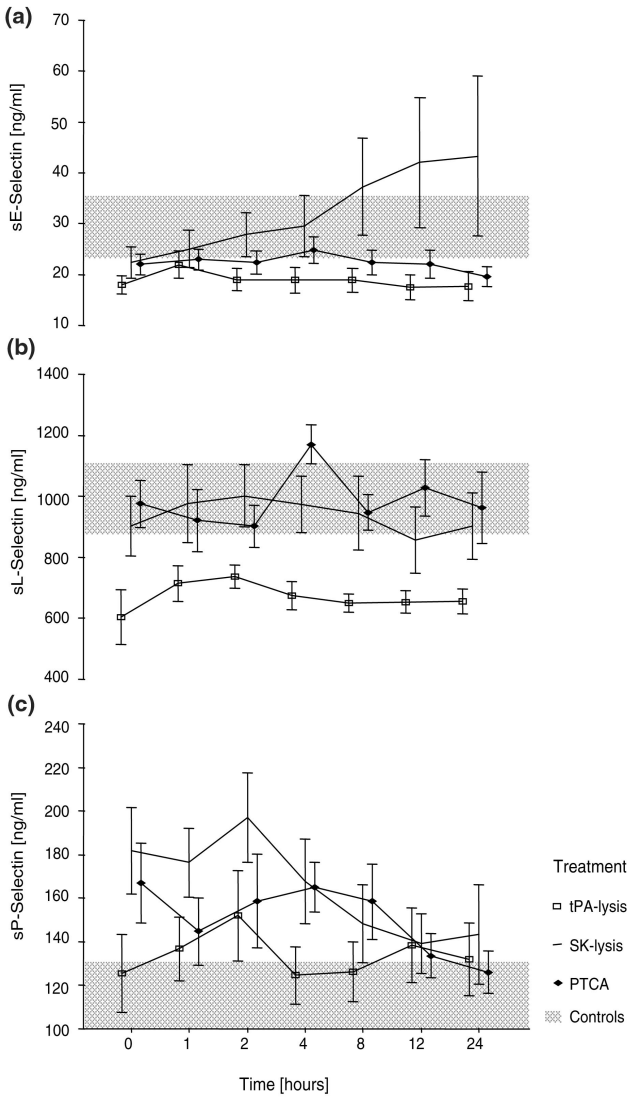
In patients undergoing PTCA, sICAM-1 levels were significantly elevated in comparison with controls and patients with tPA or SK lysis, whereas no intra-individual changes could be found. The changes observed were not due to direct interactions of tPA or SK with the assays, as confirmed by the *in vitro* assays.

Discussion

Soluble forms of adhesion molecules including selectins and members of the immunoglobulin family, most of which are generated by alternative splicing, are considered to be indicators of an activation of endothelial cells, platelets or leukocytes [5,21,22]. They have been shown to increase in patients with acute coronary syndrome, after atherosclerotic plaque rupturing, as well as in ischemic and reperfused areas (eg after receiving revascularization therapy with PTCA or lysis).

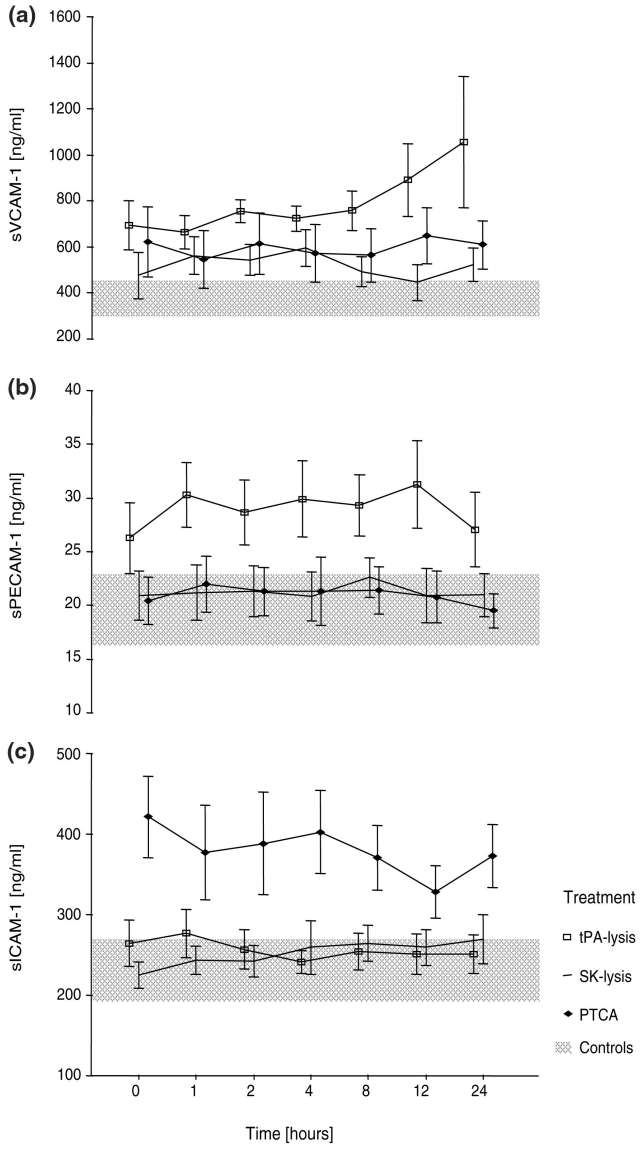
In this study, we found significantly reduced levels of sL-selectin in the tPA group compared with the controls, as well as compared with patients from the SK and PTCA groups. L-Selectin undergoes rapid cleavage at the cell

Figure 1



Soluble E-selectin **(a)**, soluble L-selectin **(b)** and soluble P-selectin **(c)** levels in patients with acute myocardial infarction compared with healthy controls. Data of patients are shown as mean and SEM, and data of controls (grey area) are shown as mean and 95% confidence interval.

Figure 2



Soluble VCAM-1 **(a)**, soluble PECAM-1 **(b)** and soluble ICAM-1 **(c)** levels in patients with acute myocardial infarction compared with healthy controls. Data of patients are shown as mean and SEM, and data of controls (grey area) are shown as mean and 95% confidence interval.

surface following the leukocyte's activation, resulting in the generation of soluble L-selectin. Whereas several cytokines, notably tumor necrosis factor-α, undergo processing similar to L-selectin, this mode is unique to L-selectin among adhesion molecules of the selectin or immunoglobulin families, and results in baseline soluble L-selectin concentrations exceeding those of any other soluble adhesion molecule. Low soluble L-selectin concentrations have been observed in patients at risk for acute respiratory distress syndrome [23], in a number of ventilated intensive care patients [24,25], and in ischemic heart disease [26]. Reduced soluble L-selectin concentrations may result from *de novo* expression of L-selectin ligands that sequester circulating L-selectin [23]. The low L-selectin concentrations observed after tPA may therefore hint to expression of such ligands, although their molecular nature remains to be defined.

The concentration of sVCAM-1 rose by 24 hours after tPA lysis, whereas sVCAM-1 concentrations did not differ

within the first hours after interventions between the three groups. The sE-selectin level was depressed after tPA and PTCA in comparison with controls, whereas the SK group showed an increase throughout the observation period. VCAM-1 and E-selectin are adhesion molecules exclusively expressed by endothelial cells. Their soluble isoforms have been reported elevated in patients with unstable angina, documented coronary artery disease, or in patients with essential hypertension [27–31]. Whereas previous studies found no effect of thrombolytic therapy with tPA or SK on circulating VCAM-1 and E-selectin during the first 24 hours after attempted reperfusion [32], we observed a gradual increase at 12–24 hours for VCAM-1 after tPA and for E-selectin after SK lysis. As both adhesion molecules are transcriptionally regulated, this slow increase is in accordance with a protracted course of events following reperfusion that may well extend beyond 24 hours.

Furthermore, we found significantly elevated serum levels for sICAM-1 after PTCA and for sPECAM-1 in the tPA group compared with controls and with both of the other therapy groups. No obvious differences between the three therapy groups emerged for sP-selectin, but sP-selectin was increased after PTCA and SK up to 8 hours after treatment compared with controls. Caution has to be exerted when interpreting circulating isoform concentrations because various cell types express ICAM-1, PECAM-1 and P-selectin. In patients with acute myocardial infarction, unstable angina, and after coronary spasm, increased levels of sP-selectin have been reported [9,12,33,34]. Soluble ICAM-1 and PECAM-1 have reported to be elevated in patients with coronary artery disease or acute myocardial infarction [11,16,35–37]. Both soluble ICAM-1 and PECAM-1 have been reported released into the circulation following reperfusion after acute myocardial ischemia, resulting in a transient increase within the first hours after reperfusion [28,32]. In the present study, we found both ICAM-1 and PECAM-1 remarkably stable after attempted reperfusion, but ICAM-1 was consistently elevated for 24 hours after PTCA whereas PECAM-1 was elevated between 1 and 12 hours after tPA.

Our findings are therefore in accordance with previous observations in finding changed levels of adhesion molecules, probably indicating endothelial activation as a result of reperfusion of the ischemic myocardium. Limitation of this study is the lack of samples taken before start of treatment, and some uncertainty is added to the interpretation of our results because serum levels of the soluble adhesion molecules are not only influenced by their synthesis and shedding, but also by their clearance or uptake by counter-receptors. Direct interactions of SK or tPA with the assays were not responsible for the observed changes.

Adhesion molecules mediating leukocyte endothelial interactions undergo complex changes in patients treated for acute myocardial infarction. Both postischemic reperfusion and the specific treatment modality chosen appear to be involved in the regulation of these adhesion molecules. Elucidation of the clinical relevance of altered adhesion molecules awaits larger studies with later endpoints.

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