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Elevation of the Soluble Thrombomodulin Levels Is Associated with Inflammation after Percutaneous Coronary Interventions

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Summary

Background: Thrombomodulin (TM) is an endothelial cell surface thrombin-binding protein with anticoagulation ability by thrombin-mediated activation of protein C. An increase of plasma soluble TM level is reported to be associated with severity and worse outcome of coronary artery disease.

Hypothesis: This prospective study investigated the relation of the elevated levels of plasma soluble TM and inflammatory and myonecrotic markers in patients undergoing percutaneous coronary intervention (PCI).

Methods: Plasma levels of soluble TM, C-reactive protein (CRP), and creatine kinase and its MB isoenzyme were measured before and after PCI in 100 patients undergoing PCIs.

Results: Peak TM levels after PCIs were significantly higher than baseline (3.39 ± 1.63 vs. 2.90 ± 1.57 ng/ml, $p < 0.001$). The peak TM levels after PCIs correlated significantly with the peak CRP and MB levels, and the maximal inflation duration ($r = 0.423$, $p < 0.001$; $r = 0.212$, $p = 0.034$; $r = 0.307$, $p = 0.002$, respectively).

Conclusions: Soluble TM levels increase significantly after PCI. The elevation of the soluble TM after PCI shows better correlation with inflammation than myocardial injury, indicating an endothelial origin. Measurement of soluble TM could be useful and calls for further studies on the prognostic effects of this marker in this clinical condition.

Key words: thrombomodulin, inflammation, percutaneous coronary intervention

Introduction

Thrombomodulin (TM) is a cell surface thrombin-binding protein that alters the macromolecular specificity of thrombin. It thereby decreases the ability of thrombin to catalyze clot formation and at the same time converts thrombin into a potent protein-C activator.[1] Once protein C is activated, it proteolytically inactivates factors Va and VIIIa, thereby effectively inhibiting propagation of the coagulant response.[1] Thrombomodulin has two forms: one is expressed on the endothelium and the other is present in circulating plasma called soluble form. The presence of soluble TM in tissue culture supernatant is considered to be the result of endothelial damage.[2] Actually, thrombin has a number of cellular effects apart from its central role in blood coagulation.[3] These effects will be mediated by the TM expression on the endothelium. Accordingly, decreased expression and increased shedding of the membrane TM are expected to participate in the processes of vascular atherogenesis, remodeling, and thrombus formation. Plasma levels of soluble TM have been reported to correlate with peripheral atherosclerosis[4] and coronary artery disease[5, 6] in humans. Percutaneous transluminal coronary angioplasty and coronary stenting have been widely used for decades in patients with coronary artery disease. Several markers of endothelial injury indicating platelet and coagulation activation have been reported after percutaneous coronary intervention

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(PCI);[7] however, the changes of soluble TM antigen are poorly understood. We hypothesize that soluble TM levels might be increased after coronary interventions and that this marker may correlate with endothelial injury.

Materials and Methods

Study Population

We prospectively evaluated 100 consecutive eligible patients with coronary artery disease undergoing PCI (75 balloon and 25 stent procedures) at our hospital from May 1998 to December 1999. Exclusion criteria included (1) documented malignancy, rheumatoid arthritis, renal insufficiency (serum creatinine > 1.5 mg/dl or creatinine clearance < 50 ml/min), and active infection; (2) acute myocardial infarction (or acute coronary syndrome with positive cardiac troponin) < 7 days. Coronary risk factors, defined elsewhere,[6] were reviewed in all study participants. All study subjects gave written informed consent.

Intervention Procedure

The presence of coronary artery disease was defined as ≥ 50% diameter narrowing in one major coronary artery or its major branches. Percutaneous coronary interventions were performed by standard Judkins technique through the femoral artery. All patients received 10,000 U of intravenous heparin before a guide were was introduced, and intermittent bolus as needed to keep activated clotting time around 250 to 350 s during the procedure. The dilatation procedure was performed with multiple balloon inflations using catheters ranging in diameter from 2.0 to 4.0 mm. The balloon: artery ratio was 1.1: 1.0. Stenting was performed after predilatation with balloons.

Measurements of Plasma Markers

Blood samples were drawn from the femoral artery before and after PCI within 24 h. Plasma concentrations of TM were measured by a monoclonal antibody-based ELISA kit (American Diagnostica Inc., Greenwich, Conn., USA). Plasma concentrations of C-reactive protein (CRP) were measured by a rate nephelometric assay on the Beckman Array system (Beckman Instruments, Fullerton, Calif.). Creatine kinase (CK) and MB activities were measured by an automatic enzyme immunoassay method. The coefficient of variation of these measurements within and between each test is < 10%.

Statistical Analysis

All analyses were performed with the Statistical Package for Social Sciences (SPSS Inc., Chicago, Ill., USA) for Window 95. All data were expressed as mean ± standard deviation. Plasma changes of soluble TM were compared by paired Student's *t*-test. Several continuous variables were used to correlate with peak TM levels after procedures by Pearson correlation. A significance level of $p \leq 0.05$ by two-tailed analysis was used in all tests.

Results

Clinical and Intervention Characteristics

The demographic and clinical characteristics of the study subjects are shown in Table I. The majority of the patients were men with a history of dyslipidemia and hypertension. The target vessel requiring intervention (Table II) was usually the left anterior descending artery. About half of the group undergoing PCI manifested chest pain during the procedure. Lesion dissection was the most common finding, and among angiographic complications occurred in 41%. Six patients had in-hospital cardiovascular events (two with small myocardial infarct, three with recurrent angina pectoris, and one with hypotension requiring vasopressor support). No patient required emergency bypass surgery because of complications and no patient died during hospitalization.

Plasma Markers

Peak TM levels after PCI were significantly higher than the baseline (3.39 ± 1.63 vs. 2.90 ± 1.57 ng/ml, $p < 0.001$). Peak creatine kinase, MB isoform, and CRP levels after PCI were all significantly higher than baseline levels (112 ± 136 vs. 75 ± 83 IU/l, $p = 0.002$; 5 ± 10 vs. 1 ± 2 IU/l, $p < 0.001$; 1.8 ± 3.6 vs. 0.8 ± 1.7 mg/dl, $p < 0.001$, respectively). Peak TM levels correlated significantly with peak levels of the CRP and MB isoform ($r = 0.423$, $p < 0.001$; $r = 0.212$, $p = 0.034$, respectively) (Fig. 1) (Table III). Among intervention parameters, only maximal inflation duration correlated significantly with peak levels of soluble TM ($r = 0.307$, $p = 0.002$).

TABLE I Demographic and clinical characteristics of the study group

	PCIs (n = 100)
Age, years	62 ± 11
Gender, M/F	73/27
Dyslipidemia	71
Cholesterol, mg/dl	205 ± 40
Triglyceride, mg/dl	172 ± 142
Hypertension	63
Diabetes mellitus	27
Current tobacco user	51
Coronary artery disease	
Single-vessel	30
Double-vessel	42
Triple-vessel	28

Values are expressed as mean ± standard deviation.
Abbreviations: PCIs = percutaneous coronary interventions, M = male, F = female.

TABLE II Angiographic and interventional characteristics of the study group

	Frequency or mean ± standard deviation
Distribution of intervention vessels	
Left anterior descending artery	54
Left circumflex artery	23
Right coronary artery	35
Others	3
Intervention lesions	
One lesion	53
Two lesions	31
Three lesions or more	16
American Heart Association type C	28
Number of inflations	4 ± 3
Total inflation duration, s	250 ± 158
Maximal inflation duration, s	79 ± 31
Maximal pressure, atm	13 ± 8
Balloon size, mm	3.1 ± 0.4
Chest pain	57
Chest pain duration, s	171 ± 89
Angiographic complications	41
Thrombus	6
Dissection	27
Spasm	3
Acute closure	1
Hypotension	2
Sidebranch compromise	4
Distal embolization	6
Recoil	1
No-reflow	2

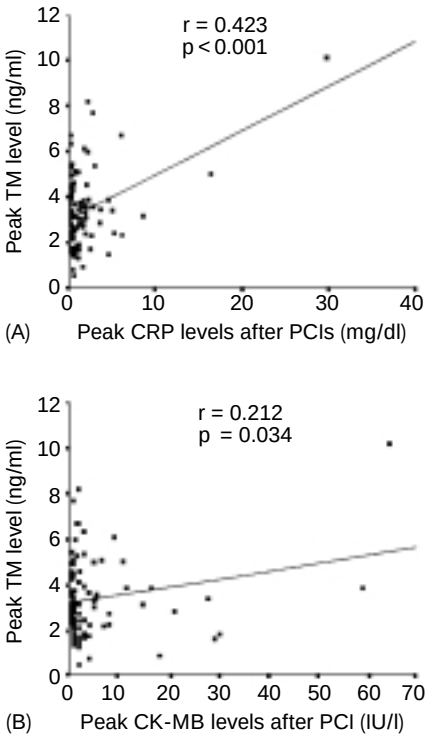

FIG. 1 Correlation of peak thrombomodulin (TM) levels with peak C-reactive protein (CRP) levels (A) and peak creatine kinase-MB levels (B) after percutaneous coronary interventions (PCIs).

TABLE III Correlations of clinical variables with peak thrombomodulin levels after percutaneous coronary interventions

	r	p Value
C-reactive protein	0.423	< 0.001
CK-MB isoform	0.212	0.034
Maximal inflation duration	0.307	0.002

Abbreviation: CK-MB = MB isoform of creatine kinase.

Discussion

Percutaneous coronary intervention causes compression and stretching of the atherosclerotic plaque. Data from the present study provided in vivo evidence that endothelial damage will enhance the release of soluble form TM and also implied that the increase of soluble TM might be due to shedding of membrane-binding TM following endothelial damage, since peak TM levels correlated positively with maximal inflation duration. Atherosclerosis is a process of responses to endothelial damage, involving the accumulation of smooth muscle cells, macrophages and T-lymphocytes, and lipids.[8] Some studies have shown previously that plasma soluble TM levels are higher in patients with atherosclerosis,[4,5] whereas studies of the relation of soluble TM with incident coronary artery disease in previously healthy persons showed totally different results.[10] Increased soluble TM in patients with atherosclerosis is a predictor of poor cardiovascular outcome.[9] The authors[4,5] postulated that atherosclerosis causes endothelial damage, thereby leading to the elevation of soluble TM based only on the in vitro evidence.[2] Our data extended the mechanism and proved the hypothesis in vivo. Maximal inflation duration is one of the factors responsible for increases in soluble TM in our study. These findings provided strong evidence that elevation of soluble TM reflects the severity of endothelial damage.

In patients with peripheral atherosclerosis[4] and coronary artery disease,[5] increased levels of soluble TM, CRP, and another inflammatory markers have been reported. These changes may reflect increased endothelial cell/leukocyte interactions, endothelial cell injury or turnover, or inflammation.[4] In addition, markers of myocardial injury, including CK-MB[11] and cardiac troponins,[12] as well as inflammatory markers[13] and platelet/coagulation profiles[14] have been discussed separately and reported to be elevated after PCI. However, the association of increased serum levels of soluble TM with CRP and CK-MB has not been described. Some mechanisms to account for the inflammatory response induced by PCI have been reported. First, PCI leads to plaque rupture, arterial wall damage, and release of inflammatory cytokines with leukocyte and platelet activa-

tion.[15] Second, the ischemia-reperfusion process induced by repeated balloon inflations may also stimulate inflammatory response.[16] Because membrane TM has anti-inflammatory properties,[17] the association of CRP and soluble TM levels after PCI, as demonstrated in our study, suggests that endothelial damage by PCI mediated systemic inflammatory response partly through TM pathway. Furthermore, correlation of soluble TM with CRP is better than that of TM with CK-MB, further implying that these findings are endothelial/arterial in origin and not directly linked to myonecrosis.

This study has some limitations. First, the effect of heparin on subsequent soluble TM levels after PCI has not been discussed. Second, the sample size does not provide enough statistical power to address restenosis, at least in the way the analysis was performed. Finally, we did not use coronary sinus blood for marker measurements. In fact, peripheral blood sampling is much easier and less time consuming than coronary sinus blood sampling.

Conclusion

Our data suggest that soluble TM levels increase significantly after PCI and that the elevation of TM levels is associated with inflammation and myocardial injury. Therefore, measurement of soluble TM could be useful. A large-scale outcome study regarding this marker after PCI is warranted.

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