Soluble E-selectin, ICAM-1 and VCAM-1 levels in systemic and coronary circulation in patients with variant angina

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Abstract

Objective: The purpose of this study was to assess whether the plasma levels of soluble adhesion molecules including E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are elevated in patients with variant angina and whether they are released in the coronary circulation. Methods: Antecubital venous plasma samples were collected from 33 patients with variant angina, 22 patients with stable effort angina and 20 control subjects. Samples were also collected from the aortic root (AO) and the coronary sinus (CS) in 18 patients with variant angina before and after left coronary spasm induced by intracoronary injection of acetylcholine. The soluble adhesion molecules were assayed by enzyme immunoassay. Results: Antecubital venous plasma soluble E-selectin \(P < .05\), ICAM-1 \(P < .01\) and VCAM-1 (NS) levels were higher in the variant angina group than in the control group, respectively. The plasma soluble ICAM-1 level was also higher \(P < .01\) in the variant angina group than in the stable effort angina group. In the variant angina group, both soluble ICAM-1 \(P < .05\) and VCAM-1 \(P < .01\) levels were significantly lower in CS than AO at baseline. In contrast, after the spasm the plasma soluble ICAM-1 level was \(P < .05\) higher in CS than AO and the CS–AO differences of soluble ICAM-1 \(P < .05\) and VCAM-1 \(P < .05\) increased as compared with the baseline, respectively. These values were remained unchanged in the stable effort angina group after rapid atrial pacing and in the control group after administration of acetylcholine. Conclusions: Circulating plasma levels of both soluble E-selectin and ICAM-1 were elevated in patients with variant angina, indicating an association of an inflammatory reaction with coronary spasm. Both soluble ICAM-1 and VCAM-1 appeared to be trapped in the coronary circulation at baseline and released into the coronary circulation following coronary spasm and reperfusion in the patients. © 1997 Elsevier Science B.V.

Keywords: Unstable angina; Variant angina; Coronary artery spasm; Ischemia/reperfusion; Soluble adhesion molecule; Human

1. Introduction

Adhesion of neutrophils and monocytes to endothelial cells of coronary arteries and subsequent leucocyte activation may be relevant in the progression and evolution of atherosclerotic coronary artery disease [1,2]. Recent data also suggest a role for inflammation including endothelial-leucocyte adhesive interactions and extravascular leucocyte accumulation [3–7] in the pathophysiology of unstable angina or acute coronary syndromes [8–10]. In order for circulatory leucocytes to reach the subendothelium, they generally must first adhere to and transverse microvascular endothelium. Specifically, inflammatory endothelium may, in response to extravascularly produced mediators, newly express cell surface molecules that are adhesive for leucocytes. Several such molecules are known, and each has specific ligands (counter-receptors) on a characteristic spectrum of leucocytes. Examples of such molecules are E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [11]. These molecules are expressed on endothelial cells after stimulation with cytokines such as tumor necrosis factor-\(\alpha\) and interleukin-1\(\beta\) [11]. Although they are released from activated endothelial cells in vitro [12], the alteration of the plasma level has not been determined in coronary artery disease and the functional significance of
the soluble form of adhesion molecules is unknown. Some soluble forms of adhesion molecules such as P-selectin have been demonstrated to selectively inhibit the adhesion process of activated neutrophils to endothelium [13].

In the present study, we therefore aimed to determine whether circulating soluble adhesion molecule levels were actually released into coronary circulation by comparing between the levels in the aortic root and coronary sinus, and also whether these molecules were released at baseline or after coronary artery spasm.

2. Methods

2.1. Peripheral blood study

Consecutive 33 patients (27 men and 6 women with a mean age of 57 ± 2 years; range: 29–73 years) in whom electrocardiographic ST-segment elevation in more than one of the standard 12 leads was confirmed during attacks occurring at rest (VA) were studied for the determination of the plasma adhesion molecule levels in peripheral blood. In all patients coronary artery spasm was angiographically demonstrated in at least one of the major coronary arteries during spontaneous or induced-attacks by intracoronary injection of acetylcholine. In 9 of them (27%) a significant (> 75% luminal narrowing) organic coronary arterial stenosis was noted, but none of them had complete or nearly complete coronary obstructive lesions. The stable effort angina group (SA) consisted of 22 patients (17 men and 5 women; mean age 58 ± 2 years; range 36–73 years) who had typical exertional angina and a significant organic narrowing of either coronary artery. For the control, 20 (15 men and 5 women with a mean age of 54 ± 3 years; range 28–69 years) without any significant systemic disease who were free from coronary artery disease (Control) were selected. None of them had positive treadmill exercise stress test results with the standard Bruce protocol. The 3 groups were matched for age and sex (Table 1).

All the medications except sublingual nitroglycerin had been stopped at least 24 h before the study. Adrenergic β receptor blocking agents were withdrawn > 48 h. Blood samples were obtained via an antecubital vein in the fasting state in the morning from all the study patients and collected into vacutainer tubes containing ethylenediaminetetraacetic acid disodium salt. Plasma was immediately separated by centrifugation and stored at −20°C until use.

2.2. Study patients for coronary circulation study

Among the study patients for the peripheral blood study, a total of 39 patients including 18 patients with active variant angina (VA), 10 patients with stable effort angina (SA) and 11 patients with atypical chest pain (Control) who underwent diagnostic coronary arteriography were subjected to the coronary circulation study. All patients gave written informed consent, and the study protocol was approved by the ethical committee of our institution. VA patients had chest pain at rest associated with transient ST-segment elevation in the precordial leads unaccompanied by serum creatine kinase elevation or a new Q wave in the electrocardiogram. Sublingual administration of nitroglycerin was effective for the prompt relief of their anginal attacks in all the patients. All patients had experienced spontaneous anginal attacks at least twice during the week prior to the study and 11 of them had at least one episode of chest pain within 48 h of coronary arteriography. VA patients had exertional angina, positive exercise stress test results and a significant organic narrowing in the left coronary artery. Control subjects had experienced chest pain but had no significant coronary arterial stenosis, and no coronary artery spasm was demonstrated by the intracoronary injection of acetylcholine. VA consisted of 16 males and 2 females with a mean age of 59 ± 2 years (range, 44 to 71). Five had single-vessel disease and the other 13 had no significant organic stenosis in the coronary arteries. In SA, there were 8 men and 2 women, with a mean age of 58 ± 3 years (range, 38 to 68). In Control, there were 8 men and 3 women, with a mean age of 55 ± 4 years (range, 29 to 72).

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control</th>
<th>VA</th>
<th>SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>20</td>
<td>33</td>
<td>22</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>54 ± 3</td>
<td>57 ± 2</td>
<td>58 ± 2</td>
</tr>
<tr>
<td>Male/Female</td>
<td>15/5</td>
<td>27/6</td>
<td>17/5</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>0</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Blood pressure ≥ 150/90 mmHg</td>
<td>6</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Smoking</td>
<td>8</td>
<td>27 a</td>
<td>12</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 25)</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>196 ± 9</td>
<td>194 ± 7</td>
<td>211 ± 9</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>125 ± 10</td>
<td>147 ± 7</td>
<td>144 ± 7</td>
</tr>
<tr>
<td>Coronary organic stenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-vessel</td>
<td>0</td>
<td>24 b</td>
<td>0</td>
</tr>
<tr>
<td>1-vessel</td>
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<td>7</td>
<td>9</td>
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<tr>
<td>3-vessel</td>
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<td>3</td>
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<td>Medication used before blood sampling</td>
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</tr>
<tr>
<td>beta-blockers</td>
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<td>12</td>
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<td>14</td>
</tr>
<tr>
<td>Aspirin</td>
<td>0</td>
<td>5</td>
<td>15</td>
</tr>
</tbody>
</table>

Control: control subjects, VA: patients with variant angina, SA: patients with stable effort angina, BMI: body mass index.

P < 0.01 vs. Control and P < 0.05 vs. SA, aP < 0.01 vs. SA.
2.3. Procedures for coronary circulation study protocol

All the medications except sublingual nitroglycerin had been stopped as described above. At the beginning of the procedure, a 6F Judkins catheter was advanced from the femoral artery and placed in the ascending aorta, and a 7.5F Opticath® (Model P7110, Oximetrix, Inc.) was inserted in the right internal jugular vein and placed in the coronary sinus. The position of the catheter was confirmed by occasional injection of the contrast medium. Blood samples were obtained simultaneously from the aortic root and coronary sinus, after the Judkins catheter was advanced to the left coronary artery ostium and the control coronary arteriography was performed. All patients were given 5000 U of heparin at the insertion of the Judkins catheter.

2.4. Intracoronary acetylcholine provocation test

Before coronary arteriography, a temporary pacing catheter was inserted into the right ventricle via a femoral vein and connected to a pulse generator with a demand-driven rate of 50 beats/min in VA and Control patients. Acetylcholine hydrochloride (Daiichi Seiyaku) dissolved in 0.9% saline solution, was injected directly into the left coronary artery over 30 s through the Judkins catheter in incremental doses of 20 and 50 µg [14]. Coronary arteriography was performed when ST-segment changes or chest pain, or both, developed, or 2 min after the initiation of the injection. When coronary artery spasm was induced, 200 µg of nitroglycerin was injected directly into the left coronary artery after angiograms. In the present study, coronary artery spasm was defined as transient severe coronary vasoconstriction (≥ 90% of luminal diameter) associated with an attack of chest pain or ischemic ST-segment changes on the electrocardiogram, or both. Blood samples were taken again simultaneously from the aortic root and the coronary sinus after angiographical confirmation of the resolution of the induced spasm or sublingual administration of nitroglycerin when intracoronary injection of acetylcholine failed to induce coronary spasm. Plasma was prepared and stored as described above.

2.5. Pacing stress test

After control blood sampling, right atrial pacing was commenced in SA patients. The pacing rate was begun at 90 beats per minute and was increased until the patients experienced angina that was sustained for 3 or 5 min. Blood samples were then collected.

2.6. Assay of soluble adhesion molecules

Levels of plasma E-selectin, ICAM-1 and VCAM-1 were measured with a commercial ELISA kit (British Biotechnology Products, Oxford, UK) using dual monoclonal antibody two-site ELISAs. Briefly, microtitre ELISA plates were coated overnight with a specific capture antibody (BBIG-E2 for E-selectin, BBIG-I1 for ICAM-1, BBIG-V4 for VCAM-1) at a final concentration of 10 µg/ml in 0.1 M bicarbonate buffer pH 8.9. Standards and samples were added to the plate, incubated for 2 h at room temperature and the bound soluble adhesion of interest was detected by sequential incubation with a specific biotin-labeled antibody followed by horseradish peroxidase-conjugated streptavidin and finally tetramethylbenzidine.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Plasma soluble adhesion molecule levels in the coronary circulation in study patients</th>
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<tbody>
<tr>
<td></td>
<td>VA (Variant angina)</td>
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<tr>
<td></td>
<td>AO</td>
</tr>
<tr>
<td>E-selectin</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>49 ± 4</td>
</tr>
<tr>
<td>ACh</td>
<td>49 ± 5</td>
</tr>
<tr>
<td>ICAM-1</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>288 ± 23</td>
</tr>
<tr>
<td>ACh</td>
<td>258 ± 19</td>
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<tr>
<td>VCAM-1</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>824 ± 70</td>
</tr>
<tr>
<td>ACh</td>
<td>730 ± 53</td>
</tr>
<tr>
<td>Control</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>AO</td>
<td>ng/ml</td>
</tr>
</tbody>
</table>

mean ± SEM: * P < 0.05 vs. AO; ** P < 0.01 vs. AO.
ACh: After intracoronary injection of acetylcholine.
Pacing: During pacing-induced angina.
AO: Aortic root.
CS: Coronary sinus.
CS-AO: Coronary sinus-aortic difference.
The reaction was stopped by the addition of 1 M HCl to each well and the O.D. 450 nm measured using a microplate reader MPR-A4i (Tosoh, Tokyo, Japan). The assays were standardized using a recombinant soluble form of adhesion molecule lacking their transmembrane and cytoplasmic domains and given an arbitrary unitage against which all samples were measured.

2.7 Statistical analysis

Values are expressed as mean ± SEM. Comparisons of antecubital plasma soluble E-selectin, ICAM-1 and VCAM-1 levels among the 3 groups were performed using one-way ANOVA followed by Dunnett’s multiple comparison test. The two-tailed paired Student’s t test was used in the analysis of changes in plasma levels of E-selectin, ICAM-1 and VCAM-1 in the coronary circulation in each group.

3. Results

Clinical and coronary angiographic data of the study patients were listed in Table 1. Current smokers were significantly more prevalent in VA 82% as compared with SA 55%, \( P < 0.05 \) and Control 40%, \( P < 0.01 \). However, there were no significant differences among the three groups in the following variables: age, sex, hypertension, diabetes mellitus, obesity, serum cholesterol, and serum triglycerides.

3.1 Soluble adhesion molecule levels in peripheral blood

Concentrations of plasma soluble E-selectin, ICAM-1 and VCAM-1 in the study patients are shown in Fig. 1, Fig. 2 and Fig. 3. Both soluble E-selectin \( P < 0.05 \) and ICAM-1 \( P < 0.01 \) levels were significantly higher in VA than in Control, respectively. The soluble ICAM-1 level was also significantly \( P < 0.01 \) higher in VA than in SA. Although the soluble VCAM-1 level was rather higher in VA, no significant difference was found among the groups. The plasma levels of soluble E-selectin, ICAM-1 and VCAM-1 were not significantly different between Control and SA.

3.2 Soluble adhesion molecule levels at baseline in coronary circulation

The plasma concentrations of soluble E-selectin, ICAM-1 and VCAM-1 in the aortic root and coronary sinus at baseline in the study patients are shown in Fig. 4, Fig. 5, Fig. 6 and Table 2 (Baseline). In VA, soluble E-selectin levels were not significantly different between the aortic root and coronary sinus. However, both soluble ICAM-1 \( P < 0.05 \) and VCAM-1 \( P < 0.01 \) levels were significantly higher in the aortic root than in the coronary sinus, respectively. In contrast, these soluble adhesion molecule levels were not significantly different between the aortic root and coronary sinus in SA or Control.

3.3 Soluble adhesion molecule levels after coronary spasm

Intracoronary injection of acetylcholine induced coronary artery spasm in either major branch in the left coro-
nary artery accompanied by chest pain and/or electrocardiographic ST-segment deviation in all the 18 patients in VA. Following coronary arteriography during angina with confirmation of coronary spasm, the spasm was resolved by intracoronary administration of nitroglycerin. The attack was relieved within 4 min and blood samples were again obtained simultaneously from both the aortic root and the coronary sinus after the complete reperfusion was confirmed angiographically. In contrast, in Control intracoronary injection of acetylcholine failed to induce spasm in the left coronary artery. In all the SA patients, rapid atrial pacing induced angina accompanied by electrocardiographic ST-segment depression.

The plasma concentrations of soluble E-selectin, ICAM-1 and VCAM-1 in the aortic root and coronary sinus, and the coronary sinus-aortic differences after intracoronary injection of acetylcholine or rapid atrial pacing in the study patients are shown in Figs. 4–6 and Table 2. In VA, the soluble E-selectin, ICAM-1 and VCAM-1 levels in the coronary sinus were rather elevated after the spasm induced by intracoronary injection of acetylcholine and reperfusion following administration of nitroglycerin while soluble ICAM-1 and VCAM-1 levels in the aortic root rather decreased and consequently, the coronary sinus-aortic differences of soluble ICAM-1 (P < 0.05) and VCAM-1 (P < 0.05) significantly increased, respectively. After the spasm and reperfusion, the soluble ICAM-1 level was significantly (P < 0.05) higher in the coronary sinus than in the aortic root in VA. On the other hand, both plasma soluble ICAM-1 and VCAM-1 levels in the coronary circulation remained unchanged after the intracoronary injection of acetylcholine in Control. In SA, the plasma soluble E-selectin level somewhat elevated both in the aortic root and the coronary sinus after pacing. Otherwise the plasma soluble adhesion molecule levels in the coronary circulation and the coronary sinus-aortic differ-
Fig. 6. Graphs illustrate plots of plasma soluble VCAM-1 levels in the aortic root (AO) and in the coronary sinus (CS) and coronary sinus-aortic differences (CS-AO) before (Baseline) and after acetylcholine provocation (ACh) in patients with variant angina (VA) (upper) and in control subjects (Control) (lower), and after atrial pacing in patients with stable effort angina (SA) (middle).

4. Discussion

This is the first report describing circulating soluble E-selectin, ICAM-1 and VCAM-1 levels in patients with variant angina, a type of unstable coronary syndrome. As compared with control subjects and also patients with stable effort angina, both circulating soluble E-selectin and ICAM-1 levels were significantly higher in patients with variant angina. These soluble adhesion molecule concentrations were also examined in the coronary circulation before and after spasm of the left coronary artery. Blood samples taken from the aortic root of patients with variant angina were found to have elevated levels of soluble ICAM-1 and VCAM-1 as compared with the coronary sinus at baseline, indicating that these molecules were trapped within coronary circulation during the attack-free period. In contrast, after the induced spasm and reperfusion, the soluble ICAM-1 level was significantly higher in the coronary sinus than in the aortic root, and the coronary sinus-aortic differences in soluble ICAM-1 and VCAM-1 significantly increased, suggesting that these molecules were released through the coronary microcirculation after the resolution of coronary spasm. As the release of soluble ICAM-1 or VCAM-1 into the coronary circulation was not observed after pacing-induced ischemia in the patients with stable effort angina, the release of these molecules is not associated with the pacing-induced ischemia related to increased oxygen demand versus reduced oxygen supply in the ischemic myocardium but to ischemia and reperfusion by coronary spasm.

4.1. Source of circulating adhesion molecules

Soluble forms of the adhesion molecules, E-selectin, ICAM-1 and VCAM-1, have been detected in supernatants from cytokine activated cultured endothelial cells [12] and their levels are elevated in the serum of patients with septic shock or other diseases [15–17]. There is as yet no evidence for the existence of soluble variants of E-selectin, ICAM-1 and VCAM-1 produced by alternative splicing. This is distinct from the case with P-selectin, where cDNA encoding a splice variant lacking the transmembrane domain has been described [18]. Although shedding of proteins from the cell-surface is a well documented phenomenon and indeed, soluble forms of adhesion molecules can also be released [12], the mechanism underlying shedding of adhesion molecules and the significance of adhesion molecule shedding is not yet understood.

4.2. Interpretation of the results

The elevated levels of circulating plasma soluble E-selectin and ICAM-1 in patients with variant angina suggest endothelial activation in the coronary circulation in these patients. However, the release of these molecules into coronary circulation was not demonstrated at baseline. In contrast, following coronary spasm in the left coronary artery and reperfusion, the coronary sinus-aortic differences in both soluble ICAM-1 and VCAM-1 levels significantly increased, indicating the release of these molecules in the coronary circulation. Proteolytic cleavage or shedding triggered by high shear stress during the reperfusion might result in the release of the soluble adhesion molecules into the coronary circulation. The soluble ICAM-1 level was significantly higher in the coronary sinus than in the aortic root after the coronary spasm and reperfusion, suggesting that an elevation of the circulating soluble ICAM-1 level may be due to an augmented release of the molecules into the coronary circulation. As the soluble form of adhesion molecules may be due to an overflow of the molecules and reflect the total expression of them on the
endothelium, the higher level of the circulating soluble adhesion molecules and/or the apparent release in the coronary circulation after spasm demonstrated in the present study, indicate that leucocyte adhesion which may lead to myocardial damage, may be potentiated in the coronary circulation in patients with coronary spasm. The apparent uptake of soluble ICAM-1 and VCAM-1 in the coronary circulation during angina-free periods in patients with variant angina may suggest the binding of these molecules to the activated leucocytes with homotypic aggregation in the coronary tree in which the counterreceptors can be upregulated in response to chemotactic factors. The recent study by Mazzone et al. [19] demonstrated a transcardiac increase in the surface expression of CD11b/CD18, a counterligand of ICAM-1, in coronary sinus monocytes and granulocytes compared with simultaneous control samples drawn from the aortic blood in patients with unstable angina. Among clinical and angiographic findings, only the occurrence of chest pain within 48 h of coronary angiography was related to significantly higher expression of CD11b/CD18 neutrophil adhesion receptors [20]. Soluble molecules may function as competitive inhibitors of membrane bound forms, thereby regulating cell adhesion. This has been demonstrated for a soluble form of P-selectin, which is able to inhibit the adhesion of activated neutrophils to endothelial cells [12]. P-selectin is known to play a role in very early neutrophil adhesion [21]. Recently plasma soluble P-selectin levels after angina were reported to be increased in patients with unstable angina [22], and also soluble P-selectin was suggested to be released into the coronary circulation after coronary artery spasm [23].

4.3. Methodologic considerations and limitations

In general, an increase in the venous-arterial difference may be the result of increased release, reduced clearance/extraction or both. In the present study, the release from the endothelium and the possible uptake in the coronary circulation of the soluble adhesion molecules were not separately estimated and therefore an increase in the coronary sinus-aortic difference does not always reflect an increased release. Further, the clearance/extraction of endogenous substances may be highly dependent on the flow. Although intracoronary injection of acetylcholine has been shown to increase coronary blood flow through dilation of resistance vessels, this effect is usually of short duration of a few minutes and may be minimal at the time of blood sampling [24].

Wide variations in the plasma levels of soluble adhesion molecules were observed among our study groups, which may relate to the nature of our control group and vagaries inherent in the assignment of clinical labels. Obviously their source, expression, kinetics of expression or destruction, and signals inducing their expression and/or release need to be further investigated.

4.4. Clinical implications

Although serum levels of some soluble adhesion molecules have been shown to be elevated in some inflammatory diseases such as sepsis and acute respiratory distress syndrome, and metastatic malignancies [15], their pathogenetic significance and clinical usefulness as markers for in vivo events are yet to be established. Serum soluble E-selectin level may be a marker for endothelial cell activation because this molecule is shed exclusively by the endothelium. Elevated levels of both circulating soluble E-selectin and ICAM-1 demonstrated in the patients with active variant angina having repetitive ischemia and reperfusion may suggest clinical usefulness as markers for inflammatory reaction related to acute coronary syndromes.

The administration of the antibody against adhesion molecules has been reported to reduce not only the infiltration of leucocytes but also the area of infarction in the reperfused canine and rat hearts [25,26] and also attenuate cardiac allograft rejection in mice [27]. In the present study an apparent uptake of soluble ICAM-1 and VCAM-1 in the coronary microcirculation was demonstrated in patients with variant angina, a model of unstable angina. However, it remains to be determined whether these soluble adhesion molecules inhibit the adhesion process by binding to the appropriate ligand on leucocytes staying in the coronary microcirculation, and thereby interfering with a step that is important in the development of myocardial cell injury.

4.5. Conclusion

The present study demonstrated elevated circulating plasma soluble E-selectin and ICAM-1 levels in patients with recurrent variant anginal episodes, suggesting an association of an inflammatory reaction with coronary spasm. Both soluble ICAM-1 and VCAM-1 appeared to be released after spasm. A significant uptake of these molecules in the coronary circulation was confirmed in these patients at baseline. However, further studies are needed to elucidate the exact mechanisms in the apparent uptake of the soluble adhesion molecules and the possible reaction between these molecules and their counterligands of activated neutrophils and monocytes.

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References

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