

## Review

# Interleukin-6 and Acute Coronary Syndrome

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**Summary:** The designation of atherosclerosis as a chronic inflammatory process represents an exciting and logical paradigm shift for cardiologists. Plasma concentrations of interleukin-6 (IL-6) and its hepatic by-product C-reactive protein (CRP) appear to reflect the intensity of occult plaque inflammation and by inference may determine vulnerability to rupture. Indeed, circulating IL-6 levels are elevated in patients with acute myocardial infarction (AMI), and also in patients with unstable, but not with stable angina. Coronary sinus IL-6 concentrations are also increased after percutaneous coronary intervention (PCI), and late restenosis correlates with an increase in IL-6 concentration after the procedure, indicating that IL-6 expression may be not only related to instability of atheromatous plaques, but also to the formation of restenotic lesions after PCI. These observations suggest the advantage of screening for circulating IL-6 concentration and the use of anti-inflammatory treatment for those thought to be at high risk to reduce the risk of future AMI.

**Key words:** myocardial infarction, angina pectoris, restenosis, cytokine, inflammation

## Introduction

Interleukin-6 (IL-6) has been shown to be a local and circulating marker of coronary plaque inflammation. It is a 26 kDa cytokine, produced by many different cells in the body, including lymphocytes, monocytes, fibroblasts, vascular smooth

muscle cells, and endothelial cells. Interleukin-6 stimulates the expression of tissue factor, monocyte chemoattractant protein-1, matrix degrading enzyme, and low-density lipoprotein receptors in macrophages,<sup>1–4</sup> and the aggregation of platelets, proliferation of vascular smooth muscle cells,<sup>5,6</sup> and production of C-reactive protein (CRP) and fibrinogen by hepatocytes (Fig. 1). It also regulates the expression of adhesion molecules and other cytokines in endothelial cells, for example, interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$ , which potently enhance the inflammatory reaction.<sup>5,7</sup> It has been well documented that elevated levels of acute-phase proteins are associated with unfavorable short- and long-term prognoses in patients with coronary artery disease.<sup>8,9</sup> In this review, we discuss the involvement of IL-6 in the pathophysiology of acute coronary syndrome.

## Acute Myocardial Infarction

Almost 10 years ago, we reported that circulating IL-6 levels were increased in patients with acute myocardial infarction (AMI).<sup>10</sup> Interleukin-6 levels became elevated following the rise of serum creatine kinase (CK) activity and showed a good correlation with levels of its hepatic by-product CRP, while there was no direct relationship between IL-6 level and CK activity. At approximately the same time, Sturk *et al.*<sup>11</sup> also reported increased plasma IL-6 levels in patients with AMI. Similar to our observations, IL-6 levels began to increase 14 h (mean; range 8–20 h) after the initial complaints and reached maximal levels of 28 to 250 U/ml (normal values < 10 U/ml) after 36 h (mean; range 24–52 h). No correlation was observed between the size of the infarction as indicated by CK assay and the extent of the IL-6 increase, while maximal IL-6 levels correlated significantly with maximal CRP levels.

As the source of circulating IL-6 at the early stage of AMI, we<sup>12</sup> and Rus *et al.*<sup>13</sup> observed that IL-6 was expressed in human atherosclerotic lesions. Kaneko *et al.*<sup>14</sup> observed the expression of IL-6 in the coronary arteries of patients with AMI. Schieffer *et al.*<sup>15</sup> reported the localization of IL-6 at the shoulder region of coronary atherosclerotic plaques where rupture of the plaques predominantly occurs. On the other hand, Gwechenberger *et al.*<sup>16</sup> reported that cardiac myocytes in the viable border zone in a canine model of myocardial infarction exhibited reperfusion-dependent expression of IL-6 mRNA.

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Received: November 27, 2000

Accepted with revision: March 12, 2001

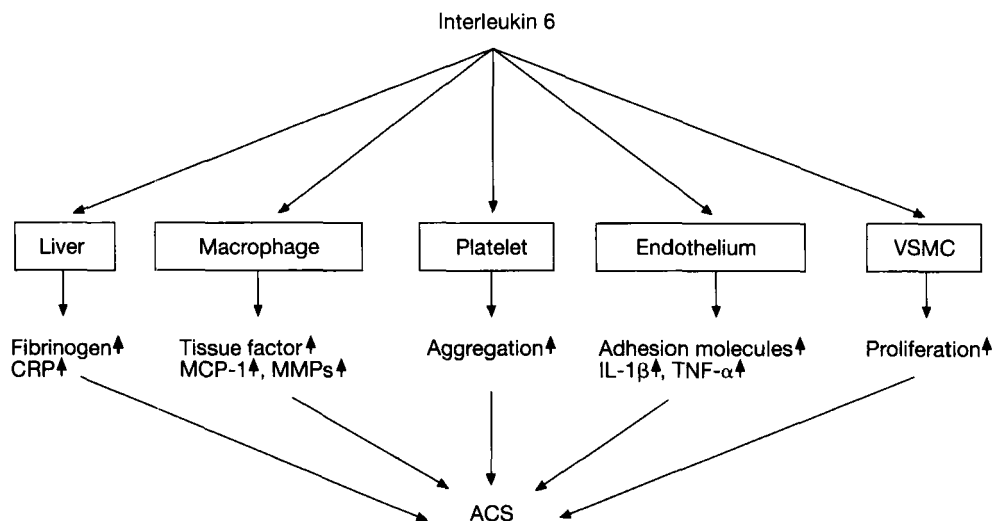


FIG. 1 The involvement of interleukin-6 in the pathogenesis of acute coronary syndrome (ACS). MCP-1 = monocyte chemoattractant protein-1, MMPs = matrix metalloproteinases, IL-1 $\beta$  = interleukin-1 $\beta$ , TNF- $\alpha$  = tumor necrosis factor- $\alpha$ , VSMC = vascular smooth muscle cell.

Mononuclear cells infiltrating the border zone also expressed IL-6 mRNA. These findings suggested that the vascular tissue, cardiac myocytes, and infiltrating inflammatory cells could all be sources of circulating IL-6 in AMI.

### Angina Pectoris

In addition to AMI, IL-6 levels are also increased in unstable angina (UA).<sup>17, 18</sup> Manten *et al.*<sup>19</sup> reported that plasma IL-6 concentrations were significantly higher in patients with UA and AMI than in those with stable angina (SA), although they were lower in UA than in AMI. Interleukin-6 was shown to be an independent predictive marker with equal discriminative power to distinguish patients with stable from unstable disease (UA + AMI). Biasucci *et al.*<sup>20</sup> measured levels of IL-6 in patients with UA at the time of admission to the coronary care unit and in patients with SA. They were detectable in 61% of patients with UA but in only 21% of patients with SA.

We also observed that plasma levels of IL-6 in patients with UA were significantly higher than those in patients with SA or in control subjects. Furthermore, levels of IL-6 in patients with UA, who had an anginal attack at rest within 48 h prior to admission (Braunwald class IIIB), were significantly higher than those in patients who did not have attacks at rest (class IB, IIB) (unpublished observation). Yazdani *et al.*<sup>21</sup> reported that IL-6 level was significantly elevated in patients with UA compared with those with SA. Furthermore, at 1 month follow-up after percutaneous coronary intervention (PCI), there were no longer any significant differences between the levels of IL-6 in patients with UA versus those with SA or healthy control subjects. These findings suggested that IL-6 levels correlate with instability of atheromatous plaques and that the decrease in IL-6 level after PCI may represent plaque re-endothelialization and stabilization.

### Restenosis after Angioplasty

Interleukin-6 expressed in the vascular tissue may be related not only to instability of atherosclerotic plaques, but also to the formation of atherosclerotic lesions. Suzuki *et al.*<sup>22</sup> measured circulating IL-6 levels in patients with SA undergoing elective PCI before, and immediately, 1, and 6 h after the procedure. They performed follow-up coronary angiography 6 months after the procedure and found that patients with restenosis showed significant increases in IL-6 concentrations 1 and 6 h after the procedure.

We also investigated links between IL-6 and restenosis in patients undergoing elective PCI for SA.<sup>23</sup> Coronary sinus blood was drawn before and after PCI and the concentration of IL-6 was measured. We found that coronary sinus IL-6 concentrations were significantly increased postoperatively. The source of this increase was the heart itself, as IL-6 concentrations in peripheral arterial blood samples taken at the same time were not increased. We performed 6-month follow-up coronary angiography and found that the late loss index (an angiographic measure of restenosis) correlated with the increase in coronary sinus IL-6 concentration after PCI. These findings suggested that enhanced IL-6 expression induces subsequent inflammatory responses in injured coronary vessels and plays an important role in late restenosis after PCI.

### Therapeutic Implications

In a prospective study involving 14,916 apparently healthy men, Ridker *et al.*<sup>24</sup> measured baseline plasma concentration of IL-6 in 202 participants who subsequently developed AMI, and in 202 study participants matched for age and smoking status who did not develop vascular disease during a 6-year follow-up. Median concentrations of IL-6 at baseline were higher among men who subsequently had AMI than among

those who did not (1.81 vs. 1.46 pg/ml). The risk of future AMI increased with increasing quartiles of baseline IL-6 concentration such that men in the highest quartile at entry had a relative risk 2.3-fold higher than those in the lowest quartile. Biasucci *et al.*<sup>25</sup> reported that patients with UA and with complicated in-hospital courses have higher IL-6 levels on admission. A drop in IL-6 48 h after admission was associated with an uneventful course, and an increase at this time point was associated with a complicated hospital course. These findings suggested a role of IL-6-mediated inflammation in the plaque formation and instability, and also therapeutic benefit of inhibition of IL-6 to prevent future AMI.

The concentrations of the inflammatory marker CRP are increased during acute coronary syndrome, and higher concentrations predict a worse outcome in patients with UA,<sup>26</sup> as observed in IL-6. It is interesting to note that the protective effects of aspirin<sup>27</sup> and hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins)<sup>28</sup> are greatest in patients with the highest baseline CRP concentrations in keeping with the anti-inflammatory properties of both drug classes.<sup>29</sup> Also, in a study by Ikonomidis *et al.*,<sup>30</sup> patients with UA had more than double the median IL-6 level compared with controls (3.9 vs. 1.7 pg/ml), and IL-6 levels were reduced after 6 weeks of aspirin treatment. On the other hand, we<sup>31</sup> and Inoue *et al.*<sup>32</sup> observed that HMG-CoA reductase inhibitors (statins) suppress IL-6 expression in human vascular smooth muscle cells, endothelial cells, and macrophages. In addition, Bickel *et al.*<sup>33</sup> recently examined the nonlipid effects of statins in 950 patients with coronary artery disease and found that, although they did not find a difference in lipid status between patients under statin therapy and without any lipid-lowering drug therapy, plasma IL-6 levels were significantly lower in the former than in the latter. These findings suggested that reduction of IL-6 level by aspirin and statins may partially explain their therapeutic effects in patients with myocardial ischemia and infarction.

## Conclusions

The designation of atherosclerosis as a chronic inflammatory or autoimmune process, much like rheumatoid arthritis or pulmonary fibrosis, represents an exciting and logical paradigm shift for cardiologists. Plasma concentrations of IL-6 appear to reflect the intensity of occult plaque inflammation and by inference may determine vulnerability to rupture and restenosis after PCI, a concept supported by the observation that the risk of cardiovascular events can be predicted by the ambient circulating concentration. These observations suggest the advantage of screening for circulating IL-6 concentrations and the use of anti-inflammatory treatment (such as aspirin and statins) for those thought to be at high risk of future AMI, although further studies are required to confirm this premise.

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