Elevated Circulating Levels of Monocyte Chemotactic Protein-1 in Patients With Restenosis After Coronary Angioplasty

To the Editor:

We read with great interest the article by Cipollone et al.1 on the expression of monocyte chemotactic protein-1 (MCP-1) after percutaneous transluminal coronary angioplasty (PTCA). In their study, plasma MCP-1 levels were significantly increased 1 day after PTCA, and patients with restenosis showed significantly higher MCP-1 levels after PTCA than those without restenosis. Several previous studies, including our own, have revealed that PTCA induces inflammatory responses.2 In addition, we reported that MCP-1 is expressed in human atherosclerotic lesions3 and that the interaction between monocytes and endothelial cells induces MCP-1 expression and enhances monocyte migration.4,5 Therefore, like Cipollone et al.,1 we hypothesized that MCP-1 played important roles in restenosis after intervention.

To prove our hypothesis, we examined 40 patients with angina pectoris who underwent elective PTCA for isolated stenotic lesions of the left coronary artery.6 A 5F Amplatz catheter was placed in the coronary sinus, and blood samples were obtained through the catheter before, immediately after, and 4 and 24 hours after angioplasty. Blood samples were also obtained from the femoral artery 24 hours after angioplasty. Plasma levels of MCP-1 and macrophage-colony stimulating factor (M-CSF) were measured by specific enzyme immunoassays. M-CSF levels in the coronary sinus blood showed a significant increase 4 and 24 hours after PTCA (from [mean ± SD] 671 ± 51 to 942 ± 63 and to 1220 ± 79 pg/mL, respectively). In the femoral arterial blood, a slight increase in M-CSF levels was found 24 hours after PTCA; however, the difference was not significant (from 681 ± 135 to 865 ± 156 pg/mL, P = 0.155). On the other hand, MCP-1 levels in the coronary sinus blood did not change significantly 4 and 24 hours after PTCA (from 441 ± 59 to 424 ± 36 and to 457 ± 45 pg/mL, respectively) and also in the femoral artery blood 24 hours after PTCA (from 469 ± 87 to 451 ± 76 pg/mL). We performed follow-up coronary angiography after 6 months; M-CSF levels in the coronary sinus blood 24 hours after PTCA in patients with restenosis were significantly higher than those in patients without restenosis (1470 ± 133 vs 1061 ± 110 pg/mL, P < 0.05). A significant positive correlation was observed between M-CSF levels and loss index (r = 0.59, P < 0.01). M-CSF promotes proliferation, differentiation, and migration of mononuclear phagocytes and has been reported to be associated with the early development of atherosclerosis. Saioto et al.7 assessed the relation between the plasma concentration of M-CSF and the incidence of acute coronary events in patients with coronary artery disease and found that an increased circulating M-CSF concentration reflected atherosclerotic progression and predicted future cardiac events. Mozes et al.8 demonstrated that gene transfer of complementarity-determining region of vascular tissue.

To the Editor:

We read with interest the letter from Ikeda and Shimada about the expression of macrophage-colony stimulating factor (M-CSF) and monocyte chemoattractant protein-1 (MCP-1) after percutaneous transluminal coronary angioplasty (PTCA). In their study, those authors found increased plasma levels of M-CSF, but not of MCP-1, in blood samples collected 4 and 24 hours after PTCA. Moreover, the M-CSF level was significantly higher in the samples collected 24 hours after PTCA in patients who developed restenosis with respect to patients without restenosis.

However, there are several differences between the 2 studies that limit a direct comparison of results. First, Ikeda and Shimada collected blood samples from the coronary sinus from only those patients with stenotic lesion of the left coronary artery. In contrast, in our study, we collected peripheral blood samples from a balanced number of patients with stenoses of the right coronary artery, anterior descending coronary artery, and left circumflex coronary artery. Thus, we cannot exclude temporal differences in the inflammatory response to injury secondary to the different reactivity of different coronary vessels.

More important, the main difference between the 2 studies is that Ikeda and Shimada limited their observation at the first 24 hours after PTCA, whereas we further extended our analysis to 5, 15, and 180 days after revascularization. Notably, our results are in agreement with the recent article by Hokimoto et al.9 which showed significantly higher plasma levels of M-CSF in samples collected 48 hours and 3 months after PTCA in patients who developed restenosis; in contrast, no differences were found in samples collected 24 hours after the procedure. Finally, our data of an increased MCP-1 level after angioplasty are consistent with previous results in rat,6 rabbit,4 and porcine models of vessel injury.

Interestingly, in our study, differences in plasma MCP-1 levels between patients who would versus those who would not develop restenosis were more significant in the samples collected 15 and 180 days after PTCA with respect to the samples collected as early as 24 hours after the procedure. Again, based on multivariate regression analysis adjusted for potential confounders (class of angina, cigarette smoking, hypercholesterolemia, diabetes, hypertension, age, comitant therapy, and variables of procedural methods), MCP-1 plasma levels at 15 days after PTCA proved to be the only significant independent predictor of restenosis. Thus, both our data1 and those of Hokimoto et al.9 point out that, in contrast to the previous focus on patients with restenosis after coronary angioplasty. Arterioscler Thromb Vasc Biol. 2001;21:327–334.


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the early expression of MCP-1 after angioplasty in animals with normal vasculature, induction of MCP-1 may be more sustained in human arteries with underlying atherosclerosis. This suggests that induction of MCP-1 after vascular injury in human occurs mainly in infiltrating macrophages rather than in vascular smooth muscle cells. In this light, the observation of Ikeda and Shimada about an early increase in M-CSF levels after PTCA well supports this hypothesis, because M-CSF may promote migration and proliferation of phagocytes. Thus, the response to injury after PTCA in human may involve 2 different phases: an early phase, including upregulation of M-CSF, thus promoting macrophage migration, and a late phase, including a more sustained induction of MCP-1 in infiltrating macrophages. Such prolonged MCP-1 production could have autocrine/paracrine effects on macrophages and smooth muscle cells at the site of the lesions and would be reflected in the apparent activation of macrophages observed in our study in patients with increased levels of MCP-1.

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