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ORIGINAL ARTICLE

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Effects of ramipril on serum monocyte chemoattractant protein 1, interleukin-18, and interleukin-10 in elderly patients with acute coronary syndrome

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Abstract Acute coronary syndrome (ACS) is a clinical syndrome caused by acute myocardial ischemia and a severe stage of coronary atherosclerosis heart disease. The aim of this study was to clarify whether ramipril was a therapeutic agent against monocyte chemoattractant protein 1 (MCP-1), interleukin 18 (IL-18), and interleukin 10 (IL-10) in elderly patients with ACS. A total of 190 subjects including 72 elderly patients with ACS (78.1% male, mean age 67.12 ± 5.06 years), 60 elderly patients with stable angina pectoris (76.9% male, mean age 68.00 ± 4.52 years), and 58 healthy volunteers (77.8% male, mean age 65.96 ± 4.18 years) were recruited into the study. Serum MCP-1, IL-10, and IL-18 were determined in 132 elderly patients by enzyme-linked immunosorbent assay (ELISA) before and after treatment with low doses of ramipril (2.5–5 mg/day), and were determined in 58 healthy volunteers. The levels of serum MCP-1 and IL-18 were much higher in elderly patients with ACS than those in elderly patients with SAP and healthy volunteers. After treating with ramipril, the levels of MCP-1 and IL-18 were decreased in elderly patients with ACS. Moreover, ramipril significantly increased serum IL-10 in elderly patients with ACS. Ramipril plays an important role in elderly patients with ACS. With decreasing MCP-1 and IL-18, it can ameliorate cytokine-associated cardiac damage. This study may provide a new recognition of angiotensin-converting enzyme inhibitor for the treatment of ACS.

Key words Acute coronary syndrome · Ramipril · Monocyte chemoattractant protein 1 · Interleukin-10 · Interleukin-18

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Introduction

Acute coronary syndrome (ACS) is the main cause of mortality worldwide. It is a clinical syndrome caused by acute myocardial ischemia and a severe stage of coronary atherosclerosis heart disease. Current research in cardiovascular pathophysiology has detected that the disruption of unstable atheromatous plaques, as well as subsequent thrombus in the coronary arteries, are the main causes of ACS. An inflammatory reaction, which is modified by monocytes/macrophages, can cause plaque instability and can commence blood clotting.[1–3] Thus, an inflammatory reaction is considered to play a pivotal role in the pathogenesis and/or development of ACS.

A considerable body of evidence supports the notion that various mediators such as adhesion molecules, cytokines, and chemokines are involved in the initiation and progression of atherosclerotic lesions. Monocyte chemoattractant protein 1 (MCP-1) is the most important chemokine that regulates migration and infiltration of monocytes/macrophages. The proinflammatory cytokine interleukin-18 (IL-18) has been suggested to play a role in atherogenesis and atheromatous plaque rupture leading to ACS. Conversely, the anti-inflammatory cytokine interleukin-10 (IL-10) seems to have an atheroprotective role.[4–7] Moreover, the IL-18/IL-10 ratio is an independent predictor of adverse in-hospital events in patients with ACS.[8]

Experimental research on the effects of angiotensin-converting enzyme inhibitors (ACEIs) on atherosclerosis revealed that ramipril was able to ameliorate endothelial dysfunction, inhibit vascular remodeling mediated by angiotensin II, and suppress excessive secretion of inflammatory mediator.[9,10] The research on the effects of ramipril on atherosclerosis patients demonstrated that ramipril could decrease cardiac events and the mortality of these patients. The aims of the present study were to determine the circulating levels of MCP-1, IL-18, and IL-10 in elderly patients with ACS or stable angina pectoris (SAP), and clarify whether ramipril was a therapeutic agent against MCP-1, IL-18, and IL-10 in elderly patients with ACS.

Patients and methods

Subjects

This investigation was based on a large-scale epidemiological study in China with cross-sectional parts. From December 2006 to August 2007, the study covered 190 subjects including 72 elderly patients with ACS and 60 elderly patients with SAP who were registered as outpatients in the Department of Geriatrics of Qi-Lu Hospital of Shandong University, and 58 healthy volunteers who were examined in the Center of Health Examination of Qi-Lu Hospital of Shandong University. Moreover, 72 elderly patients with ACS and 60 elderly patients with SAP had been diagnosed with coronary arteriography, according to the 1999 diagnostic guidelines of the World Health Organization (WHO). Fifty-eight healthy volunteers were recruited for this study. Prior to commencement of the trial, the selection criteria were generated from the records of participating health care providers. Inclusion criteria were general good health and mobility, and agreement to conform to the trial guidelines or provide notification of noncompliance. They had no medical history of atherogenic diseases, cardiovascular diseases, renal insufficiency, or other diseases requiring medical treatment. A "healthy subject" was defined by the following criteria: blood pressure <140/90 mmHg, fasting blood glucose <110 mg/dl, total cholesterol <240 mg/dl, triglycerides <150 mg/dl, uric acid <7.5 mg/dl, body mass index <25, and no history of smoking. Exclusion criteria were any recent history of acute or chronic debilitating illness, any record of hypertension (HP), diabetes mellitus (DM), coronary heart disease (CHD) and stroke, peripheral vascular disease, or hyperlipemia, according to the 1999 diagnostic guidelines of the WHO. All subjects gave their informed consent. All subjects and the clinical data were collected cross-sectionally from medical records. The study protocol was approved by Qi-Lu Hospital of Shandong University Ethics Board. Our hospital was the certified unit for these patients being enrolled in the study. There were no dropouts.

Medical history and examinations

All participants were administered a standardized questionnaire that provided information about their occupation, medical history, drug use, smoking, personal habits, and their family medical histories. The weight and height of subjects were measured while they were wearing light clothes without shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters.

Treatment protocols

Thirty-six elderly patients with ACS were given routine pharmacotherapy without ramipril (group 1, ACS1). The other 36 elderly patients with ACS were given routine pharmacotherapy with ramipril (group 2, ACS2). Thirty elderly patients with SAP were given routine pharmacotherapy without ramipril (group 3, SAP1). The other 30 elderly patients with SAP were given routine pharmacotherapy with ramipril (group 4, SAP2). The patients were not receiving treatment with ACEIs or angiotensin receptor blockers before being enrolled in the study, and were randomized to treatment according to a random number method. Routine pharmacotherapy includes antiplatelet (aspirin, ticlopidine, or clopidogrel), calcium channel blocker, β-blocker, and nitrates. Ramipril (Sanofi-Aventis, Paris, France) was given by oral dose of 2.5–5 mg daily. The 18 elderly patients with ACS were given routine pharmacotherapy with ramipril (2.5 mg). The other 18 elderly patients with ACS were given routine pharmacotherapy with ramipril (5 mg). The 17 elderly patients with SAP were given routine pharmacotherapy with ramipril (2.5 mg). The 16 elderly patients with SAP were given routine pharmacotherapy with ramipril (5 mg). We gave 5 mg ramipril to the ACS patients with hypertension (BP ≥ 140/90 mmHg) and SAP patients with hypertension. An oral dose of ramipril was maintained for 56 days.

Blood collection

Blood samples of all subjects were taken before treatment. Moreover, other blood samples of the elderly patients with ACS and SAP were taken after treatment with ramipril for 56 days. Plasma was separated and stored at –80°C until analysis.

Measurements of MCP-1, IL-18, and IL-10

The levels of MCP-1, IL-18, and IL-10 were determined using specific enzyme-linked immunosorbent assay (ELISA) kits (Biosource, Camarillo, CA, USA). The cytokine levels were evaluated in ACS patients at admission for ACS, and after hospitalization for 56 days.

Statistical methods

All data were analyzed by SPSS 10.0 for Windows. Continuous variables were given as the mean ± SD. Comparisons between means were evaluated by unpaired *t*-test or one-way analysis of variance for continuous variables. Values of $P < 0.05$ were considered statistically significant. The results were analyzed in a multivariable analysis.

Results

Baseline characteristics of healthy subjects and patients

Table 1 lists the baseline characteristics of healthy subjects, and patients with ACS and SAP. The patients with hypertension in the four groups were 20, 18, 15, and 16, respectively, of groups ACS1, ACS2, SAP1, and SAP2. Age, BMI,

Table 1. Baseline characteristics of healthy subjects and patients

Risk factors	Healthy subjects (n = 58)	Patients with SAP (n = 60)	Patients with ACS (n = 72)
Age (years)	65.96 ± 4.18	67.51 ± 4.89	67.12 ± 5.06
Male	14 (77.8%)	20 (76.9%)	25 (78.1%)
Female	4 (22.2%)	6 (23.1%)	7 (21.9%)
BMI, kg/m^2	24.65 ± 4.21	25.49 ± 4.45	25.77 ± 6.24
SBP, mmHg	126.41 ± 9.24	134.65 ± 8.68**	139.29 ± 8.66**$^{\#}$
DBP, mmHg	74.25 ± 8.74	83.13 ± 8.12**	85.46 ± 8.56**
MAP, mmHg	91.64 ± 9.13	100.30 ± 8.45**	103.40 ± 8.62**
PP, mmHg	52.16 ± 8.72	51.52 ± 9.26	53.83 ± 8.24
HR, beats/min	70.78 ± 10.45	71.43 ± 11.96	70.96 ± 11.25
HP patients, n	0	31	38
MCP-1, μg/l	71.54 ± 48.89	138.91 ± 41.03**	209.02 ± 84.98**$^{\#\#}$
IL-18, ng/l	202.32 ± 113.63	379.39 ± 118.72**	519.30 ± 131.09**$^{\#\#}$
IL-10, ng/l	30.47 ± 7.62	20.17 ± 4.13**	16.33 ± 4.87**$^{\#\#}$
IL-18/IL-10	6.64 ± 1.02	18.81 ± 2.14**	31.98 ± 5.24**$^{\#\#}$

SAP, stable angina pectoris; ACS, acute coronary syndrome; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; HR, heart rate; HP, hypertension; MCP-1, monocyte chemoattractant protein 1; IL-18, interleukin 18; IL-10, interleukin 10

* $P < 0.05$, ** $P < 0.01$, healthy subjects vs others; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, patients with ACS vs patients with SAP

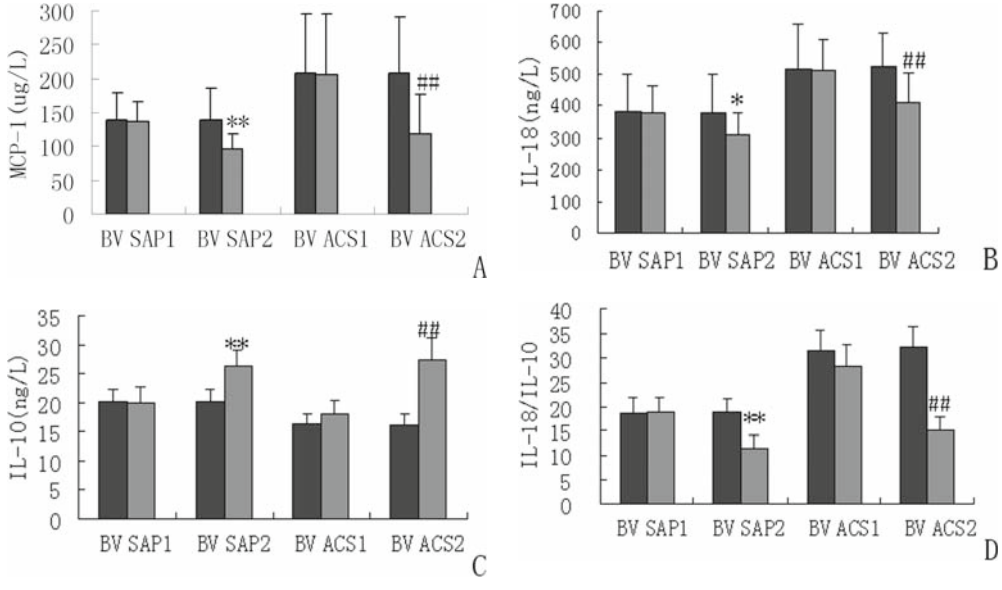

Fig. 1A–D. Effects of ramipril on monocyte chemoattractant protein 1 (*MCP-1*), interleukin-18 (*IL-18*), interleukin-10 (*IL-10*), and IL-18/IL-10 of patients with acute coronary syndrome (*ACS*) and stable angina pectoris (*SAP*). **A** Effects of ramipril on MCP-1 of patients with ACS and SAP. **B** Effects of ramipril on IL-18 of patients with ACS and SAP. **C** Effects of ramipril on IL-10 of patients with ACS and SAP. **D** Effects of ramipril on IL-18/IL-10 of patients with ACS and SAP. *$P < 0.05$, **$P < 0.01$, SAP2 vs SAP1; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, ACS2 vs ACS1. *BV*, baseline values. *SAP1*: patients with SAP were given routine pharmacotherapy without ramipril; *SAP2*: patients with SAP were given routine pharmacotherapy with ramipril; *ACS1*: patients with ACS were given routine pharmacotherapy without ramipril; *ACS2*: patients with ACS were given routine pharmacotherapy with ramipril

and heart rate were not significantly different between healthy subjects and patients with ACS and SAP ($P > 0.05$). But SBP, DBP, and MAP of patients was higher than those of healthy subjects ($P < 0.01$). Moreover, the levels of MAP-1, IL-18, and the ratio of IL-18 to IL-10 in the patients with ACS and SAP increased as compared to healthy subjects ($P < 0.01$). The level of IL-10 in the patients with ACS and SAP decreased as compared to healthy subjects ($P < 0.01$).

Effects of ramipril on MCP-1, IL-18, IL-10, and IL-18/IL-10 in patients with ACS and SAP

Figure 1 shows the comparisons of MCP-1, IL-18, IL-10, and the ratio of IL-18 to IL-10 among SAP1, SAP2, ACS1, and ACS2 in the elderly patients. In the elderly patients with ACS and SAP, ramipril significantly reduced MCP-1, IL-18, and the ratio of IL-18 to IL-10, and increased IL-10 ($P < 0.05$ or $P < 0.01$). The results were corrected for blood

pressure values. The baseline values of cytokines are also shown in Fig. 1. The baseline values of MCP-1, IL-18, and the ratio of IL-18 to IL-10 in the elderly patients with ACS were higher than those of the elderly patients with SAP ($P < 0.01$). The baseline value of IL-10 in the elderly patients with ACS was lower than that of the elderly patients with SAP ($P < 0.01$).

Discussion

The research on the etiology of atherosclerosis has revealed that the damage of vascular endocrines due to the long-term action of hyperlipemia or other harmful factors results in monocytes adhering and migrating to the inferior vascular retina.[11] Then the monocytes are transformed into activated histiocytes, which secrete an amount of cytokines, growth factors, some forms of enzymes, and oxygen-derived free radicals. These substances cause chronic inflammation of the vascular retina, resulting in arterio-atheromatous plaques.[2,12–15] The stability of atheromatous plaques determines the progress and severity of atherosclerosis. Proinflammatory cytokines have the potential to induce excessive extracellular matrix degradation and cell death, and thus can play an important part in plaque instability and vulnerability toward rupture.[3,16] They may also be responsible for the activation of other cells such as neutrophils, macrophages, or mast cells. However, the inflammatory response is known to be balanced by anti-inflammatory cytokines.[17]

It was reported that circulating MCP-1 levels may be a useful marker for determining the clinical state, stable or not, of coronary artery disease. Under some inflammatory conditions, MCP-1 is expressed by many kinds of cells and modifies the movement of monocytes into an inflammatory lesion.[4,18,19] A previous clinical study showed significant expression of IL-18 in human carotid atherosclerotic plaques. Moreover, the plasma IL-18 level was associated with the extent of coronary artery disease in unstable angina patients.[20] Indeed, human atheroma in situ expressed IL-18 and its receptor compared with nondiseased arterial tissue. Interleukin-18 on the other hand may aggravate the proinflammatory response through interferon-γ production, increased expression of cell adhesion molecules, and proinflammatory mediators, particularly tumor necrosis factor α and IL-1, as well as promote the development of T-helper-1 (Th1) responses. Interleukin-10 has anti-inflammatory properties including inhibition of the proinflammatory transcription factor nuclear factor kappa B, leading to suppressed cytokine production, reduced matrix metalloproteinase production, reduced tissue factor expression, and promotion of the phenotypic switch of lymphocytes to Th2 phenotype. Interleukin-10 expression has been demonstrated in advanced human atherosclerotic plaques with high levels of expression associated with significantly decreased cell death and inducible nitric oxide synthase expression, again suggesting a protective antiatherogenic role.[7,8,21–25] Therefore, the IL-18/IL-10 ratio remained a significant predictor of prognosis in the patients with ACS and SAP.

This was the first study on the effect of ramipril on MCP-1, IL-18, IL-10, and the ratio of IL-18 to IL-10 of Chinese patients with SAP and ACS. In this study, we demonstrated that the levels of MAP-1, IL-18, and the ratio of IL-18 to IL-10 provided important information about the severity of myocardial damage in patients with acute coronary syndrome. This study also showed that ramipril significantly improved MAP-1, IL-18, IL-10, and the ratio of IL-18 to IL-10 in the patients with ACS and SAP. The results of this study are consistent with previous studies.

Ramipril is an ACEI widely used clinically because of its properties of vasodilatation and angiotensin-converting enzyme inhibition. Some researchers reported that ACEIs suppressed IL-1 and tumor necrosis factor synthesis at a post-transcriptional level and might therefore influence cytokine-mediated cell growth.[26] Furthermore, high-dose ramipril (10 mg) markedly suppressed plasma levels of interleukin-6, tumor necrosis factor α, E-selectin, von Willebrand factor, and soluble vascular cell adhesion molecule in patients who had undergone coronary artery bypass graft surgery.[27] Moreover, it was reported that ramipril had anti-atherogenic effects and reduced myocardial infarction, revascularization, and cardiovascular death.[28–30] Our study was based on relatively old outpatients; it was not fully generalizable to a large population. Nonetheless, our results clearly showed that ramipril has an anti-inflammatory effect in the patients with ACS and SAP.

In conclusion, it was shown that ramipril had an anti-inflammatory effect via reducing MCP-1, IL-18, and the ratio of IL-18 to IL10. This study provides new evidence for the therapeutic potential of the patients with ACS and SAP, and ramipril may also be helpful in preventing and/or delaying the onset of ACS.

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