Plasma Resistin Associated With Myocardium Injury in Patients With Acute Coronary Syndrome

Songyun Chu, MD, PhD; Wenhui Ding, MD; Kang Li, MD*; Yongzheng Pang, MD**; Chaoshu Tang, MD**

Background Resistin, a novel adipocytokine, has been suggested as representing a link between metabolic signals, inflammation and atherosclerosis. The aim of the present study was to investigate the alteration in level of plasma resistin in patients with acute coronary syndrome (ACS) to uncover the role of resistin.

Methods and Results The 39 patients with ACS and 26 age-matched healthy subjects in this cross-sectional study were investigated. Plasma resistin levels were measured using radioimmunoassay. Plasma resistin levels were significantly increased in patients with ACS at 24 h after symptoms onset and remained at a high level for 1 week, and were significantly higher in patients with acute myocardial infarction than in those with unstable angina. In addition, plasma resistin level was correlated positively with peak plasma creatine kinase (CK), the MB isomform of CK and troponin I, and was correlated negatively with left ventricular ejection fraction. No correlation was found between plasma resistin level with level of metabolic parameters or inflammatory markers.

Conclusions Plasma resistin levels in patients with ACS are elevated significantly within the first week after symptoms onset. Increased resistin levels may be a marker of myocardial ischemia and injury in ACS. (Circ J 2008; 72: 1249–1253)

Key Words: Acute coronary syndrome; Resistin

Resistin was first found in 2001 by Steppan and co-workers as a novel peptide synthesized and secreted from murine adipocytes. Circulating resistin level was increased in diet-induced and genetic forms of obesity but could be decreased using rosiglitazone therapy. Administration of anti-resistin antibodies improved blood glucose control and insulin action in mice with diet-induced obesity. Resistin is thought to be an adipokine associated with insulin resistance.

Subsequent studies of its role in human obesity and insulin resistance, however, showed conflicting results. Contrary to the distribution in rodents, in humans, the main sources of resistin seem to be monocytes and macrophages. Resistin level was positively associated with levels of inflammatory markers, including soluble tumor necrosis factor-α receptor-2, interleukin-6 and lipoprotein-associated phospholipase A2. Moreover, resistin up-regulates the expression of adhesion molecules in cultured endothelial cells and promotes the proliferation of smooth muscle cells, which suggests that it may be an inflammatory marker. Metabolic abnormalities, insulin resistance and inflammatory states are thought to be important risk factors of atherosclerosis, and resistin may represent a link between metabolic signals, inflammation and atherosclerosis. Indeed, resistin levels were also correlated with high-sensitivity C-reactive protein (hs-CRP) level, insulin level and homeostasis model assessment of insulin resistance. In a study adjusting for age, sex and established risk factors, the concentration of resistin was also associated with increasing coronary artery calcification (CAC); resistin levels further predicted CAC in subjects with metabolic syndrome. Also, Ohmori reported resistin levels increased in 157 patients with coronary artery disease, even after adjusting for age and gender. Resistin levels were found to increase stepwise, depending on number of stenotic vessels and/or segments.

Acute coronary syndrome (ACS) is an acute cardiac event resulting from rupture of vulnerable atherosclerotic plaque in the coronary artery. In ACS, a large amount of inflammatory cells and cytokines are released to the circulation and accelerate the development of atherosclerosis, which results from chronic metabolic abnormality. In the present study, we observed plasma resistin level in patients with ACS during the first week after symptom onset, analyzed the relation of plasma resistin level and clinical index, and investigated the potential significance of resistin in ACS pathogenesis.

Method

Subjects

The study was reviewed and approved by the Ethics Committee of Peking University First Hospital, and informed consent was obtained from each subject before the study began. A total of 39 patients with ACS [28 men; mean age 64 years; 20 with acute myocardial infarction (AMI) and 19 unstable angina pectoris (UAP)] who were admitted to our hospital were recruited from October 2002 through June 2003. The patients fulfilled the World Health Organi-
Table 1  Clinical Characteristics of Patients With ACS Including UAP and AMI

<table>
<thead>
<tr>
<th></th>
<th>UAP (n=19)</th>
<th>AMI (n=20)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>14/5</td>
<td>14/6</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>66.47±9.21</td>
<td>62.37±15.49</td>
<td>0.348</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.96±2.21</td>
<td>24.26±3.13</td>
<td>0.081</td>
</tr>
<tr>
<td>BF (%)</td>
<td>34.84±6.56</td>
<td>28.40±7.24</td>
<td>0.010*</td>
</tr>
<tr>
<td>TG (nmol/L)</td>
<td>2.05±2.19</td>
<td>1.29±0.58</td>
<td>0.153</td>
</tr>
<tr>
<td>CHL (nmol/L)</td>
<td>4.36±0.94</td>
<td>4.26±0.89</td>
<td>0.750</td>
</tr>
<tr>
<td>LDL (nmol/L)</td>
<td>2.61±0.60</td>
<td>2.68±0.73</td>
<td>0.765</td>
</tr>
<tr>
<td>HDL (nmol/L)</td>
<td>1.08±0.26</td>
<td>0.99±0.26</td>
<td>0.317</td>
</tr>
<tr>
<td>UA (U/lmol/L)</td>
<td>312±96</td>
<td>311±73</td>
<td>0.971</td>
</tr>
<tr>
<td>Cr (U/ml)</td>
<td>91±22</td>
<td>89±15</td>
<td>0.759</td>
</tr>
<tr>
<td>WBC (x10⁹/L)</td>
<td>7.64±1.60</td>
<td>7.78±3.58</td>
<td>0.885</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>13.46±2.99</td>
<td>21.67±22.08</td>
<td>0.219</td>
</tr>
<tr>
<td>CKmax (u/L)</td>
<td>59.50±2.53</td>
<td>135.53±1.640.58</td>
<td>0.002*</td>
</tr>
<tr>
<td>CK-MBmax (u/L)</td>
<td>1.26±1.79</td>
<td>134.44±146.52</td>
<td>0.001*</td>
</tr>
<tr>
<td>TnImax (ng/ml)</td>
<td>0.16±0.46</td>
<td>42.47±45.10</td>
<td>0.001*</td>
</tr>
<tr>
<td>FBG (mmol/L)</td>
<td>5.99±2.91</td>
<td>6.37±2.41</td>
<td>0.672</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>74.18±9.21</td>
<td>53.10±49.91</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>137.24±19.44</td>
<td>122.68±22.10</td>
<td>0.045*</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77.88±22.21</td>
<td>72.32±48.88</td>
<td>0.379</td>
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<tr>
<td>FIB (g/L)</td>
<td>3.50±0.94</td>
<td>3.89±0.96</td>
<td>0.296</td>
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</table>

ACS, acute coronary syndrome; UAP, unstable angina pectoris; AMI, acute myocardial infarction; BMI, body mass index; BF, body fat; TG, triglyceride; CHL, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; UA, uric acid; Cr, creatinine; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; CK, peak value of creatine kinase; CK-MB, peak value of creatine kinase-MB; TnI, peak value of troponin I; FBG, fasting blood glucose; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; FIB, fibrinogen.

P<0.01; #compared with patients with UAP, P<0.01. ACS, acute coronary syndrome; UAP, unstable angina pectoris; AMI, acute myocardial infarction.

Fig1. Comparison of plasma resistin levels between control subjects and patients with ACS, UAP or AMI. *Compared with control, P<0.01; #compared with patients with UAP, P<0.01. ACS, acute coronary syndrome; UAP, unstable angina pectoris; AMI, acute myocardial infarction.

Radioimmunoassay for Resistin
Plasma resistin level was determined using ELISA (Phoenix Pharmaceuticals, Belmont, CA, USA). The reactivity with human resistin was 100%. No cross-reactivity was found with human insulin, leptin, AGRP, Ghrelin and Orexin A, MCH or neuropeptide Y. The intra- and inter-assay coefficients of variation for blood samples were both <10%. All measurements followed the manufacturer’s instructions.

Statistical Analysis
Results are expressed as mean±SD, unless otherwise specified. The data were analyzed using SPSS 11.5 (SPSS Institute, Chicago, IL, USA). Data were tested for normality of distribution by the Shapiro–Wilk test. Continuous variables between 2 groups were compared using the Student’s t-test for normally distributed data and Wilcoxon rank-sum test for data not normally distributed. Comparisons across more than 2 groups involved one-way ANOVA followed by the Student–Newman–Keuls test. Relations between variables of interest were assessed using Pearson correlation coefficient or Spearman rank order correlation for variables not normally distributed. Differences were considered statistically significant with P<0.05.

Results
Subjects’ Profiles
The characteristics of the subjects are in Table 1. Patients

essay. White blood cell (WBC) count and erythrocyte sedimentation rate (ESR) were also determined. Patients underwent physical examination for height, weight, body mass index (BMI, weight [kg]/height² [m²]) and blood pressure (repeated 3 times, and systolic and diastolic pressure recorded). Weight and height were measured with subjects in light clothing.

Left ventricular ejection fraction (LVEF) on echocardiography was recorded at 5±2 days after admission.

Records of cardiovascular events at 4 years since the onset of ACS were collected to investigate prognosis of patients. Cardiovascular events identified as cardiovascular death, myocardial infarction (MI), stroke, re-hospitalization caused by cardiovascular reason or need for emergent/elective PCI.

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with UAP and AMI did not differ in age, sex, BMI or lipid profile. However, the plasma level of cardiac injury biomarkers (CK<sub>max</sub>, CK-MB<sub>max</sub> and TnI<sub>max</sub>) was significantly higher with AMI than with UAP, whereas LVEF and systolic blood pressure were lower with AMI. Of the 39 patients with ACS, 14 had type 2 diabetes and 20 had essential hypertension. Seven of 20 patients with AMI performed reperfusion therapy with an average time of 3.71±1.50 h since symptoms occurred. Other patients with AMI did not receive emergent reperfusion therapy because their symptoms had resolved or late admission (present at least 12 h after symptoms onset). All the patients with UAP and the patients with AMI who did not received reperfusion therapy underwent their elective PCI in 7–14 days after the acute coronary event. Blood-flow of Thrombolysis In Myocardial Infarction (TIMI) III grade was observed in all the patients who received PCI. Thrombolysis therapy in patients with AMI was identified successfully based on the clinical index. These patients are thought to have a TIMI III grade blood flow as well. Collateral networks were observed in 7 patients with ACS in coronary angiography. Nine of 20 patients with AMI had experienced angina pectoris before the AMI event occurred, and thought to show ischemic preconditioning.

Changes in Plasma Resistin Levels

The plasma resistin level was markedly increased, to 2.8-fold of the control level at 24 h, in patients with ACS (11.69±5.86 μg/L) as compared with controls (4.17±2.24 μg/L) (p<0.01) and remained at a high level for 1 week after symptom onset (10.29±5.33 μg/L at day 7, p>0.05) (Fig 1). Plasma resistin levels in patients with AMI were higher than that in patients with UAP; it was 105% higher at 24 h (15.12±5.06 vs 7.34±3.44 μg/L; p<0.01) and 138% higher at day 7 (14.13±3.75 vs 5.93±2.93, p<0.01) (Fig 1).

Analyses of Plasma Resistin and Clinical Variables

Univariate analysis revealed no significant correlation between level of plasma resistin and metabolic parameters (ie, body weight, BMI, plasma glucose and lipid profile) or inflammatory markers (WBC count, ESR and hs-CRP level). However, from 24 h to day 7 after symptom onset, plasma resistin level was correlated with CK<sub>max</sub> (only at 24 h), CK-MB<sub>max</sub> and TnI<sub>max</sub> values and inversely correlated with LVEF (Figs 2–5). No difference of resistin levels was observed whether patients with AMI received emergent reperfusion, had good collateral networks or ischemic preconditioning.
Discussion

Resistin was first found by Steppan and coworkers as a novel active peptide secreted by adipocytes. It acts on adipose tissue, liver and skeletal muscle, causing blood glucose elevation, obesity and insulin resistance. The mechanism involves insulin resistance and transcription of metabolic enzymes.

In contrast to its production in rodents, in humans resistin is produced primarily in inflammatory cells, especially macrophages, rather than adipocytes. Recent studies have shown that resistin upregulates inflammatory and adhesion molecules in endothelial cells. Therefore, it is considered an inflammatory marker of atherosclerosis in humans and may represent a novel link between metabolic signals, inflammation and atherosclerosis.

Subjects with preclinical atherosclerosis, with a family history of premature coronary artery disease, showed increased plasma resistin level. Those with premature coronary artery disease showed increased serum resistin level. Resistin is also associated with CAC, a measure of coronary atherosclerosis, even in patients without established risk factors, metabolic syndrome or increased CRP level.

It was proposed that serum resistin might be a biological marker for coronary artery disease and restenosis after PCI in type 2 diabetes mellitus patients. Circulating resistin level is further increased during an acute event in patients with UAP, ST-segment-elevation myocardial infarction (STEMI) or non-STEMI as compared with patients with stable angina. Thus, resistin level intends to be increasingly elevated with atherosclerosis progression. In the present study, plasma resistin level increased markedly to 2.8-fold the control level at 24 h in patients with ACS and remained at a high level for 1 week after symptoms onset. Plasma resistin level in patients with AMI was higher than that in patients with UAP. These results were consistent with prior reports.

We also found that plasma resistin level was correlated with levels of cardiac injury biomarkers and inversely correlated with LVEF, thus suggesting that resistin level increased with severity of ischemic injury to the myocardium. Furthermore, plasma resistin might represent a marker of myocardium injury parallel the severity of ACS.

Results of circulating resistin levels and their pathophysiologic significance in a population with obesity and insulin resistance are conflicting in different groups. One explanation might be the different origin of resistin between different species. In the present study, we found no significant correlation between levels of plasma resistin and metabolic parameters such as body weight, BMI, blood glucose and lipid profile. Further research is warranted to clarify the effects of resistin in human metabolic syndrome. Also, plasma resistin level was not correlated with inflammatory index (WBC count, ESR and hs-CRP level). These results differed from those of Reilly and Yaturu, who reported plasma resistin level correlated positively with multiple inflammatory markers in patients with coronary heart disease (CHD) or with family history of premature CHD.

The difference in results may stem from the different stages of CHD investigated. Prior studies involved largely patients with chronic but stable disease, in whom metabolic dysfunction and the chronic inflammatory state have important roles in the process of atherosclerosis. In the present study, however, our patients were experiencing ACS. Acute myocardial ischemia and injury could be more prominent stimuli elevating plasma resistin level and may be superior to metabolic and inflammatory factors, thus concealing the influence of the latter.

ACS results from a rupture of vulnerable plaques in coronary atherosclerosis and leads to severe coronary ischemia injury. In the present study, plasma resistin level was correlated positively with severity of myocardial injury and negatively with LVEF, which represent cardiac function state. Plasma resistin level in patients with AMI was higher than that in patients with UAP. All these data indicate that cardiac ischemia injury was an important factor inducing synthesis and release of resistin. Resistin is concentrated in atherosclerotic plaques and its expression is increased with the development of atherosclerosis. Acute rupture of atherosclerotic plaques could be an important origin of circulating resistin. Myocardial injury induces inflammation reactions as well. Macrophages and multiple active factors in ruptured plaques are released into the circulation in ACS. Activated inflammatory cells release multiple cytokines, and inflammatory cytokines and endotoxemia lead to a cascade of inflammation and stimulate macrophages to secrete resistin, which could be another pathway to increasing resistin levels in ACS. Furthermore, increasing levels of glucocorticoid in a stressed state such as ACS could stimulate elevated levels of plasma resistin as well.

The increasing level of plasma resistin could influence the cardiovascular system via several mechanisms. Resistin could induce insulin resistance and lead to metabolic disorders of glucose, lipid and free fatty acid, which further accelerate metabolic dysfunction in ACS. Resistin could activate endothelial cells and promote expression of inflammatory cytokines, chemokines and adhesion cytokines, thus accelerating endothelial dysfunction. It could also suppress the expression of eNOS and induce superoxide anion production in endothelial cells, which weaken the endothelial-dependent vascular relaxation and impair normal contraction-relaxation regulation in coronary vessels. Furthermore, it could stimulate migration and proliferation of smooth muscle cells to accelerate the progression of coronary atherosclerosis. Thus, increasing levels of resistin in patients with ACS may not favor rehabilitation from an acute coronary event through several mechanisms. Indeed, in a study of patients hospitalized for heart failure, in which 27% patients were ischemic cardiomyopathy, serum resistin was related to the severity of heart failure and a high risk for adverse cardiac events.

Recently revascularization by PCI or thrombolysis have become the main therapy in ACS. However, ischemia reperfusion injury is an emerging problem that impairs myocardium and cardiac function. Therefore we could analyze whether ischemia reperfusion further influences resistin levels in patients with ACS. In contrast, good collateral networks or ischemic preconditioning could reduce ischemia reperfusion injury and be associated with a better prognosis. We also observed a difference of resistin levels between patients with or without preconditioning and collaterals. No difference of resistin level was observed though whether patients with AMI received emergent reperfusion, had good collateral networks or had ischemic preconditioning. At the end of a 4-year follow-up, no correlation was found between resistin levels and new onset cardiovascular events (cardiovascular death, MI, stroke, re-hospitalization caused by cardiovascular reason or need for emergent/elective PCI). However, the possible relationship between resistin levels and these variables could not be excluded. Our sample for the observational study is small. A relatively low rate
of emergent revascularization and cardiovascular events in follow-up might mask the underlying relationship. Large scale and long-term observation are needed.

Conclusions

Plasma resistin levels in patients with ACS are elevated significantly within the first week after symptom onset. Plasma levels of resistin in patients with an acute myocardial event (AMI) were much higher than those in patients with less acute disease (UAP). Resistin level was correlated positively with levels of plasma myocardium injury markers and negatively with LVEF, but not parameters of metabolism or inflammation. Plasma resistin level in patients with ACS may serve as a marker of myocardial ischemia and injury.

References