Circulating CD14⁺CD16⁺ Monocyte Subsets as Biomarkers of the Severity of Coronary Artery Disease in Patients With Stable Angina Pectoris

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Background: Circulating monocytes can be divided into 2 subsets typically identified by the expression of CD14 and CD16. Although previous studies have shown that circulating monocytes contribute to the progression of coronary atherosclerotic lesions, the relationship between the severity of coronary artery disease (CAD) and the 2 distinct monocyte subsets has not previously been evaluated. We investigated the relationship between the monocyte subsets and the severity of CAD assessed by coronary angiography (CAG) in patients with stable angina pectoris (SAP).

Methods and Results: We enrolled 125 patients who underwent diagnostic CAG. Patients were divided into 3 groups: those without CAD, those with single-vessel disease (SVD), and those with multiple-vessel disease (MVD). In addition, the severity of CAD was evaluated by Gensini score. The 2 monocyte subsets (CD14⁺CD16⁻ and CD14⁺CD16⁺) were measured by flow cytometry. Circulating CD14⁺CD16⁺ monocytes were more frequently observed in patients with MVD than in those with SVD or without CAD. The proportion of CD14⁺CD16⁺ monocytes positively correlated with Gensini score (r=0.618, P<0.001). Multivariate logistic regression analysis revealed that the proportion of CD14⁺CD16⁺ monocytes was an independent contributor to MVD (odds ratio: 1.475; 95% confidence interval: 1.273–1.708, P<0.001).

Conclusions: A preferential increase in peripheral CD14⁺CD16⁺ monocytes may be closely related to the severity of CAD in patients with SAP. (Circ J 2012; 76: 2412–2418)

Key Words: Coronary angiography; Coronary artery disease; Monocytes; Soluble CD40 ligand; Stable angina pectoris

Recruitment of monocytes into the vessel wall is an important step for the onset and progression of atherosclerosis. Indeed, a reduction in circulating monocytes suppresses atherosclerotic changes in animal models, and blood monocyte counts are an independent risk factor for coronary artery disease (CAD) in humans. Circulating monocytes in humans fall into subsets typically identified by the expressions of CD14 and CD16. Differential expression of CD14 and CD16 allows monocytes to be divided into 2 subsets: CD14⁺CD16⁻ monocytes expressing C-C motif chemokine receptor 2 (CCR2) and CD14⁺CD16⁺ monocytes expressing C-X3-C motif chemokine receptor 1 (CX3CR1). The discovery that monocytes comprise distinct subsets in humans suggests a specialization of function, and has stimulated interest in approaches that discriminate between “harmful” and “beneficial” subsets. Functionally, CD14⁺CD16⁻ monocytes are professional phagocytes that ingest native low-density lipoprotein (LDL), and generate reactive oxygen species (ROS). In contrast, CD14⁺CD16⁺ monocytes do not generate ROS and are weak phagocytes that preferentially take up oxidized LDL but substantially secrete inflammatory cytokines such as tumor necrosis factor-α after Toll-like receptor-dependent activation by viruses and nucleic acids. It was previously reported that CD14⁺CD16⁺ monocytes contribute to CAD, but, to the best of our knowledge, the relationship between the severity of CAD and human monocyte subsets has not yet been examined. Whether the circulating monocyte subsets affect the severity of CAD is important from the perspective of prevention. In the present study, we investigated whether human monocyte subsets are associated with the severity of CAD assessed by coronary angiography (CAG) in patients with stable angina pectoris (SAP).
Methods

Patient Population
We enrolled 125 patients who underwent diagnostic CAG at our institution. Exclusion criteria were as follows: (1) recent (<12 weeks) acute coronary syndrome (ACS); (2) dialysis; (3) evidence of malignant disease; (4) systemic inflammatory conditions, including peripheral vascular disease, autoimmune disease, advanced liver disease, and inflammatory disease; and (5) unwillingness to participate.

This study complied with the Declaration of Helsinki with regard to investigation in humans, and the protocol for this study was approved by the Ethics Committee of Wakayama Medical University. We also obtained written informed consent from all the participants.

Clinical Parameters
The clinical parameters assessed were age, sex, and coronary risk factors, which consisted of hypertension (blood pressure ≥140/90 mmHg and/or a history of antihypertensive medication), diabetes mellitus (DM) (fasting plasma glucose ≥126 mg/dl, casual plasma glucose ≥200 mg/dl, or a diabetic pattern on the 75-g oral glucose tolerance test), dyslipidemia (serum total cholesterol ≥220 mg/dl or LDL cholesterol ≥140 mg/dl), current smoking, and body mass index.

Cytometric Analysis
For cytometric analysis, monoclonal antibodies against CD14 (fluorescein isothiocyanate [FITC]-conjugated, clone M5E2; BD Bioscience, San Jose, CA, USA) and CD16 (phycoerythrin [PE]-Cy™5-conjugated, clone 3G8; BD Bioscience) were used as described previously.9-12 Matched-isotype antibodies (FITC-conjugated mouse IgG2ak isotype, clone G155-178, and PE-Cy™5 mouse IgG1k isotype, clone MOPC-21; BD Bioscience) were used as negative controls. A total of 100 μl of blood was incubated for 15 min at room temperature in the dark. For erythrocyte lysis and leukocyte fixation, 1 ml of lysis solution was added (BD FACS Lyse, Lysing Solution; Becton Dickinson, Germany).

Figure 1. Fluorescence-activated cell scanner analysis. (A) Monocytes were gated in a FSC/SSC dot-plot. (B–D) CD14⁺CD16⁻ cells were defined as monocytes expressing CD14 but not CD16 (lower right quadrant). CD14⁺CD16⁺ cells were defined as monocytes expressing CD16 and either high levels of CD14 (upper right quadrant; CD14brightCD16⁺) or lower levels of CD14 (upper left quadrant; CD14dimCD16⁺). FSC/SSC, forward scatter/sideward scatter.
Cytometric analysis was performed in a flow cytometer (BD FACSAria™, Becton Dickinson) using BD FACSDiva Software Systems (Becton Dickinson). As shown in Figure 1, monocytes were first gated in a forward scatter/sideward scatter (FSC/SSC) dot-plot, and 2-color fluorescence was then measured within the monocyte gate. CD14+CD16+ cells were defined as monocytes expressing CD14 but not CD16. CD14+CD16− cells were defined as monocytes expressing CD16 and either a high level of CD14 (CD14brightCD16+) or a lower level of CD14 (CD14dimCD16+). The recently updated classification of monocyte heterogeneity acknowledges the existence of 3 monocyte subsets, that is, classical monocytes (CD14++CD16−), intermediate monocytes (CD14+++CD16−), and nonclassical monocytes (CD14+CD16+). However, most clinical and experimental studies have thus ignored this, or analyzed intermediate and nonclassical monocytes as a single subset. Therefore, we provide data regarding CD14+CD16+, CD14brightCD16+, and CD14dimCD16− subsets in this study, because Ancuta et al reported that CD16-positive monocytes can be subdivided into phenotypically distinct CD14++CD16+ and CD14+++CD16− cells. Leukocytes were counted by an automated method (Coulter Counter; Beckman Coulter, Miami, FL, USA).

### Blood Sampling and Analysis

Peripheral blood samples were collected from all subjects on admission in preparation for CAG. Plasma samples were collected in ethylenediaminetetraacetic acid anticoagulant tubes and stored at −80°C until required for assay. High-sensitivity C-reactive protein (hs-CRP) was analyzed using a commercially available kit (N-Latex CRP II; Dade Behring GmbH, Marburg, Germany). Plasma levels of soluble CD40 ligand (sCD40L), which is reported to be a feasible biomarker for CAD, were determined using an enzyme-linked immunosorbent assay (ELISA) kit from Biosource (Bender Medsystems, Marburg, Germany). Plasma levels of soluble CD40 ligand (sCD40L), which is reported to be a feasible biomarker for CAD, were determined using an enzyme-linked immunosorbent assay (ELISA) kit from Biosource (Bender Medsystems Human sCD40L Instant ELISA) with a sensitivity of 62.5 pg/ml, according to the manufacturer’s instructions.

### Angiographic Analysis

All patients received an intravenous bolus injection of 5,000 IU heparin and intracoronary isosorbide dinitrate (2 mg) before angiography. CAG was performed according to the Judkins technique and images of the coronary tree were obtained in routine standardized projections with the digital quantitative Philips Allura Xper FD system (Philips, The Netherlands) in all patients. All angiographic images were reviewed separately

<table>
<thead>
<tr>
<th>Table 1. Patients’ Characteristics</th>
<th>Non-CAD (n=27)</th>
<th>Single-VD (n=47)</th>
<th>Multiple-VD (n=51)</th>
<th>P value</th>
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<tr>
<td>Age, years</td>
<td>66±12</td>
<td>70±10</td>
<td>69±9</td>
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<td>Sex, male</td>
<td>19 (70)</td>
<td>38 (81)</td>
<td>40 (78)</td>
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<td>Coronary risk factors</td>
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<td>Hypertension</td>
<td>21 (78)</td>
<td>36 (77)</td>
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<td>Diabetes mellitus</td>
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<td>14 (30)</td>
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<td>Dyslipidemia</td>
<td>19 (70)</td>
<td>30 (64)</td>
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<tr>
<td>Current smoking</td>
<td>10 (37)</td>
<td>28 (60)</td>
<td>27 (53)</td>
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<td>Body mass index, kg/m²</td>
<td>23.8±3.4</td>
<td>24.2±2.9</td>
<td>24.5±3.7</td>
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<td>History of PCI</td>
<td>12 (44)</td>
<td>18 (39)</td>
<td>16 (31)</td>
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<td>Laboratory parameters on admission</td>
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<td>Triglyceride, mg/dl</td>
<td>154±106</td>
<td>144±101</td>
<td>135±66</td>
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<td>Total cholesterol, mg/dl</td>
<td>186±42</td>
<td>178±40</td>
<td>173±36</td>
<td>0.40</td>
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<td>LDL-C, mg/dl</td>
<td>103±33</td>
<td>103±30</td>
<td>100±31</td>
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<tr>
<td>HDL-C, mg/dl</td>
<td>50±16</td>
<td>43±12</td>
<td>42±11</td>
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<td>LDL-C/HDL-C ratio</td>
<td>2.3±0.9</td>
<td>2.5±0.9</td>
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<td>HbA1c %</td>
<td>6.1±1.4</td>
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<td>eGFR, ml·min⁻¹·1.73m⁻²</td>
<td>64.6±18.8</td>
<td>67.3±15.6</td>
<td>61.4±27.3</td>
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<td>White blood cells, cells/μl</td>
<td>6,119±1,723</td>
<td>6,451±1,551</td>
<td>6,244±1,444</td>
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<tr>
<td>Monocytes, cells/μl</td>
<td>315±134</td>
<td>411±168</td>
<td>399±136</td>
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<td>hs-CRP, mg/dl</td>
<td>0.07 [0.04–0.13]</td>
<td>0.12 [0.05–0.20]</td>
<td>0.13 [0.05–0.58]</td>
<td>0.13</td>
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<td>sCD40L, pg/ml</td>
<td>96.7 [62.5–169.0]</td>
<td>128.0 [88.7–184.0]</td>
<td>133.0 [79.5–278.0]</td>
<td>0.08</td>
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<td>Medications on admission</td>
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<td>Aspirin</td>
<td>17 (63)</td>
<td>40 (85)</td>
<td>44 (86)</td>
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<td>ACEI or ARB</td>
<td>19 (70)</td>
<td>29 (62)</td>
<td>29 (57)</td>
<td>0.51</td>
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<td>CCB</td>
<td>12 (44)</td>
<td>23 (49)</td>
<td>25 (49)</td>
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<td>β-blocker</td>
<td>12 (44)</td>
<td>11 (23)</td>
<td>22 (43)</td>
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<td>Statin</td>
<td>14 (52)</td>
<td>23 (49)</td>
<td>30 (59)</td>
<td>0.61</td>
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<td>Insulin</td>
<td>3 (11)</td>
<td>1 (2)</td>
<td>7 (14)</td>
<td>0.12</td>
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<td>Gensini score</td>
<td>6.0 [2.5–16.0]</td>
<td>29.0 [21.5–41.5]</td>
<td>75.0 [49.0–85.5]</td>
<td>&lt;0.001</td>
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</table>

Data are mean value ± SD, n (%) or median [interquartile range]. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CAD, coronary artery disease; CCB, calcium-channel blocker; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; sCD40L, soluble CD40 ligand; VD, vessel disease.
by 2 independent experienced cardiologists (H.K. and K.K.) who were unaware of the patient’s clinical characteristics and biochemical results. Coronary arteries were considered to have significant stenosis in the presence of ≥75% reduction in lumen diameter, as in previous studies.16,21

In each coronary angiogram, the number of major coronary arteries presenting significant stenosis was assessed and patients were subdivided into 3 groups: those without CAD, if no coronary artery showed a reduction in lumen diameter ≥75%; those with single-vessel disease (SVD), if stenosis was detected in only 1 coronary artery; and those with multiple-vessel disease (MVD), if stenosis was detected in 2 or more coronary arteries.

Gensini Score
The Gensini scoring system was used to evaluate the severity of CAD. The Gensini score22 was calculated for each patient from the coronary arteriogram by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing and its geographic importance. Reduction in the lumen diameter, and the roentgenographic appearance of concentric lesions and eccentric plaques were evaluated (reductions of 25%, 50%, 75%, 90%, 99%, and complete occlusion were given Gensini scores of 1, 2, 4, 8, 16, and 32, respectively). Each principal vascular segment was assigned a multiplier in accordance with the functional significance of the myocardial area supplied by that segment: the left main coronary artery ×5; the proximal segment of the left anterior descending coronary artery (LAD) ×2.5; the proximal segment of the circumflex artery ×2.5; the mid-segment of the LAD ×1.5; the right coronary artery, the distal segment of the LAD, the posterolateral artery and the obtuse marginal artery ×1; and others ×0.5. Scoring was performed by 2 observers (A.T. and T.T.) and averaged.23

Statistical Analysis
All statistical analyses were performed using the statistical software package SPSS version 11.0 (SPSS Inc, Chicago, IL, USA). Continuous variables are expressed as mean±standard deviation for variables with a normal distribution and median [interquartile range] for skewed variables. One-way analysis of variance (post hoc Bonferroni test) was applied for variables with a normal distribution and the Kruskal-Wallis test was applied for skewed variables. Categorical variables are presented as number (%) and were compared by the chi-square test. Spearman’s rank correlation coefficient was used for assessing the correlation between Gensini score and proportion of CD14+CD16+ monocytes, proportion of CD14+/CD16+ monocytes, hs-CRP and sCD40L. The correlation coefficient was calculated to test the intra- and interobserver agreements for Gensini score. A multivariable logistic regression model was used to determine contributors to MVD. Those variables that had shown P<0.1 in the univariate analysis (DM, proportion of CD14+CD16+ monocytes, and sCD40L) and clinically influential factors for MVD (age, sex, hypertension, dyslipidemia, current smoking, body mass index, renal function, aspirin use, statin use, and hs-CRP) were included in the multivariable logistic analysis. P<0.05 was considered statistically significant. Receiver-operating characteristic (ROC) curve analysis of sCD40L, hs-CRP, and the proportion of CD14+CD16+ monocytes for predicting MVD was performed.

Results

Patients’ Characteristics
A total of 125 patients, including 46 (37%) with a history of percutaneous coronary intervention, were enrolled. Angiographic results demonstrated that 27 (21%) of them had no significant coronary artery stenosis, 47 (38%) had SVD, and 51 (41%) had MVD. Patients without significant stenosis included 4 patients with vasospastic angina and the others were unclear. Baseline clinical characteristics, coronary risk factors, medical treatments, and laboratory parameters in all patients on admission are summarized in Table 1. There were no statistically significant differences in the patients’ characteristics (except for the presence of DM and aspirin use) among the 3 groups. Hs-CRP and sCD40L tended to be higher in patients with SVD or MVD compared to those without CAD (non-CAD), but the differences were not significant. Patients with MVD presented a higher Gensini score among the 3 groups (non-CAD, 6.0 [2.5–16.0] vs. SVD, 29.0 [21.5–41.5] vs. MVD, 75.0 [49.0–85.5]; P<0.001). The correlation coefficients were high for

![Figure 2. Comparison of (A) proportion and (B) counts of CD14+CD16+ monocytes among 3 patient groups. Data are presented as a box and whisker plot with median and 25th to 75th percentiles (boxes) and 10th to 90th percentiles (whiskers).](image-url)
repeated measurements of Gensini score by the same observer (r=0.936) and by 2 different observers (r=0.912).

**CD14+CD16+ Monocytes and Severity of CAD**

Peripheral blood samples were obtained from patients on admission and analyzed for 2 distinct monocyte subsets (CD14+CD16− and CD14+CD16+). Patients with MVD had a significantly higher proportion of CD14+CD16+ monocytes (24.4 [18.5–29.8]%) than those with SVD (vs. 12.8 [10.0–16.2]%, P<0.001) or without CAD (vs. 8.9 [7.6–10.2]%, P<0.001) (Figure 2A). Although no significant differences were seen among the 3 groups in terms of peripheral total monocyte counts, CD14+CD16+ monocyte counts were significantly higher in patients with MVD (84 [58–120] cells/μl) than in those with SVD (vs. 47 [35–63] cells/μl, P<0.001) or without CAD (vs. 28 [20–35] cells/μl, P<0.001) (Figure 2B). However, CD14+CD16− monocyte counts were not significantly different among the 3 groups. In addition, the proportion of CD14+CD16+ monocytes positively correlated with Gensini score (r=0.618, P<0.001) (Figure 3A). However, no significant correlations were demonstrated between Gensini score and hs-CRP (r=0.111, P=0.223) or sCD40L (r=0.158, P=0.079) (Figures 3C,D). Furthermore, the proportion of CD14brightCD16+ monocytes was significantly higher in patients with MVD (21.3 [17.1–26.9]%) than in those with SVD (vs. 6.2 [4.8–7.2]%, P<0.001) and the proportion of CD14brightCD16+ monocytes positively correlated with Gensini score (r=0.678, P<0.001) (Figure 3B).

**CD14+CD16+ Monocytes as Predictive Markers of MVD**

The results of univariate logistic regression analysis indicated that DM (odds ratio [OR]: 2.699; 95% confidence interval [CI]: 1.289–5.654, P=0.008) and the proportion of CD14+CD16+ monocytes (OR: 1.390; 95% CI: 1.243–1.555, P<0.001) were contributors to MVD. Multivariate logistic regression analysis demonstrated that the proportion of CD14brightCD16+ monocytes (OR: 1.475; 95% CI: 1.273–1.708, P<0.001) was an independent contributor to MVD (Table 2). The effect of DM on the proportion of CD14+CD16+ monocytes was not significant in patients with MVD (non-DM, 23.1±6.6% vs. DM, 24.2±7.3%; P=0.58). Furthermore, the proportion of CD14brightCD16+ monocytes (OR: 1.659; 95% CI: 1.354–2.034, P<0.001) was an independent contributor to MVD (Table 2).
independent contributor to MVD, as well as the proportion of CD14^+CD16^+ monocytes.

The ROC curves for sCD40L, hs-CRP, and the proportion of CD14^+CD16^+ monocytes are shown in Figure 4. The areas under the ROC curve of sCD40L, hs-CRP, and the proportion of CD14^+CD16^+ monocytes for predicting MVD were 0.592, 0.532, and 0.921, respectively. In terms of the proportion of CD14^+CD16^+ monocytes, a threshold level of 16.2% had the highest combined sensitivity (84%) and specificity (86%) for the identification of MVD.

### Discussion

The evaluation of the severity of CAD is the focus of research efforts. This study demonstrated a significant association between the proportion of CD14^+CD16^+ monocytes and the severity of CAD in patients with SAP. In addition, a preferential increase in peripheral CD14^+CD16^+ monocytes was found to be an independent contributor to MVD.

Monocytes play a key role in atherosclerosis. Cross-sectional studies have demonstrated increased numbers of circulating monocytes in individuals with prevalent atherosclerotic disease. Consistently, results from prospective studies suggest that the monocyte count can independently predict cardiovascular events. Numerous studies have suggested that an elevated hs-CRP level in patients with ACS reflects inflammation of the coronary arteries. Necrotic debris and inflammatory mediators from coronary plaque are released into the systemic circulation, with a subsequent increase in the hepatic release of acute-phase reactants such as hs-CRP. However, the results of the present study indicated that the severity of angiographically determined CAD was not significantly associated with hs-CRP level in patients with SAP, and we found no relation between hs-CRP level and the CD14^+CD16^+ monocyte subset. Although our results suggest that a relative increase in CD14^+CD16^+ monocytes might be superior to hs-CRP for determining the severity of CAD in patients with SAP, further studies will be needed for clarification.

Recently, we showed that an imbalance in the monocyte subsets, namely, a relative increase in CD14^+CD16^+ monocytes, may be relevant to coronary plaque vulnerability assessed by 64-slice multidetector computed tomography in patients with SAP. We also showed that upregulation of CD14^+CD16^+ monocytes is associated with plaque rupture in patients with unstable angina pectoris. Consistent with our results, 2 other groups have reported that an increased proportion of CD14^+CD16^+ monocytes is associated with an increased incidence of CAD. In addition, gene polymorphisms at amino acids 249 and 280 of CX3CR1 in humans are reported to constitute a genetic risk factor for CAD. In the present study, we extended these previous findings by demonstrating a close relationship between CD14^+CD16^+ monocytes and the severity of CAD in patients with SAP.

It has been suggested that the CD40/CD40L system is implicated in the progression of atherosclerosis. Clinical studies have evaluated sCD40L as a biomarker of cardiovascular risk. It has also been reported that apparently healthy women with elevated levels of CD40L have an increased risk of myocardial infarction, stroke, and cardiovascular death; this finding was unaffected by adjustment for traditional cardiovascular risk factors. Thus, sCD40L may serve as a clinically useful biomarker for risk stratification in the setting of ACS. Unexpectedly, we found that a relative increase in CD14^+CD16^+ monocytes might be superior to sCD40L for determining the severity of CAD in patients with SAP. However, further studies will be needed to clarify such differences.

### Study Limitations

First, the results were prospective in terms of patient enrollment but were observational in nature. Thus, our study does not provide a mechanistic explanation for the effect of specific monocyte subsets on the severity of CAD. Second, we could not determine whether the elevation of the peak CD14^+CD16^+ monocyte numbers reflected the extent of monocyte infiltration into a coronary artery. Finally, although we excluded pa-
tients with inflammatory conditions, we cannot exclude the possibility of occult inflammation.

Conclusions
Our present results are the first to show a significant association between an increased proportion of CD14+CD16+ monocytes and the severity of CAD assessed by CAG in patients with SAP. In addition, a preferential increase in peripheral CD14+CD16+ monocytes was also found to be an independent contributor to MVD. These findings suggest that CD14+CD16+ monocytes might be closely related to the pathophysiology of CAD progression.

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References