The Monocyte to High-Density Lipoprotein Cholesterol Ratio Is Associated with Left Ventricular Diastolic Function in Patients with No Significant Perfusion Abnormality

Assessment by Myocardial Perfusion Single-Photon Emission Computed Tomography

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Summary

The monocyte to high-density lipoprotein cholesterol (HDL-C) ratio has been considered to be a prognostic marker. Whether this ratio is associated with left ventricular (LV) diastolic function remains undetermined. We tested the hypothesis that the monocyte to HDL-C ratio is associated with LV diastolic parameters derived from gated myocardial perfusion single-photon emission computed tomography (SPECT) in patients with no significant perfusion abnormality.

The study population included 196 patients with no significant perfusion abnormalities and preserved ejection fraction. The peak filling rate (PFR) and one-third mean filling rate (1/3 MFR) were obtained as LV diastolic parameters using gated SPECT. Monocyte counts and plasma HDL-C levels were also examined.

Significant associations were observed between the monocyte to HDL-C ratio and PFR ($r = -0.20$; $P = 0.005$) and 1/3 MFR ($r = -0.19$; $P = 0.009$). Multivariate linear regression analysis was performed to determine factors associated with LV diastolic parameters. Age ($\beta = -0.27$; $P < 0.001$), LV end-diastolic volume ($\beta = -0.19$; $P = 0.034$), and monocyte to HDL-C ratio ($\beta = -0.15$; $P = 0.027$) were determined to be significantly associated with PFR. Moreover, age ($\beta = -0.13$; $P = 0.007$), LV mass index ($\beta = -0.18$; $P = 0.037$), and the monocyte to HDL-C ratio ($\beta = -0.13$; $P = 0.045$) were significantly associated with 1/3 MFR.

These results demonstrated that the monocyte to HDL-C ratio is associated with LV diastolic function, as derived from gated SPECT in patients with no significant perfusion abnormality.

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Key words: Monocyte counts, Inflammation, Myocardial imaging

Monocytes have been defined as essential immune system cells that play an important role during the inflammatory response.¹⁾ In addition, the level of high-density lipoprotein cholesterol (HDL-C) has long been considered to be a marker indicating protection from the risk of cardiovascular disease.²⁾ Several studies have demonstrated that monocyte counts or low HDL-C are related to heart failure,^{3,4)} suggesting a possible linkage between chronic inflammation and heart failure. In the general population, monocytes and HDL-C have been found to exert joint effects on cardiovascular mortality,⁵⁾ heart failure hospitalization,⁶⁾ and asymptomatic organ damage,⁷⁾ which could be possibility related to the proinflammatory characteristics of monocytes and the fact that low HDL-C diminishes the controlling monocyte activation. However, whether the monocyte to HDL-C ratio is associated with left ventricular (LV) diastolic function, with regard to inflammation, in patients with no significant perfusion abnormality, remains unclear.

Gated myocardial perfusion single-photon emission computed tomography (SPECT) has been identified as a suitable modality for the assessment of LV diastolic function and myocardial perfusion.^{8,9)} In the present study, we tested the hypothesis that the monocyte to HDL-C ratio is associated with LV diastolic parameters derived from gated SPECT, in patients with no significant perfusion abnormality.

Methods

Study population: Between July 2012 and May 2018, 282 patients with known or suspected coronary artery disease underwent laboratory testing, gated SPECT, and transthoracic echocardiography (TTE) at our center. All examinations were completed within 1 month. Patients with a summed stress score of 4 or higher were excluded from the study,¹⁰⁾ as its purpose was to determine the association between the monocyte to HDL-C ratio and LV dia-

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stolic function in patients with no significant perfusion abnormality. In addition, patients with the following conditions that could affect the LV diastolic parameters or monocyte counts were excluded: significant valvular heart disease, previous cardiac surgery, reduced LV ejection fraction (LVEF) less than 50%, atrial fibrillation, ventricular pacing, hemodialysis, hematological disease, ongoing malignant diseases, systemic inflammation, current smoking¹¹⁾ white blood cell count greater than 12,000 cells/ μ L, and high-sensitivity C-reactive protein (hs-CRP) levels greater than 0.35 mg/dL.¹²⁾ In total, 196 patients with no evidence of myocardial ischemia were included. This study was approved by the Ethics Committee at the Hiroshima University Graduate School of Biomedical and Health Sciences.

Laboratory measurements: Blood samples were collected after at least 8 hours of overnight fasting. Total cholesterol, low-density lipoprotein cholesterol, HDL-C, and plasma triglycerides were measured enzymatically, and plasma levels of hs-CRP were determined by immunoturbidimetry (BioMajesty JCA-BM6070; JEOL, Tokyo, Japan). Hematological parameters were measured using an automated blood counter (Sysmex XE-5000; Sysmex Corporation, Kobe, Japan). The monocyte to HDL-C ratio was also computed as the absolute monocyte count divided by HDL-C. Four quartile groups were formed based on the monocyte to HDL-C ratio: quartile 1 (0.41-4.42), quartile 2 (4.47-6.06), quartile 3 (6.08-8.69), and quartile 4 (8.84-21.35).

Gated SPECT: All patients fasted overnight and underwent gated SPECT. Adenosine was infused over 6 minutes (120 μ g/kg/minute), and thallium-201 (111 MBq [3.0 mCi]) was injected 3 minutes after the adenosine infusion initiation.^{13,14)} The stress thallium-201 SPECT acquisition began 5 minutes after the pharmacological stress test, and the redistribution image was obtained 4 hours later. Gated SPECT images were acquired using a dual-detector 90-degree γ -camera (Brightview X; Philips Healthcare, Milpitas, CA, USA). The imaging parameters were as follows: total number of projections, 36; arc, 180 degrees (from right anterior oblique to left posterior oblique with a non-circular orbit); matrix, 64 $\times$ 64; pixel size, 6.4 mm; number of frames, 16 per cardiac cycle; collimation, low energy and high resolution; and acquisition time, 40 seconds per stop. Images were reconstructed using ordered-subset expectation maximization (iteration, 2; subset, 9) with a Butterworth filter (order, 8; cutoff frequency, 0.50 cycles/pixel for stress images and 0.45 cycles/pixel for redistribution images).

LV volume and function: LV end-diastolic volume (LVEDV) and LVEF were determined on the redistribution images using quantitative gated SPECT software (Cedars-Sinai Medical Center, Los Angeles, CA).⁸⁾ The transient ischemic dilation ratio has been defined as the ratio of LVEDV on the stress image to LVEDV on the redistribution images. The following parameters for the LV diastolic function were obtained from the redistribution images: peak filling rate (PFR), defined as the maximum dV/dt divided by LVEDV and expressed as EDV/second, and one-third mean filling rate (1/3 MFR), defined as the average dV/dt in the first third of the filling time and also

expressed as EDV/second.^{13,14)}

Transthoracic echocardiography: TTE evaluations were performed by three experienced cardiac sonographers blinded to the patients' clinical status, using a Vivid E9 ultrasound system with a 2.5 MHz transducer (GE Vingmed Ultrasound, Horten, Norway). All imaging data were digitized and stored on an optical disk for offline analysis (EchoPAC software, version 112; GE Vingmed Ultrasound). The LV internal dimension (LVID), interventricular septal thickness, and posterior wall thickness were measured at end diastole. The LV mass was calculated using the following formula:¹⁵⁾ LV mass (g) = $0.8 \times 1.04 [(LVID + \text{interventricular septal thickness} + \text{posterior wall thickness})^3 - (LVID)^3] + 0.6$. The LV mass index has been defined as the LV mass indexed for the body surface area. Tissue Doppler imaging parameters were obtained in the apical four-chamber view. Septal and lateral peak mitral annular motion velocities during early diastole (E') were obtained, and their average was used for analysis.

Statistical analysis: Standard statistical methods were utilized in this study. Continuous variables with a normal distribution were presented as means $\pm$ standard deviations. Triglycerides and hs-CRP were found to be not normally distributed. Therefore, these variables were presented as medians with interquartile ranges. Categorical variables were expressed as numbers and percentages. Continuous variables were compared among groups using analysis of variance or Kruskal-Wallis tests. Categorical variables were compared among groups using the chi-squared test or Fisher's exact test. Pearson's correlation coefficient was used to evaluate correlations between the monocyte to HDL-C ratio and the PFR, 1/3 MFR. Univariate and multivariate linear regression analyses were performed to determine the predictors of PFR and 1/3 MFR among clinical and quantitative gated SPECT parameters. A two-tailed *P* value less than 0.05 was considered statistically significant. All statistical analyses were performed using JMP version 14 software (SAS Institute Inc., Cary, NC).

Results

Study participant characteristics: Results of the comparisons in the clinical parameters among the quartile groups are summarized in Table I. The study participants had an average age of 71 ± 9 years, and 117 patients (60%) were male. The average time interval between laboratory measurements and the gate SPECT examination was 21 ± 9 days. The quartile groups were separated according to the monocyte to HDL-C ratio, with mean values of 3.19 ± 0.90 , 5.22 ± 0.52 , 7.20 ± 0.80 , and 11.55 ± 2.75 for quartiles 1, 2, 3, and 4, respectively. No significant differences were noted among the groups in terms of sex, age, systolic blood pressure, heart rate, risk factors, serum creatinine, medication, and lipid profile, except for HDL-C. LVEDV, the transit ischemic dilation ratio, and LVEF were similar among the groups.

Relationships between the monocyte to HDL-C ratio and LV diastolic parameters: Significant differences among the quartile groups were found for the diastolic parameters' PFR ($P < 0.001$) and 1/3 MFR ($P = 0.020$).

Table I. Comparison of Patient Characteristics in Monocyte to HDL-C Ratio Quartile

Variables	All (<i>n</i> = 196)	Quartile 1 (0.41–4.42) (<i>n</i> = 49)	Quartile 2 (4.47–6.06) (<i>n</i> = 49)	Quartile 3 (6.08–8.69) (<i>n</i> = 49)	Quartile 4 (8.84–21.35) (<i>n</i> = 49)	<i>P</i> value
Male	117 (60%)	25 (51%)	34 (69%)	27 (55%)	31 (63%)	0.244
Age (years)	71 ± 9	70 ± 9	73 ± 10	70 ± 11	71 ± 8	0.564
Body mass index (kg/m ²)	23 ± 3	23 ± 3	23 ± 3	22 ± 4	24 ± 2	0.348
Systolic blood pressure (mmHg)	134 ± 21	131 ± 19	131 ± 21	137 ± 23	138 ± 20	0.190
Heart rate (bpm)	66 ± 12	64 ± 10	66 ± 10	65 ± 11	69 ± 14	0.203
Hypertension	136 (69%)	33 (67%)	29 (59%)	39 (80%)	35 (71%)	0.167
Diabetes mellitus	65 (33%)	17 (35%)	14 (29%)	15 (31%)	19 (39%)	0.716
Dyslipidemia	138 (70%)	32 (65%)	36 (73%)	33 (67%)	37 (76%)	0.644
Former smoker	56 (29%)	12 (24%)	15 (31%)	14 (29%)	15 (31%)	0.894
Prior myocardial infarction	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.000
Prior coronary intervention	16 (8%)	2 (4%)	2 (4%)	4 (8%)	8 (16%)	0.108
Medications						
ACEIs or ARBs	80 (41%)	19 (39%)	19 (39%)	20 (41%)	22 (45%)	0.918
Beta blockers	48 (24%)	10 (20%)	11 (22%)	15 (31%)	12 (24%)	0.678
Calcium channel blockers	71 (36%)	11 (22%)	18 (37%)	23 (47%)	19 (39%)	0.077
Statins	108 (55%)	27 (55%)	27 (55%)	24 (49%)	30 (61%)	0.685
White blood cell count (μL)	5977 ± 1631	5104 ± 1285	5384 ± 964	6234 ± 1189	7287 ± 2029	< 0.001
Monocyte count (μL)	362 ± 134	232 ± 81	321 ± 62	391 ± 83	504 ± 129	< 0.001
Serum creatinine (mg/dL)	0.87 ± 0.23	0.81 ± 0.19	0.87 ± 0.25	0.89 ± 0.26	0.92 ± 0.20	0.077
Hemoglobin A1c (%)	6.3 ± 1.0	6.3 ± 1.0	6.1 ± 0.6	6.3 ± 1.0	6.5 ± 1.2	0.361
Total cholesterol (mg/dL)	187 ± 38	192 ± 36	188 ± 37	193 ± 46	175 ± 28	0.078
LDL-C (mg/dL)	110 ± 32	107 ± 31	109 ± 35	119 ± 35	104 ± 26	0.116
HDL-C (mg/dL)	58 ± 16	73 ± 17	62 ± 11	55 ± 12	44 ± 9	< 0.001
Triglycerides (mg/dL)	111 (82–175)	99 (69–157)	98 (80–155)	119 (97–173)	120 (97–201)	0.300
hs-CRP (mg/dL)	0.05 (0.03–0.12)	0.04 (0.02–0.08)	0.06 (0.03–0.13)	0.05 (0.03–0.11)	0.08 (0.04–0.22)	0.023
LV mass index (g/m ²)	87 ± 23	86 ± 17	84 ± 23	91 ± 26	88 ± 24	0.485
QGS variables						
LVEDV (mL)	62 ± 20	57 ± 16	63 ± 22	63 ± 23	65 ± 20	0.272
Transit ischemic dilation ratio	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	0.804
LVEF (%)	66 ± 8	68 ± 7	67 ± 8	66 ± 8	65 ± 8	0.520

Values are mean ± standard deviation, median (interquartile), or count (percentage). HDL-C indicates high-density lipoprotein cholesterol; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LDL-C, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LV, left ventricular; QGS, quantitative gated single-photon emission computed tomography; LVEDV, left ventricular end-diastolic volume; and LVEF, left ventricular ejection fraction.

These parameters were decreased with increased monocyte to HDL-C ratio (Figure 1). The monocyte to HDL-C ratio was inversely correlated with the PFR ($r = -0.20$; $P = 0.005$) and 1/3 MFR ($r = -0.19$; $P = 0.009$) (Figure 2). In the multivariate linear regression analysis, age ($\beta = -0.27$; $P < 0.001$), LVEDV ($\beta = -0.19$; $P = 0.034$), and the monocyte to HDL-C ratio ($\beta = -0.15$; $P = 0.027$) were significantly associated with PFR (Table II Model 2). Furthermore, age ($\beta = -0.13$; $P = 0.007$), LV mass index ($\beta = -0.18$; $P = 0.037$), and the monocyte to HDL-C ratio ($\beta = -0.13$; $P = 0.045$) were significantly associated with 1/3 MFR (Table III Model 2). PFR ($r = 0.34$; $P < 0.001$) and 1/3 MFR ($r = 0.37$; $P < 0.001$) were positively correlated with E' as the reference standard for the LV diastolic function (Figure 3).

Discussion

This present study demonstrated that the monocyte to HDL-C ratio is associated with, and an independent predictor of, PFR and 1/3 MFR derived from gated SPECT in study participants with no significant perfusion abnor-

malities.

Gated SPECT is a unique modality that allows the assessment of both myocardial perfusion and LV function with a single test. Myocardial ischemia is a major factor inducing impaired LV diastolic function.¹⁶⁾ The present study included only patients with no significant perfusion abnormality, based on the summed stress score with the transit ischemic dilation ratio, to clarify implications of the monocyte to HDL-C ratio in terms of the LV diastolic function. As a result, the study has demonstrated that the monocyte to HDL-C ratio was associated with the LV diastolic parameters of PFR and 1/3MFR. Thus, gated SPECT was deemed useful in selecting the study population and in assessing the association between the monocyte to HDL-C ratio and the LV diastolic function.

Our present findings denoting a link between the monocyte to HDL-C ratio and the LV diastolic function might be explained by several potential mechanisms. One mechanism involves known associations among the monocyte to HDL-C ratio, systemic inflammation, and microvascular dysfunction. Dogan, *et al.* reported that elevated monocyte to HDL-C ratio was significantly associ-

Figure 1. PFR (left) and 1/3 MFR (right) in the monocyte to HDL-C quartile. PFR indicates peak filling rate; 1/3 MFR, one-third mean filling rate; HDL-C, high-density lipoprotein cholesterol; and EDV, end-diastolic volume.

Figure 2. Correlations of the monocyte to HDL-C ratio with PFR (left) and 1/3 MFR (right). HDL-C indicates high-density lipoprotein cholesterol; PFR, peak filling rate; 1/3 MFR, one-third mean filling rate; and EDV, end-diastolic volume.

ated with the presence of cardiac syndrome X, which is mainly caused by microvascular dysfunction.¹⁷⁾ Canpolat, *et al.* also found that elevated monocyte to HDL-C ratio was significantly associated with the presence of coronary slow flow in patients with normal coronary arteries.¹⁸⁾ Besides, the monocyte to HDL-C ratio was positively correlated with the serum hs-CRP level as a systemic inflammation marker. Conversely, Yang, *et al.* demonstrated that the coronary flow reserve measured by diagnostic coronary angiography was a good representation of the LV diastolic function in patients with heart failure with a preserved ejection fraction.¹⁹⁾ Blomster, *et al.* also presented similar results using TTE.²⁰⁾ These results suggest that inflammation, which is associated with an increase in the monocyte to HDL-C ratio, results in microvascular dysfunction and, consequently, in the LV diastolic dysfunction.

Another possible mechanism is the presence of an association between the monocyte to HDL-C ratio and arterial stiffness. Kaplan, *et al.* found that there was a rela-

tionship between elevated monocyte to HDL-C ratio and LV hypertrophy in hypertensive patients.²¹⁾ In addition, the detrimental effect of low HDL-C levels on aortic stiffness and LV hypertrophy has been associated with the LV diastolic dysfunction in hypertensive subjects.^{22,23)} Increased arterial stiffness imposes a higher afterload and systolic wall stress,²⁴⁾ leading to LV hypertrophy and LV diastolic dysfunction. As a result, the combination of monocyte counts and HDL-C might improve detection of LV diastolic dysfunction. Our findings suggest that, especially in patients with high monocyte to HDL-C ratio, the LV diastolic function should be examined in some way to prevent progression into heart failure.

The present study has several limitations. First, TI-201 was used for gated SPECT. Compared with TI-201, higher doses of technetium agents can provide better image quality without increasing the radiation burden and were deemed suitable for assessing the LV diastolic function. Nakajima, *et al.* showed the lower limits of PFR or 1/3 MPR using technetium-99 m MIBI in Japanese pa-

Table II. Linear Regression Analysis to Determine Factors Associated with PFR

Variables	Univariate		Multivariate			
	β	<i>P</i> value	Model 1		Model 2	
	β	<i>P</i> value	β	<i>P</i> value	β	<i>P</i> value
Male	-0.22	0.002	-0.13	0.067	-0.14	0.060
Age	-0.22	0.002	-0.27	< 0.001	-0.27	< 0.001
Body mass index	-0.16	0.026	-0.13	0.057	-0.13	0.051
Systolic blood pressure	-0.13	0.061	-0.03	0.703	-0.03	0.645
Hypertension	-0.06	0.380				
Diabetes mellitus	0.04	0.575				
Serum creatinine	-0.15	0.032	-0.04	0.574	-0.04	0.558
LVMl	-0.29	< 0.001	-0.12	0.148	-0.11	0.159
LVEDV	-0.30	< 0.001	-0.19	0.038	-0.19	0.034
hs-CRP	-0.12	0.102				
Monocyte count	-0.16	0.022	-0.10	0.112		
HDL-C	0.19	0.007	0.12	0.071		
Monocyte to HDL-C ratio	-0.20	0.005			-0.15	0.027

PFR indicates peak filling rate; LVMl, left ventricular mass index; LVEDV, left ventricular end-diastolic volume; hs-CRP, high sensitivity C-reactive protein; and HDL-C, high-density lipoprotein cholesterol.

Table III. Linear Regression Analysis to Determine Factors Associated with 1/3 MFR

Variables	Univariate		Multivariate			
	β	<i>P</i> value	Model 1		Model 2	
	β	<i>P</i> value	β	<i>P</i> value	β	<i>P</i> value
Male	-0.17	0.015	-0.14	0.059	-0.15	0.052
Age	-0.15	0.037	-0.13	0.076	-0.13	0.007
Body mass index	-0.13	0.077	-0.11	0.133	-0.11	0.117
Systolic blood pressure	-0.16	0.021	-0.08	0.249	-0.09	0.217
Hypertension	-0.10	0.166				
Diabetes mellitus	0.03	0.636				
Serum creatinine	-0.14	0.044	-0.05	0.513	-0.05	0.490
LVMl	-0.25	< 0.001	-0.18	0.034	-0.18	0.037
LVEDV	-0.17	0.015	-0.01	0.971	-0.01	0.998
hs-CRP	-0.12	0.328				
Monocyte count	-0.15	0.041	-0.09	0.175		
HDL-C	0.19	0.009	0.12	0.084		
Monocyte to HDL-C ratio	-0.18	0.010			-0.13	0.045

1/3 MFR indicates one-third mean filling rate; LVMl, left ventricular mass index; LVEDV, left ventricular end-diastolic volume; hs-CRP, high sensitivity C-reactive protein; and HDL-C, high-density lipoprotein cholesterol.

Figure 3. Correlations of the peak mitral annular motion velocity (E') with PFR (left) and 1/3 MFR (right). E' indicates peak mitral annular motion velocity; PFR, peak filling rate; and 1/3 MFR, one-third mean filling rate.

tients.²⁵⁾ By contrast, the lower limits of PFR or 1/3 MPR based on TI-201 have not been established. Future analyses in our population are needed to clarify the association between these lower limits and the monocyte to HDL-C ratio. Second, there may be a selection bias because patients who underwent laboratory measurements, gated SPECT, and TTE were enrolled as the study participants. Third, monocyte subsets, particularly intermediate monocytes that are strongly associated with heart failure, were not assessed. Finally, the small sample size was a major limitation of this study.

Conclusion

Our findings suggest that the monocyte to HDL-C ratio, a comprehensive indicator reflecting systemic inflammation status, is correlated with LV diastolic parameters derived from gated SPECT in patients with no significant perfusion abnormality.

Disclosure

Conflicts of interest: The authors declare that there are no conflicts of interest.

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