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Peripheral microvascular dysfunction predicts residual risk in coronary artery disease patients on statin therapy

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ABSTRACT

Objective: Although lowering of low-density lipoprotein cholesterol (LDL-C) by statins is essential in treatment of coronary artery disease (CAD) patients, there is considerable residual risk of secondary coronary artery events (CAE). We examined whether microvascular dysfunction (MiD), measured by peripheral artery tonometry (PAT), can predict prognosis of CAD patients previously treated with statins.
Methods: We measured log-transformed reactive hyperemia index (L_RHI) in 213 CAD patients who had already achieved LDL-C <100 by statin therapy. Patients were followed-up for secondary CAE for a median of 2.7 years. Patients were divided into two groups: L_RHI $\geq$ 0.54 (n = 99) and L_RHI < 0.54 (n = 114).
Results: During follow-up, CAE occurred in 4 (4.0%) patients in the L_RHI $\geq$ 0.54 group and 18 (15.8%) patients in the L_RHI < 0.54 group (P = 0.006). Cox regression analysis indicated that L_RHI was an independent predictor for CAE even after adjustment by Framingham traditional risk factors (FRF; age, T-C/HDL-C ratio, systolic blood pressure, diabetes, current smoker, and gender) and estimated glomerular filtration rate (eGFR) for secondary CAE (HR 0.79, 95% CI: 0.66–0.95). ROC analysis for CAE prediction showed that the AUC for models including FRF only, FRF + eGFR, and FRF + eGFR + L_RHI were 0.60, 0.71, and 0.77, respectively. Moreover, adding eGFR to FRF only (0.63, P = 0.003) and adding L_RHI to the FRF + eGFR model were associated with significant improvement of net reclassification improvement (0.79, P = 0.007).
Conclusion: MiD measured by non-invasive PAT adds incremental predictive ability to traditional risk factors for prognosis of CAD patients successfully treated with statins.

1. Introduction

Cholesterol lowering therapy by 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) is an essential treatment for improving the outcome of patients with coronary artery disease (CAD). Low-density lipoprotein cholesterol (LDL-C) is a very important target for treatment, and the National Cholesterol Education Program Adult Treatment Panel recommends an LDL-C goal of <100 mg/dL for prevention of secondary coronary artery events (CAE) in all patients with CAD and <70 mg/dL for individuals at very high risk, such as those with acute coronary syndromes or diabetics with any manifestation of cardiovascular (CV) disease [1]. These LDL-C lowering strategies have been shown to significantly reduce morbidity and mortality in a number of large randomized control trials. However, the relative risk reduction compared to placebo was around 20%–30% [2,3], which was similar between high-dose and standard-dose statin therapy [4–6]. Therefore, approximately 70% of the secondary CV events could not be prevented. As patients with myocardial infarction have a high mortality rate even within a few years after initial presentation [7,8], risk stratification to identify the high-risk population is crucial to reduce this residual risk in CAD patients.

Endothelial dysfunction (ED) is considered an initial step of atherosclerosis, and is also a key factor in the progression of CAD.

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Some studies have shown that macrovascular ED is related to traditional risk factors [9], plaque vulnerability [10], indicators of response to optimal medical therapy [11], and prognosis [12].

Recently, digital peripheral artery tonometry (PAT) has emerged as a novel noninvasive tool for assessing microvascular dysfunction (MiD). Although MiD is assessed by measuring pulse amplitude in the fingertip after the induction of reactive hyperemia, this measure and macrovascular ED measured by flow-mediated dilatation (FMD) only show a weak correlation [13].

MiD defined as impaired reactive hyperemia in PAT is correlated with the presence of CV risk factors [14,15], coronary artery endothelial dysfunction [16], and poorer prognosis in low-risk CV patients [17]. However, it is not yet clear whether MiD has implications for stratifying residual risk in established CAD patients.

Therefore, we hypothesized that MiD can be used to stratify this residual risk in CAD patients treated successfully with statin therapy.

2. Methods

2.1. Study subjects

This was a prospective observational study conducted between September 2009 and December 2012 in a single center and was approved by the Human Research Committee of Kameda Medical Center. All subjects provided written informed consent prior to enrollment in the study.

During the study period, consecutive outpatients with CAD who had been referred to our vascular function laboratory were assessed for eligibility. The patients who fulfilled the inclusion criteria and did not meet the exclusion criteria were enrolled in this study with informed consent. Men and women aged >20 years and <74 years with clinically evident CAD, LDL-C <100 mg/dL with statin therapy for more than 3 months, and who agreed to participation were included in the study. CAD was defined as previous myocardial infarction (MI), previous or present angina with objective evidence of atherosclerotic CAD (at least one coronary stenosis > 70%), and previous coronary revascularization procedure. Major exclusion criteria included any of the following: MI, coronary revascularization procedure, or severe/unstable angina within 1 month of screening; any planned surgical procedure for treatment of atherosclerosis; New York Heart Association functional classification ≥ III; left ventricular ejection fraction < 30%; end-stage renal disease (estimated glomerular filtration rate < 15 mL/min/1.73 m^2 or requiring hemodialysis); any malignancy; concurrent therapy with long-term immunosuppressants; or familial hypercholesterolemia. Blood samples were collected from all patients on the same day as measurement of MiD. MiD was evaluated by PAT as log-transformed reactive hyperemia index (L_RHI) (Endo-PAT 2000; Itamar Medical Ltd., Caesarea, Israel) [18]. Patients were also advised to continue their current medication and lifestyle for the duration of the study. The patients were not allowed any caffeine-containing drinks or tobacco consumption on the day of a visit.

2.2. Endpoints

All enrolled CAD patients were prospectively followed up for first subsequent CAE after measuring MiD. The definitions of CAE were as follows: angina pectoris requiring coronary revascularization, recurrent angina pectoris with proven myocardial ischemia, non-fatal myocardial infarction, and death from coronary heart disease. Whether a given event could be validated as an endpoint was confirmed by two reviewers who were blinded to the L_RHI values, and a third physician who is a trained cardiologist (M.S.) and was also blinded to L_RHI resolved disparities in the event of disagreement in the validity of endpoints.

2.3. Assessment of microvascular endothelial function

MiD was measured via L_RHI according to the principle described previously [14,19]. Briefly, this system consists of a finger probe to assess digital volume changes accompanying pulse waves. All patients were instructed to avoid eating or drinking, taking only water, for 8 h before measuring L_RHI. The same dim room maintained at a temperature of 26.5 °C was used for measurement of L_RHI in all patients. Before commencing measurement of L_RHI, patients remained in bed for 15 min.

The probe was positioned on the middle finger of each hand and set by computer to inflate to 70 mmHg, and then the baseline pulse amplitude was recorded from both fingers. After this procedure, the blood pressure cuff was inflated on one arm to 200 mmHg or 60 mmHg plus systolic blood pressure for 5 min and released.

Throughout the period of inflation and release, recordings were taken simultaneously from both fingers. The increase in pulse amplitude in the hyperemic finger was recorded digitally and analyzed using an automated operator-independent proprietary algorithm as reactive hyperemia index, and L_RHI was calculated for use in subsequent analyses [20]. Previous studies have demonstrated good reproducibility of RHI, and the intraclass correlation coefficient was reported to range from 0.73 to 0.78 [21–24].

2.4. Biochemical analyses

A venous blood sample was obtained after an overnight fast. Plasma total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels were measured using an automated analyzer. LDL-C was calculated by the Friedewald formula. Serum high-sensitive C-reactive protein concentration was also measured by high-sensitivity immunoturbidimetric assay (Roche Diagnostics, Tokyo, Japan).

2.5. Statistical analysis

Baseline characteristics were analyzed for significance of differences between groups by one-way analysis of variance or Student's *t* test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. Distribution was tested with the Kolmogorov–Smirnov test. Receiver operating characteristic (ROC) curves were constructed, and an appropriate cut-off value to predict CAE was decided according to the Youden index [25].

To examine whether the value of L_RHI did or did not improve the performance of the predictive model in CAD patients, we constructed a ROC curve for logistic regression model of Framingham traditional risk factors (FRF) for subsequent secondary CAE derived from the Framingham Heart Study for established CAD patients (age, log-transformed T-C/HDL-C, log-transformed systolic blood pressure, diabetes, current smoker, and gender) [26]. Moreover, as renal function impairment has recently been shown to be a robust and powerful predictor of future CV events, we also constructed a logistic regression model including eGFR as a continuous variable. Therefore, ROC curves were constructed in three models: FRF only, FRF + eGFR, and FRF + eGFR + L_RHI. Areas under the curves (AUC) were compared according to the method of DeLong et al. [27], and continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) with corresponding 95% confidence interval (CI) were also calculated [28].

Event-free survival curves were constructed using the Kaplan–Meier survival method and were compared using log-rank statistics. Survival period was defined as the interval between the day of discharge and the time of CAE.

Due to the limited number of patients and events, we calculated hazard ratios (HR) derived from the Cox proportional hazard model to evaluate the prognostic effects of L_RHI by adjusting for FRF over the study period. The results are shown as means ± SD, numbers (%), and HR with 95% CI. Data analysis was performed with R version 2.14. All statistical test values were two-sided, and $P < 0.05$ was taken to indicate significance in all analyses.

3. Results

3.1. Patient characteristics

A total of 442 patients were initially assessed for eligibility, and 213 patients were finally included in the study after exclusion of 229 patients: 187 did not fulfill the inclusion criteria, 37 had LDL-C >100 mg/dL on the day of measurement, and 5 refused to participate in the study.

The median follow-up period was 2.6 years (interquartile range: 0.8–2.8 years). All patients completed the study and none of the patients underwent cardiac transplantation.

The mean L_RHI value was 0.55 ± 0.27 (median 0.52) for all cohorts. We divided the whole cohort into two groups based on the results of ROC curve analysis: those with L_RHI ≥ 0.54 ($n = 99$) and those with L_RHI < 0.54 ($n = 114$).

The baseline patient characteristics of the whole cohort are shown in Table 1. The subjects were predominantly male (73.7%), with a mean age of 66.7 years, and 74 patients had a history of diabetes mellitus. With regard to CAD history, 166 patients had previously undergone percutaneous coronary intervention, 131 patients had a history of myocardial infarction, and 42 patients had previously undergone coronary artery bypass grafting. Mean total cholesterol and LDL-C levels were 144.9 mg/dL and 69.9 mg/dL, respectively. There were no significant differences in baseline characteristics between the L_RHI ≥ 0.54 group and L_RHI < 0.54 group except the significantly lower baseline heart rate in the L_RHI ≥ 0.54 group. Estimated glomerular filtration rate was low in the L_RHI < 0.54 group, but the difference was not statistically significant.

Table 1
Baseline patient characteristics.

Variables	L_RHI ≥ 0.54 ($n = 99$)	L_RHI < 0.54 ($n = 114$)	*P*-value
Male (%)	75 (75.8)	82 (71.9)	0.54
Age (years)	69 (61–72)	69 (63–72)	0.96
BMI (kg/m^2)	24.0 ± 3.4	24.6 ± 3.7	0.27
Blood pressure (mmHg)			
Systolic	134.0 ± 19.5	130.5 ± 16.2	0.15
Diastolic	75.1 ± 10.3	74.6 ± 10.3	0.74
Heart rate (beats per minute)	58.7 ± 9.7	61.6 ± 10.1	0.03
Risk factors (%)			
Hypertension	81 (81.8)	90 (78.9)	0.61
Diabetes	34 (34.3)	40 (35.1)	>0.99
Current smoker	13 (13.1)	21 (18.4)	0.35
Family history of CAD	5 (5.1)	11 (9.6)	0.30
History of CAD (%)			
Angiographic CAD	1 (1.0)	1 (0.9)	>0.99
Angina with documented ischemia	41 (41.4)	39 (34.2)	0.32
Myocardial infarction	57 (57.6)	74 (64.9)	0.32
Percutaneous coronary revascularization	80 (80.8)	86 (75.4)	0.41
Coronary artery bypass surgery	18 (18.2)	24 (21.1)	0.61
Medications (%)			
ACE-I/ARB	73 (73.7)	80 (70.2)	0.65
Beta blocker	65 (65.7)	67 (59.8)	0.40
Calcium channel blocker	42 (42.4)	46 (40.4)	0.78
Aspirin	99 (100)	114 (100)	
Thienopyridine	22 (22.2)	34 (29.8)	0.22
eGFR (mL/min/1.73 m^2)	70.1 ± 18.6	66.9 ± 18.9	0.09
HbA1c (%)	5.8 (5.5–6.2)	5.8 (5.5–6.1)	0.68
High-sensitive CRP (ng/mL)	381 (221.0–621.5)	376.0 (245.5–708.0)	0.20
T-C (mg/dL)	145.1 ± 17.7	144.7 ± 18.8	0.90
TG (mg/dL)	119.0 ± 45.6	118.9 ± 39.9	0.91
HDL-C (mg/dL)	50.3 ± 11.4	52.0 ± 11.7	0.28
LDL-C (mg/dL)	70.9 ± 13.8	69.0 ± 12.9	0.27
LDL-C<70 mg/dL (%)	44 (44.4)	60 (52.6)	0.27
L_RHI	0.78 ± 0.19	0.36 ± 0.12	<0.001

Values are means ± SD, %, or median (IQR).
ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; L_RHI, logarithmic reactive hyperemia index; T-C, total cholesterol; TG, triglyceride.

3.2. Survival analysis

A total of 22 events occurred during follow-up, consisting of non-fatal MI ($n = 6$), recurrent angina pectoris requiring coronary revascularization ($n = 10$), recurrent angina pectoris with proven myocardial ischemia ($n = 2$), and death from coronary heart disease ($n = 4$). CAE occurred in 4 (4.0%) patients in the L_RHI ≥ 0.54 group and 18 (15.8%) patients in the L_RHI < 0.54 group ($P = 0.006$). The Kaplan–Meier curve is shown in Fig. 1, and the rate of CAE was higher in the L_RHI < 0.54 group (log-rank test, $P = 0.007$). The mean L_RHI of the event group and non-event group were 0.41 and 0.57, respectively ($P = 0.007$).

Cox regression analysis was performed for this endpoint, and L_RHI was an independent predictor of future CAE on univariate analysis (HR: 0.80; 95% CI: 0.67–0.96; $P = 0.014$), and even after adjusting for FRF (HR: 0.81; 95% CI: 0.67–0.97; $P = 0.02$). We also adjusted predictive ability of L_RHI by both FRF and eGFR as continuous variables, but L_RHI remained an independent predictor of future CAE (HR: 0.79; 95% CI: 0.66–0.95; $P = 0.012$).

ROC analysis was performed for the logistic regression models of only FRF, FRF + eGFR, and FRF + eGFR + L_RHI, and the AUC were compared (Fig. 2). The results of ROC analysis indicated that AUC

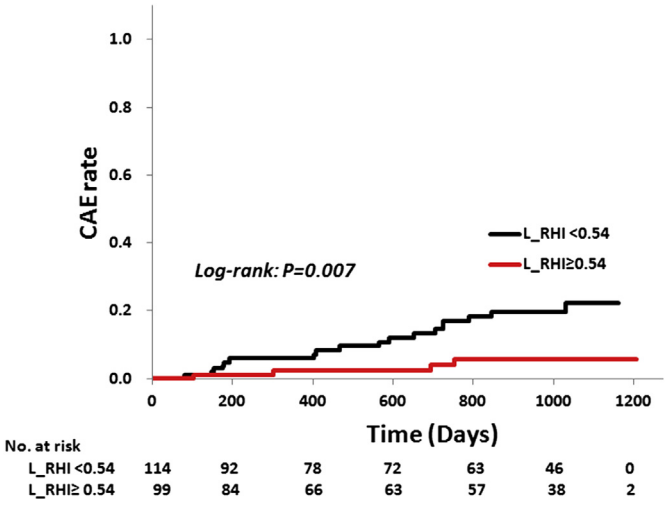

Fig. 1. Kaplan–Meier Survival Curves of CAD patients with L_RHI ≥ 0.54 and L_RHI < 0.54. Cumulative probabilities of CAE in CAD patients with L_RHI ≥ 0.54 (black line) and L_RHI < 0.54 (red line). The rate of CAE was significantly lower in the L_RHI ≥ 0.54 group (log-rank test).

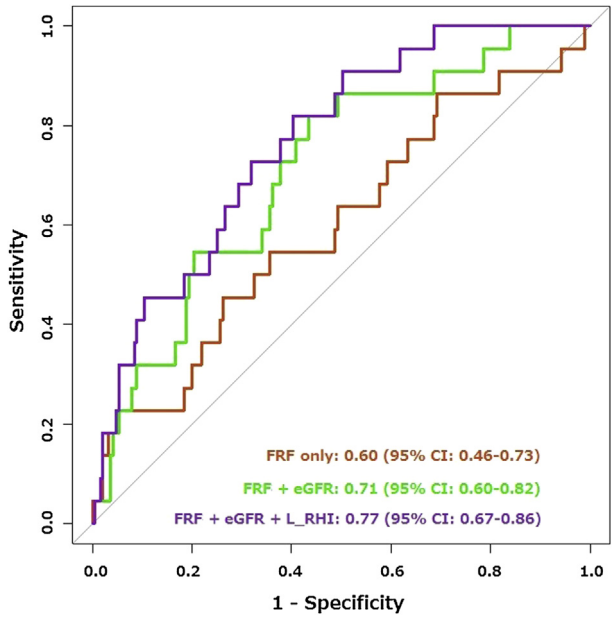

Fig. 2. Receiver-operating characteristic curves of FRF only, FRF + eGFR, and FRF + eGFR + L_RHI for CV events. AUC of FRF only, FRF + eGFR, and FRF + eGFR + L_RHI were 0.60 and 0.71, and 0.77, respectively.

was 0.60 (95% CI: 0.46–0.73) for only FRF and did not reach statistical significance. However, AUC increased to 0.71 (95% CI: 0.60–0.82) and was statistically significant after adding eGFR to FRF. Moreover, AUC increased to 0.77 (95% CI: 0.67–0.86) with combination of FRF, eGFR, and L_RHI. Although the difference in AUC was significant between FRF only and FRF + eGFR + L_RHI, the increases in AUC with addition of eGFR to FRF only and L_RHI to FRF + eGFR models did not reach significance ($P = 0.165$ and 0.145, respectively). However, calculated NRI were significant not only between FRF only and FRF + eGFR, but also between FRF + eGFR (0.63) and FRF + eGFR + L_RHI (0.79) (Table 2).

4. Discussion

The results of the present study indicated that patients with MiD defined by L_RHI have poorer prognosis compared to non-MiD patients. MiD was an independent predictor of prognosis even after adjusting for traditional risk factors, which were represented by FRF. In ROC curve analysis, FRF alone failed to predict future secondary CAE in patients with CAD treated with statin. However, adding L_RHI measurement to FRF in the logistic regression model significantly improved the predictive ability for future CAE. To our knowledge, this is the first study to demonstrate the prognostic implications of MiD measured by PAT in patients with CAD treated with statins.

Table 2
Statistics for model improvement with the addition of eGFR and L_RHI.

Models	FRF only	FRF + eGFR
FRF + eGFR	$AUC_{difference}$: $P = 0.165$ cNRI: 0.63 (0.21–1.06), $P = 0.003$ IDI: 0.04 (0.005–0.075) $P = 0.03$	
FRF + eGFR + L_RHI	$AUC_{difference}$: $P = 0.033$ cNRI: 0.79 (0.40–1.19), $P < 0.001$ IDI: 0.078 (0.034–0.123) $P < 0.001$	$AUC_{difference}$: $P = 0.145$ cNRI: 0.57 (0.15–0.98), $P = 0.007$ IDI: 0.04 (0.014–0.063) $P = 0.002$

AUC, area under the curve; cNRI, continuous net reclassification improvement; eGFR, estimated glomerular filtration rate; FRF, Framingham risk factors; IDI, integrated discrimination improvement; L_RHI, log-transformed reactive hyperemia index.

The rate of adverse CV events is high even after treatment with medication. The results of multicenter randomized trials in large cohorts of CAD patient have shown that the subsequent CV event rate is around 20%–30% even with optimized medical therapy [5,29,30]. In the COURAGE trial, the incident rates of composite outcome, including cardiac death, myocardial infarction, and acute coronary syndrome, over a follow-up period of 4.6 years were 22.6% in the optimal medical therapy group and 23.5% in the percutaneous coronary intervention plus optimal medical therapy group [29]. Traditional CV risk factors identified in the Framingham study have been used to estimate the future CV event rate as Framingham risk score in primary prevention [31]. However, there is no robust evident prediction model for estimating secondary CV events in pharmacologically treated CAD patients. Some previous studies indicated that traditional risk factors were inversely related to poorer prognosis in CAD patients [32,33]. These results support our observations that traditional risk factors are not good means of predicting future CV events.

Although some studies demonstrated the prognostic implications of ED in CAD patients [11,34,35], almost all of these studies assessed ED using FMD as conduit macrovascular dysfunction, and little is known about MiD as a prognostic factor.

In the Firefighters and Their Endothelium (FATE) study, hyperemic velocity (an indicator of MiD) predicted future CV events even after adjusting for FRF, whereas FMD did not [36]. Furthermore, adding MiD to Framingham risk score showed significant improvement of risk reclassification. In another study, the prognostic implications of FMD and MiD were evaluated in a community-based cohort of 1016 subjects, and only MiD but not FMD showed incremental prognostic implications to Framingham risk score [37]. Similar results were reported in a study evaluating MiD using Endo-PAT. Recently, Rubinshtein et al. reported that ED was an independent predictor of future adverse CV events in intermediate risk patients according to Framingham risk score without a history of coronary artery disease [17]. Although these studies suggested prognostic implications of MiD, they included only non-CAD patients. The present study is the first to demonstrate the prognostic significance of MiD in established CAD patients even after adjusting for known risk factors of substantial CV events. As traditional risk factors account for only half of all CV events [38], MiD may be a promising predictor of residual risk for future CV events.

It seems clear that LDL-C is one of the most powerful surrogate markers for the effects of pharmacological and non-pharmacological therapy in current strategies for preventing CV events. However, many studies have shown that MiD measured by Endo-PAT is reversible by both pharmacological and non-pharmacological treatments [39–41], which suggests that MiD *per se* may be a therapeutic target for reducing residual risk even in CAD patients successfully treated with statins. Thus, improving MiD (if present) by pharmacological or non-pharmacological intervention after achieving optimal LDL-C level by statin treatment may be a promising strategy for reducing residual risk in CAD patients. However, this speculation must be examined in future randomized clinical trials.

4.1. Limitations

This study had some limitations. First, this study was based on a small number of patients in a single center, with a small number of adverse events and short follow-up period. Second, we excluded patients aged ≥75 years old because FRF was derived from the

cohort below this age. Therefore, it remains unclear whether our results are applicable for elderly patients. Fourth, we did not adjust our model according to other emerging new biomarkers of atherosclerosis. Fifth, we did not change the target LDL-C value for patients at high risk. In the current guidelines for secondary prevention of CAD, aggressive LDL-C lowering therapy (<70 mg/dL) is thought to be "reasonable" as Class IIa, level of evidence B. However, this strategy remains controversial and was not adopted in the present study.

5. Conclusions

MiD is an independent predictor of future secondary CV events in patients with CAD in whom LDL-C has been treated successfully with statin, while FRF is not. As there is marked residual risk even after treating atherosclerotic risk factors, MiD measured by PAT may be useful for future risk stratification of secondary CV events in CAD patients.

Conflict of interest

None declared.

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