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Digital Assessment of Endothelial Function and Ischemic Heart Disease in Women

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Objectives We investigated the utility of digital reactive hyperemia peripheral arterial tonometry (RH-PAT) in predicting ischemic heart disease (IHD), including obstructive coronary artery disease (CAD) and nonobstructive coronary artery disease (NOCAD), in women.

Background IHD is the leading cause of mortality, and its pathogenesis is diverse in women. Fingertip RH-PAT is a new device that provides noninvasive, automatic, and quantitative evaluation of endothelial dysfunction.

Methods RH-PAT was measured using Endo-PAT2000 (Itamar Medical, Caesarea, Israel) before cardiac catheterization in 140 stable women scheduled for hospitalization to examine chest pain. NOCAD was diagnosed by angiography with measurement of coronary blood flow and cardiac lactate production during intracoronary acetylcholine provocation test and cardiac scintigraphy with stress tests.

Results Sixty-eight women (49%) had obstructive CAD and 42 women (30%) had NOCAD. RH-PAT indexes were significantly attenuated in both obstructive CAD and NOCAD as compared with non-IHD ($n = 30$) (obstructive CAD: median 1.57, interquartile range [IQR] 1.42 to 1.76; NOCAD: median 1.58, IQR 1.41 to 1.78; non-IHD: median 2.15, IQR 1.85 to 2.48, $p < 0.001$). By multivariate logistic regression analysis, only RH-PAT index was significantly associated with IHD, including obstructive CAD and NOCAD (odds ratio 0.51; 95% confidence interval: 0.38 to 0.68; $p < 0.001$). In receiver-operating characteristic analysis, RH-PAT index was a significant predictor of IHD (area under the curve 0.86; $p < 0.001$). Furthermore, only RH-PAT was useful for the prediction of NOCAD after excluding obstructive CAD (area under the curve 0.85; $p < 0.001$; RH-PAT index of <1.82 had 81% sensitivity and 80% specificity).

Conclusions RH-PAT indexes were significantly attenuated in women with IHD. Digital RH-PAT can predict patients with IHD, especially NOCAD before angiography. RH-PAT is potentially useful for identifying high-risk women for IHD. (Endothelial Dysfunction and Coronary Artery Spasm; NCT00619294) (J Am Coll Cardiol 2010;55:1688–96)

Coronary artery disease (CAD) is the leading cause of mortality in post-menopausal women (1). Women with clinical features of myocardial ischemia remain a clinical challenge due to the diverse pathogenic mechanisms of ischemic heart diseases (IHD) in women. The WISE (Women's Ischemia Syndrome Evaluation) study found no significant coronary artery stenoses (i.e., <50% stenosis) in any major coronary artery in 69% of women suspected of having IHD (2). Nonobstructive coronary artery disease (NOCAD) also presents a high risk for women with myocardial ischemia (3–5).

See page 1697

Thus, cardiovascular prognosis of women with NOCAD is not benign, and there is a need for effective strategies for the identification and treatment of these patients.

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The pathogenesis of NOCAD is unclear at present, but it could be due to physiological abnormality in coronary circulation, coronary spastic angina, coronary microvascular spasm, microcirculatory insufficiency, or diffuse arteriosclerosis. The assessment of NOCAD is not yet established enough. Coronary spastic angina can be diagnosed only by the acetylcholine-provocation test during coronary angiography (CAG) (6), and microvascular coronary spasm can be diagnosed by measurements of coronary blood flow and myocardial lactate production during acetylcholine-provocation test (7). Abnormal residual function of the oxygen supply due to microcirculatory insufficiency and diffuse arteriosclerosis can be evaluated by the measurement of coronary blood flow during adenosine-provocation and stress myocardial scintigraphy (8,9). Because plural complicated vascular function tests are necessary, NOCAD is not fully diagnosed definitely in the routine clinical practice.

Vascular endothelial dysfunction is found from the early phase of arteriosclerosis to the advanced atheroma resulting in obstructive CAD (10). Furthermore, regarding NOCAD, not only coronary spastic angina, but also microvascular spasm and microcirculatory insufficiency have been shown to be associated with coronary endothelial dysfunction (7,11,12), thus it could be possible to identify all these patients with IHD by physiological examination and evaluating endothelial dysfunction.

Endothelial dysfunction in peripheral arteries is assessed by forearm flow-mediated vasodilation (13). However, the results of forearm flow-mediated vasodilation can vary due to technical problems encountered during measurement, and thus forearm flow-mediated vasodilation is not standardized among institutions (14). Kuvin et al. (15) described a new method to evaluate endothelial dysfunction called reactive hyperemia peripheral arterial tonometry (RH-PAT). It is a noninvasive, automatic, and quantitative clinical test for digital measurement of hyperemic response. Using this test, the Framingham Heart Study reported that RH-PAT indexes correlated inversely with various cardiovascular risk factors (16), indicating the practical usefulness of RH-PAT test.

We hypothesized that endothelial function measured by fingertip RH-PAT is impaired in patients with IHD, including NOCAD, and that the RH-PAT indexes can predict the presence of IHD, especially NOCAD, in women complaining of chest pain.

Methods

Study population and protocol. One hundred fifty-eight consecutive stable post-menopausal women with angina-like chest pain who were referred and scheduled for hospitalization at Kumamoto University Hospital between August 2006 and April 2009 for CAG were registered. We excluded 17 patients for the following reasons: severe aortic valve regurgitation or stenosis (n = 2), hypertrophic cardiomyopathy (n = 6), uncontrolled hypertension (n = 1), severe collagen disease (n = 6), and neuromuscular disease (n = 2).

Abbreviations and Acronyms

ACh-CBF = acetylcholine-induced increase in coronary blood flow ratio

Ad-CFR = adenosine-induced coronary flow reserve

AUC = area under the curve

CAD = coronary artery disease

CAG = coronary angiography

IHD = ischemic heart disease

NOCAD = nonobstructive coronary artery disease

RH-PAT = reactive hyperemia peripheral arterial tonometry

ROC = receiver-operating characteristic

SPECT = single-photon emission computed tomography

RH-PAT was monitored using Endo-PAT2000 (Itamar Medical, Caesarea, Israel) on the day before CAG. CAG and RH-PAT studies were performed in the fasting state in the early morning after >3-day discontinuation of vasodilators. Cardiologists blinded to the results of the RH-PAT performed cardiac catheterization. On the basis of the results of CAG and after excluding 1 patient for incomplete cardiac catheterization data, patients with atherosclerotic organic coronary artery stenosis (≥50%) were diagnosed as having obstructive CAD, whereas those with no significant epicardial coronary artery stenosis (<50%) on CAG (NOCAD suspected) underwent acetylcholine-provocation test. Patients who showed myocardial ischemia during acetylcholine-provocation test were divided into 2 groups: patients with epicardial coronary spasm and patients with microvascular spasm, those with coronary blood flow decrease by acetylcholine provocation without epicardial coronary spasm. Patients with negative results in the acetylcholine-provocation test were further examined by adenosine-induced coronary flow reserve and stress thallium-201 single-photon emission computed tomography (SPECT). Patients with abnormal results of these tests were diagnosed as having microcirculatory insufficiency, and patients who had no abnormal results were defined as the nonischemic heart disease group (non-IHD group) (Fig. 1). The Reynolds Risk Score was calculated for each patient as described previously (17).

Risk factors for cardiovascular disease were defined as current smoking (smoking within 1 year), hypertension (>140/90 mm Hg or taking antihypertensive medication), dyslipidemia (high-density lipoprotein cholesterol <40 mg/dl, low-density lipoprotein cholesterol ≥140 mg/dl, or triglycerides ≥150 mg/dl or taking medication for dyslipidemia), and diabetes mellitus (symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dl, fasting plasma glucose concentration ≥126 mg/dl, 2-h plasma glucose concentration ≥200 mg/dl during 75-g oral glucose tolerance test, or taking medication for diabetes mellitus).

Written informed consent was obtained from each patient before participation. The study was conducted in accordance with the guidelines approved by the ethics committee of our institution.

RH-PAT. The principle of RH-PAT has been described previously (18). Briefly, a blood pressure cuff was placed on 1 upper arm, while the contralateral arm served as a control.

JACC Vol. 55, No. 16, 2010
April 20, 2010:1688–96

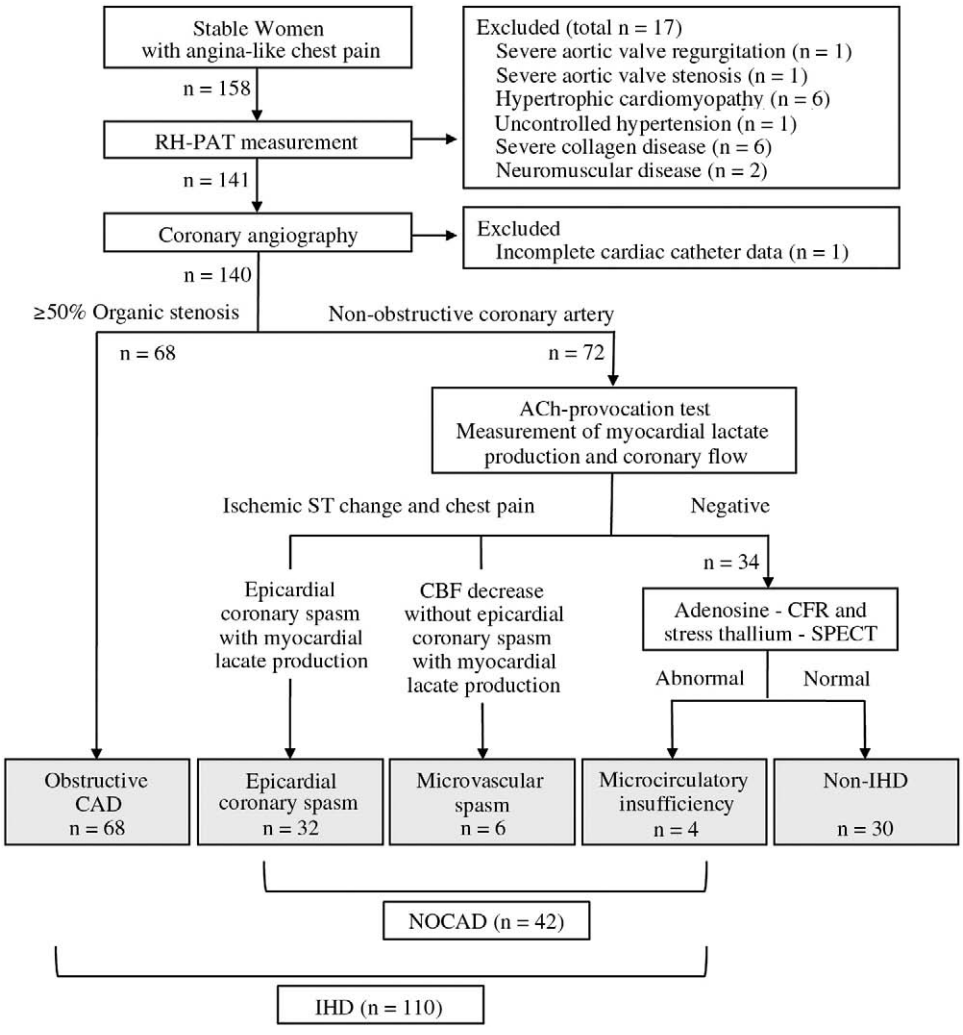

Figure 1 **Flow Chart of Patient Enrollment Used in the Present Study**

ACh = acetylcholine; CAD = coronary artery disease; CBF = coronary blood flow; CFR = coronary flow reserve; IHD = ischemic heart disease; NOCAD = nonobstructive coronary artery disease; RH-PAT = reactive hyperemia peripheral arterial tonometry; SPECT = single-photon emission computed tomography.

PAT probes were placed on 1 finger of each hand. After a 5-min equilibration period, the cuff was inflated to 60 mm Hg above the systolic pressure or 200 mm Hg for 5 min and then deflated to induce reactive hyperemia.

The RH-PAT data were digitally analyzed online (Endo-PAT2000 software version 3.0.4). The RH-PAT index reflects the extent of reactive hyperemia and was calculated as the ratio of the average amplitude of PAT signal over 1 min starting 1.5 min after cuff deflation (control arm, A; occluded arm, C) divided by the average amplitude of PAT signal of a 2.5-min time period before cuff inflation (baseline) (control arm, B; occluded arm, D). Thus RH-PAT index = (C/D)/(A/B) × baseline correction.

Cardiac catheterization. After baseline CAG, patients without obstructive CAD underwent the acetylcholine-provocation test. A 6-F catheter was placed in the coronary sinus to sample blood for measurement of lactate concentrations. A 0.014-inch Flow-Wire Doppler flow probe (REF 1400J-FloWire, Volcano, San Diego, California) was inserted into the proximal side of the left anterior descending coronary artery, and acetylcholine was injected into the left coronary artery as described previously (6,19). Briefly, incremental doses (20, 50, and 100 μg) of acetylcholine were injected into the left coronary artery, and angiography was performed 1 min after each injection. Then, 50 μg of acetylcholine was injected into the right coronary artery, followed by angiography. At baseline and acetylcholine-induced coronary spasm or 1 min after the maximum dose of acetylcholine was injected into the left coronary artery, paired samples of 2 ml of blood were collected simultaneously from the main trunk of the left coronary artery and coronary sinus to measure the myocardial lactate extraction rate, as reported previously (20).

Using Flow-Wire, we measured changes in coronary blood flow in response to low-dose acetylcholine (20 μg

injected into the left coronary artery) to determine coronary endothelial function (21):

Acetylcholine-induced increase in coronary blood flow ratio (ACh-CBF) = acetylcholine-induced hyperemia coronary blood flow/baseline coronary blood flow, where coronary flow = π(average peak velocity/2)(vessel diameter/2)^2

At the end of the acetylcholine test, nitroglycerin was injected into each coronary artery when acetylcholine-induced coronary spasm did not resolve spontaneously within 5 min, angina chest pain persisted for more than 2 min, or upon the development of ischemia-related hemodynamic instability. After intracoronary nitroglycerin, adenosine (150 μg/kg/min) was injected intravenously until maximal hyperemia was achieved. Then coronary flow reserve was calculated using the following equation:

Adenosine-induced coronary flow reserve (Ad-CFR) = adenosine-induced hypermia coronary blood flow/baseline coronary blood flow

Coronary spasm was defined as >90% lumen narrowing of the epicardial coronary artery associated with chest pain, transient ST-segment depression (>0.1 mV) or elevation (>0.1 mV) from baseline levels occurring at 60 to 80 ms after the J point, and lactate production in the coronary circulation. Microvascular spasm was defined as decreased coronary blood flow during acetylcholine provocation associated with chest pain, transient ST-segment depression or elevation, and myocardial lactate production without epicardial coronary spasm. In a subject without positive results in acetylcholine-provocation test, we defined the patients who showed Ad-CFR <3.0 and myocardial perfusion abnormality in adenosine-provocation thallium SPECT as having microcirculatory insufficiency.

Statistical analysis. The results of normally distributed continuous variables were expressed as mean (SD), whereas those with skewed distribution were expressed as the median value (interquartile range [IQR]). Continuous variables were analyzed by the unpaired *t* test and Mann-Whitney *U* test, as appropriate. Categorical variables were presented by percent, and intergroup comparisons were analyzed by chi-square test (and Fisher exact test). Pearson's correlation coefficient was used for evaluation of possible association between ln[RH-PAT index] and ln[ACh-CBF]; ln[RH-PAT index] and ln[Ad-CFR]. Associations between the presence of IHD or NOCAD and other significant parameters in simple logistic analysis were analyzed by multiple logistic regression analysis with the forced entry method, and the Hosmer-Lemeshow

Table 1 Baseline Clinical Characteristics of 140 Women With Chest Pain

	Non-IHD	Obstructive CAD	NOCAD
n	30	68	42
Age (yrs)	63 (10)	73 (9)*	64 (10)†
Body mass index (kg/m^2)	23 (3)	24 (5)	24 (4)
Hypertension (%)	53	84*	62†
Diabetes (%)	20	50*	29†
Dyslipidemia (%)	67	91*	64†
Current smoking (%)	3	7	14
Family history of CAD (%)	3	19	21*
Systolic blood pressure (mm Hg)	124 (17)	131 (20)	130 (17)
Diastolic blood pressure (mm Hg)	77 (13)	72 (12)	78 (12)†
Fasting blood glucose (mg/dl)	89 [85–94]	97 [88–115]	92 [86–105]
Hemoglobin A1c (%)	5.5 (0.6)	6.1 (1.2)*	5.6 (1.0)†
HOMA-IR	1.0 [0.8–1.7]	1.4 [1.0–2.5]*	1.4 [0.8–1.8]
Total/high-density lipoprotein cholesterol ratio	3.5 (1.2)	3.5 (1.1)	3.3 (0.9)
Triglycerides (mg/dl)	92 [65–123]	101 [76–136]	99 [80–139]
Left ventricular ejection fraction (%)	66 (7)	65 (7)	66 (5)
B-type natriuretic peptide (pg/ml)	18 [10–26]	48 [21–120]*	20 [12–30]†
High-sensitivity C-reactive protein (mg/l)	0.5 [0.3–1.0]	1.2 [0.5–2.8]*	0.5 [0.3–0.9]†
Reynolds Risk Score (%)	1.3 [0.5–3.5]	5.6 [2.6–10.2]*	1.8 [1.0–4.0]†
Mild-to-moderate coronary atherosclerosis (%)	33	—	43
Aspirin (%)	27	90*	46†
HMG-CoA reductase inhibitors	33	79*	38†
Calcium-channel blockers (%)	46	71*	49†
ACE-I or ARB (%)	27	62*	29†
Beta blockers (%)	3	46*	0†

Data are mean (SD), median [25th to 75th percentile range], or %. Mild-to-moderate coronary atherosclerosis: >25% but <50% coronary stenosis. *Significantly different from non-IHD. †Significantly different from obstructive CAD.

ACE-I = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; CAD = coronary artery disease; HMG-CoA = 3-hydroxy-3-methylglutanyl coenzyme A; HOMA-IR = homeostasis model assessment insulin resistance; IHD = ischemic heart disease; NOCAD = nonobstructive coronary artery disease.

goodness-of-fit statistic was calculated. Receiver-operating characteristics (ROC) curves were constructed for Reynolds Risk Score and RH-PAT index. The area under the curve (AUC), sensitivity, and specificity were calculated to predict the ability to detect subjects with obstructive CAD, NOCAD, and IHD, with an AUC value of 0.50 indicating no accuracy and a value of 1.00 indicating maximal accuracy. AUC values are compared using an algorithm suggested by DeLong et al. (22,23). We defined optimal thresholds of RH-PAT index by maximizing the sum of sensitivity and specificity (24). A p value of <0.05 denoted statistical significance; all tests were 2-tailed. Statistical analyses were performed using SPSS version 17.0J (SPSS Inc., Tokyo, Japan) and STATA version 10 (Stata Corp., College Station, Texas).

Results

Clinical characteristics of stable women with chest pain. CAG indicated that 68 patients (49%) had obstructive CAD (30 patients had single-vessel disease, 38 patients had

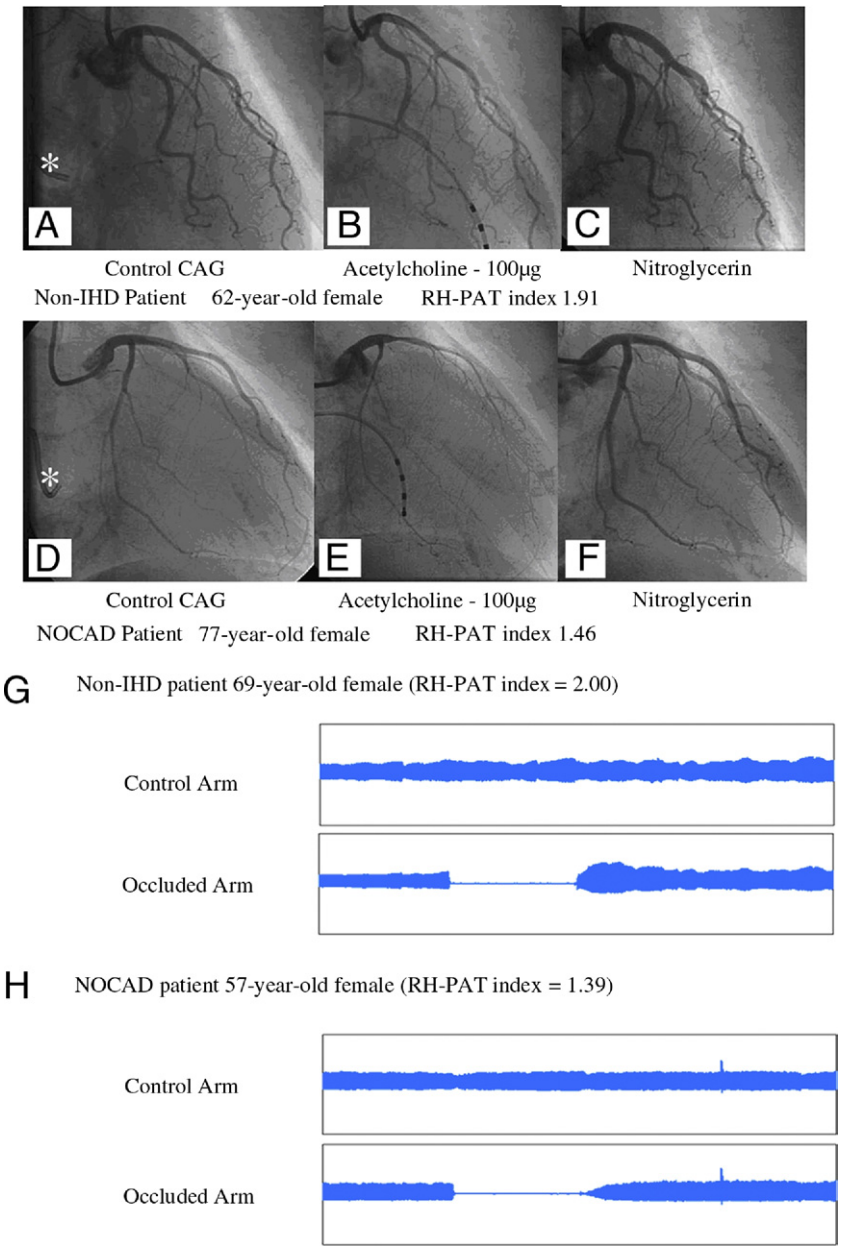

Figure 2 Acetylcholine-Provocation Test

(A to C) Non-IHD group. **(D to F)** Epicardial coronary spasm group. **(E)** Coronary artery spasm after intracoronary injection of acetylcholine. *Sampling catheter in the coronary sinus. RH-PAT results of representative **(G)** non-IHD and **(H)** NOCAD cases. Abbreviations as in Figure 1.

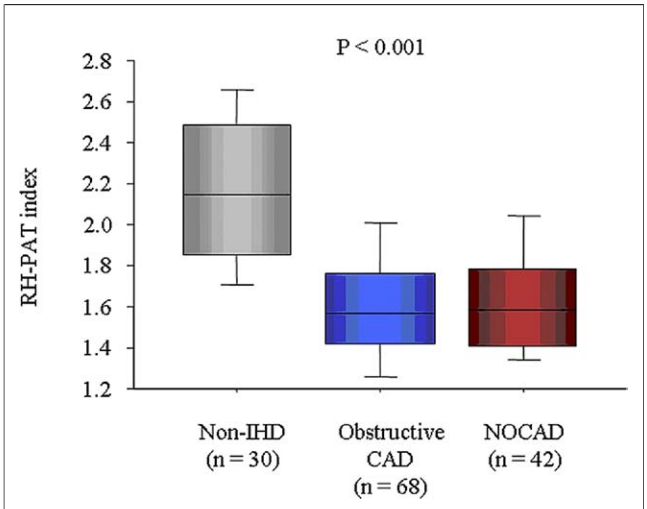

Figure 3 RH-PAT Index and IHD

Box-and-whisker plots of RH-PAT indexes. In these plots, **lines within the boxes** represent median values; the **upper and lower lines of the boxes** represent 25th and 75th percentiles, respectively; and the **upper and lower bars outside the boxes** represent the 90th and 10th percentiles, respectively. Abbreviations as in Figure 1.

multivessel disease), and 72 patients (51%) were suspected to have NOCAD (44 patients had no stenosis, 28 patients had mild-to-moderate coronary atherosclerosis [25% to 50% coronary artery stenosis]) (Table 1). Among the latter group (n = 72; NOCAD suspected), coronary spasm was induced in 32 patients (15 with ST-segment elevation, 17 with ST-segment depression) and microvascular spasm was induced in 6 patients (1 with ST-segment elevation, 5 with ST-segment depression). Among another 34 patients without positive results in acetylcholine-provocation test, 4 patients were diagnosed as having microcirculatory insufficiency, and 30 patients had no evidence of myocardial ischemia (non-IHD group) (Fig. 1).

Patients in the obstructive CAD group were significantly older, had a higher prevalence of conventional cardiovascular risk factors, higher homeostasis model assessment insulin resistance, B-type natriuretic peptide, high-sensitivity C-reactive protein, and Reynolds Risk Score. In contrast, patients in the NOCAD group were not significantly different from those in the non-IHD group, except for family history of CAD (Table 1).

RH-PAT indexes and IHD including obstructive CAD and NOCAD. Figure 2 shows representative records of RH-PAT signals and CAG in patients with non-IHD and NOCAD. RH-PAT indexes were lower in patients with obstructive CAD and NOCAD than in non-IHD patients (non-IHD: median 2.15 [IQR 1.85 to 2.48]; obstructive-CAD: median 1.57 [IQR 1.42 to 1.76]; NOCAD: median 1.58 [IQR 1.41 to 1.78]; $p < 0.001$) (Fig. 3). There was no significant difference in RH-PAT indexes between NOCAD and obstructive CAD groups.

RH-PAT indexes and ACh-CBF among patients with NOCAD. We were successful in obtaining complete coronary flow data from 51 patients without obstructive CAD. ACh-CBF was attenuated in patients with NOCAD relative to the non-IHD group (NOCAD: median 1.52 [IQR 1.23 to 1.90]; non-IHD: median 2.12 [IQR 1.82 to 2.42]; $p < 0.001$). However, Ad-CFR was comparable in the 2 groups (NOCAD: median 3.25 [IQR 3.01 to 3.58]; non-IHD: median 3.09 [IQR 2.78 to 3.60]; $p = 0.36$). There was a significant correlation between ln[RH-PAT index] and ln[ACh-CBF] ($r = 0.52$; $p < 0.001$), but not Ad-CFR ($r = 0.21$; $p = 0.12$).

RH-PAT indexes and presence of IHD. Simple logistic regression analysis demonstrated that age, B-type natriuretic peptide, Reynolds Risk Score, and RH-PAT index significantly predicted the presence of IHD in women complaining of chest pain (Table 2). Multiple logistic regression analysis identified only RH-PAT index as the

Table 2 Logistic Regression Analysis for the Presence of Ischemic Heart Disease in Female Patients Complaining of Chest Pain

	Simple Regression			Multiple Regression		
Variable	OR	95% CI	p Value	OR	95% CI	p Value
Age (per yr)	1.06	1.02–1.10	0.004	0.99	0.92–1.07	0.81
Body mass index (per kg/m^2)	1.06	0.95–1.18	0.28			
Current smoking (yes)	3.22	0.40–26.0	0.27			
Systolic blood pressure (per mm Hg)	1.02	1.00–1.05	0.06			
Diastolic blood pressure (per mm Hg)	0.98	0.95–1.01	0.24			
Ln[Fasting blood glucose] (per 0.1)	1.23	0.96–1.57	0.10			
Total/High-density lipoprotein cholesterol (per 1)	0.95	0.65–1.42	0.81			
Ln[Triglycerides] (per 0.1)	1.03	0.94–1.12	0.54			
Ln[B-type natriuretic peptide] (per 0.1)	1.05	1.01–1.09	0.01	1.03	0.98–1.09	0.21
Ln[High-sensitivity C-reactive protein] (per 0.1)	1.01	0.99–1.03	0.31			
Left ventricular ejection fraction (per %)	0.98	0.92–1.05	0.60			
Ln[Reynolds Risk Score] (per 0.1)	1.07	1.04–1.11	<0.001	1.06	1.00–1.13	0.05
Ln[RH-PAT index] (per 0.1)	0.50	0.38–0.65	<0.001	0.51	0.38–0.68	<0.001

CI = confidence interval; OR = odds ratio; RH-PAT = reactive hyperemia peripheral arterial tonometry; other abbreviations as in Table 1.

JACC Vol. 55, No. 16, 2010
April 20, 2010:1688–96

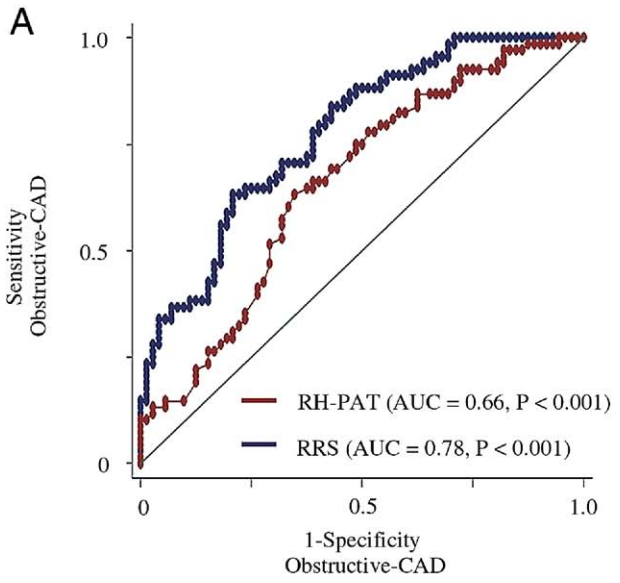

Figure 4 ROC Curves to Identify Obstructive CAD and IHD

Receiver-operating characteristic (ROC) curves for the Reynolds Risk Score (RRS) and RH-PAT index to identify patients with obstructive CAD and patients with IHD in stable women complaining of chest pain. AUC = area under the curve; other abbreviations as in Figure 1.

significant predictor of IHD, including obstructive CAD and NOCAD (odds ratio: 0.51; 95% confidence interval [CI]: 0.38 to 0.68; p < 0.001) (Table 2). Hosmer-Lemeshow goodness of fit chi-square and p are 12.1 and 0.15, respectively. Furthermore, we found that only RH-PAT index was also a significant factor for predicting NOCAD in women complaining of chest pain by multiple logistic regression analysis (odds ratio: 0.78; 95% CI: 0.63 to 0.96; p = 0.02). Hosmer-Lemeshow goodness of fit chi-square is 11.4 and the p value is 0.18.

ROC analysis for Reynolds Risk Score and RH-PAT index to predict patients with obstructive CAD and IHD in women complaining of chest pain. ROC curves were constructed to assess the ability of Reynolds Risk Score and RH-PAT index to predict obstructive CAD and IHD. The AUC for detection of obstructive CAD was 0.78 (95% CI: 0.70 to 0.85; p < 0.001) of Reynolds Risk Score and 0.66 (95% CI: 0.57 to 0.75; p < 0.001) of RH-PAT index (Fig. 4A). The AUC for detection of IHD, including obstructive CAD and NOCAD, was 0.73 (95% CI: 0.63 to 0.83; p < 0.001) of Reynolds Risk Score and 0.86 (95% CI: 0.79 to 0.93; p < 0.001) of RH-PAT index (Fig. 4B). There was no significant (borderline) difference between AUCs of RH-PAT index and Reynolds Risk Score for prediction of obstructive CAD (p = 0.06) or IHD (p = 0.05). Reynolds Risk Score was comprehensively useful for prediction of obstructive CAD, and RH-PAT index was particularly useful for prediction of overall IHD. Using an RH-PAT index cutoff value of <1.82, the sensitivity and specificity for the detection of IHD were 80% and 80%, respectively.

RH-PAT index has high ability to predict NOCAD, particularly in patients without obstructive CAD. We can diagnose obstructive CAD simply on anatomical examination such as CAG or multidetector computed tomographic CAG. Therefore, we examined whether RH-PAT was useful for a prediction of NOCAD after excluding the presence of obstructive CAD. We found that only the RH-PAT index was a significantly associated factor of NOCAD in women without obstructive CAD by simple logistic regression analysis (odds ratio 0.49; 95% CI: 0.35 to

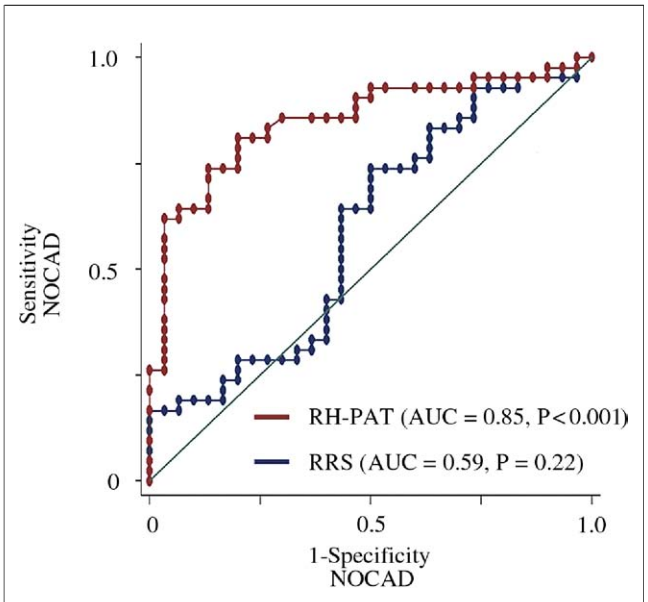

Figure 5 ROC Curves to Identify NOCAD

Receiver-operating characteristic (ROC) curves for Reynolds Risk Score (RRS) and RH-PAT index to identify patients with NOCAD among women without obstructive CAD. Abbreviations as in Figures 1 and 4.

0.69; $p < 0.001$). Among women without obstructive CAD, Reynolds Risk Score could not predict NOCAD (AUC 0.59; 95% CI: 0.45 to 0.73; $p = 0.22$), but RH-PAT index could significantly predict NOCAD (AUC 0.85; 95% CI: 0.76 to 0.94; $p < 0.001$) (Fig. 5). The AUC of RH-PAT index for prediction of NOCAD was significantly higher compared with Reynolds Risk Score ($p = 0.003$). The cutoff value of RH-PAT index of <1.82 had sensitivity of 81% and specificity 80% for prediction of NOCAD in patients without obstructive CAD.

Discussion

The present study of stable women complaining of angina-like symptoms showed significant impairment of digitally recorded endothelial function in patients with IHD, especially NOCAD, and such impairment was equivalent to that seen in patients with organic obstructive CAD. Reynolds Risk Score and RH-PAT index significantly predicted IHD. RH-PAT index was particularly superior in predicting NOCAD. In other words, noninvasive measurement of RH-PAT can predict patients with IHD, including NOCAD, before angiography. Thus, RH-PAT is potentially useful for identification of women at high risk for IHD.

Over the years, cardiovascular mortality has declined substantially, but this improvement in prognosis had been restricted to men (25,26). IHD is sometimes not diagnosed correctly in women; therefore, the prognosis of such women is worse than that of men (2). It is important that more women are diagnosed correctly with IHD and receive appropriate treatment. NOCAD is more common in women, and women have been recognized recently as a high-risk population (3–5). The underlying mechanisms of NOCAD are not fully known, though it is likely caused by a multitude of pathogenic mechanisms (3). Women with myocardial ischemia are still a clinical challenge. Obstructive CAD could be diagnosed by CAG (anatomical examination), but NOCAD cannot be simply diagnosed with anatomical tests. Although the Reynolds Risk Score predicts obstructive CAD well, it may not be useful for prediction of NOCAD in women. The design of a new and noninvasive test for the assessment of NOCAD is strongly desirable. Coronary endothelial dysfunction plays an important pathogenic role in NOCAD (7,11,12,27). The present study demonstrated that noninvasive digital assessment of peripheral endothelial function by RH-PAT significantly predicted IHD, particularly NOCAD. Thus, RH-PAT can potentially provide useful and noninvasive clinical assessment of IHD, including NOCAD, in women. We could noninvasively provide superior identification of high-risk patients for IHD with a combination of the physiological examination with RH-PAT and the anatomical examination with computed tomography.

The vascular endothelium plays a crucial role in regulation of vasomotor tone, thrombosis, and platelet adhesion (10,13), and endothelial dysfunction is a significant risk factor of future cardiovascular events (28,29). Invasive measurement of coronary vasodilator response by acetylcholine infusion is an established method for assessment of coronary endothelial function (21). On the other hand, digital RH-PAT can evaluate peripheral endothelial function, and the results are correlated with traditional and metabolic cardiovascular risk factors (15,16,18). Bonetti et al. (30) demonstrated that RH-PAT index significantly predicted coronary endothelial dysfunction. Similar to their study, we also found that RH-PAT index was correlated significantly with ACh-CBF. In addition, we also found that RH-PAT index was significantly attenuated in patients with NOCAD who were diagnosed by simultaneous measurement of coronary flow and cardiac lactate production. Measurement of RH-PAT index, which can reflect coronary endothelial function, may also have a useful predictive value for future cardiovascular events. Recently, Rubinshtein et al. (31) reported that assessment of peripheral vascular function by RH-PAT in addition to the Framingham Risk Score may be useful for identification of risk for cardiac events.

Our results showed significant impairment of RH-PAT index in women with IHD. Endothelial dysfunction could be a modifiable risk factor of future cardiovascular events and a potential clinical therapeutic target. Because RH-PAT is a noninvasive, quantitative, and repeatable test, the values of RH-PAT index could be used for evaluation of vascular condition and treatment efficacy.

Study limitation. The predictive value of RH-PAT index in NOCAD is limited to a modest number of patients and needs confirmation in larger patient populations.

Conclusions

Digital fingertip endothelial function was significantly impaired in post-menopausal women with NOCAD equivalent to those with obstructive CAD. RH-PAT noninvasively predicted the presence of IHD, especially NOCAD, before CAG. RH-PAT is a potentially useful clinical test and can effectively help to identify high-risk women with chest pain.

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