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Peripheral Reactive Hyperemia Index and Coronary Microvascular Function in Women With no Obstructive CAD

The iPOWER Study

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ABSTRACT

OBJECTIVES This study investigated whether digital reactive hyperemia index (RHI) measured by digital pulse amplitude tonometry is a sensitive indicator of coronary microvascular dysfunction (CMD).

BACKGROUND CMD is an early marker of cardiovascular disease. However, CMD is a complex diagnosis and consists of multiple abnormalities of the coronary circulation. Impaired RHI is a noninvasive measure of peripheral vascular dysfunction that can identify individuals with acetylcholine induced coronary vascular dysfunction. It is largely unknown whether there is also an association between RHI and the endothelial-independent aspect of CMD assessed as a coronary flow velocity reserve (CFVR).

METHODS We included 339 women with chest pain suggestive of angina pectoris and a diagnostic invasive coronary angiogram without significant coronary artery stenosis (<50%). CFVR was measured by transthoracic pulsed wave Doppler echocardiography during dipyridamole infusion (0.84 mg/kg). RHI was assessed by digital pulse amplitude tonometry. Participants were categorized in 3 RHI and 3 CFVR groups. We examined the association between CFVR and RHI and the distribution of cardiovascular risk factors between the CFVR and RHI groups.

RESULTS CFVR and RHI were successfully measured in 322 participants. Median CFVR was 2.3 (interquartile range: 2.0 to 2.8) and median RHI was 2.1 (interquartile range: 1.6 to 2.6). No correlation was found between CFVR and RHI (Spearman's rho = -0.067, p = 0.23), and mean RHI did not differ between CFVR categories (p = 0.39). Participants with low CFVR were significantly older and had a significantly greater burden of hypertension, whereas participants with an impaired RHI had a higher body mass index and were more likely to have diabetes and be current smokers.

CONCLUSIONS RHI does not identify individuals with CMD assessed as impaired CFVR by dipyridamole stress echocardiography in women with no obstructive coronary artery disease. The two methods are likely to identify different aspects of vascular pathology, as indicated by the different association with cardiovascular risk factors. (J Am Coll Cardiol Img 2016;9:411–7) © 2016 by the American College of Cardiology Foundation.

Impairment of vascular function is gaining interest as an independent and early predictor of developing cardiovascular disease (1). The presence of either peripheral or coronary microvascular dysfunction (CMD) is associated with cardiovascular risk factors and a poor cardiovascular prognosis (2–9). CMD is a complex diagnosis and consists of multiple abnormalities of the coronary circulation including coronary spastic angina, coronary microvascular spasm, and impaired regulation of the resistance

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CAG = coronary angiography

CFVR = coronary flow velocity reserve

CMD = coronary microvascular dysfunction

HDL = high-density lipoprotein

iPOWER = Improving Diagnosis and Treatment of Women With Angina Pectoris and Microvascular Disease study

LAD = left anterior descending artery

LDL = low-density lipoprotein

PAT = pulse amplitude tonometry

RHI = reactive hyperemia index

of the microcirculation. Moreover, the pathogenesis for these different aspects of CMD is unclear and disease mechanisms appear to be several. Accordingly, various vascular diagnostic tests are necessary for a more complete understanding of CMD (10). Despite the fact that CMD has been extensively studied, the complicated pathophysiology and many diagnostic tests make it difficult to diagnose patients in clinical practice.

Reactive hyperemia index (RHI) measured by digital pulse amplitude tonometry (PAT) is a simple method to assess vascular function peripherally. Although PAT was originally designed to measure endothelial-dependent function, it is now considered a combined measure of the endothelial and other vasodilator components (11). Studies indicate that RHI is attenuated in individuals with mainly acetylcholine-induced coronary vascular dysfunction (10,12). It is largely unknown whether there is also an association between RHI and endothelial-independent CMD assessed as coronary flow velocity reserve (CFVR). If RHI as a noninvasive, automatic vascular measure can identify some aspects of CMD, it could potentially reduce the number of invasive and noninvasive diagnostic tests necessary to diagnose CMD.

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We investigated whether peripheral vascular function measured by PAT is associated with coronary microvascular function measured by CFVR in women with angina-like chest pain and no obstructive coronary artery disease (CAD). We also examined the relation of the 2 vascular measures to cardiovascular risk factors.

METHODS

POPULATION. Participants for the iPOWER (Improving Diagnosis and Treatment of Women With Angina Pectoris and Microvascular Disease) study were recruited from the Patient Analysis & Tracking System database (Dendrite Clinical Systems, Portland, Maine). This consists of patients undergoing invasive evaluation for investigation of chest pain suggestive of angina pectoris from Eastern Denmark with approximately 3 million inhabitants. Participants were women, ages 18 to 80 years, who had no obstructive CAD at invasive coronary angiography (CAG) (stenosis <50%). Participation rate was 45%. For a thorough description of inclusion and exclusion criteria, refer to our published article of the design (13). Selection to this sub-study was random and based on time-slot availability. Each day approximately 4 participants were examined in the iPOWER study and 2 had a PAT examination before the echocardiographic CFVR examination.

EXAMINATIONS. Basic assessment included clinical and demographic data. Information regarding cardiovascular risk factors was acquired from interviews undertaken by trained health professionals. Information regarding the results of the CAG was retrieved from the Patient Analysis & Tracking System database where the degree of atherosclerosis was evaluated visually by the cardiologist performing the angiography. Blood samples were analyzed for cholesterol levels (total, low-density lipoprotein [LDL], and high-density lipoprotein [HDL] cholesterol), triglycerides, creatinine level, and glycosylated hemoglobin (HbA1C). Spot urine was analyzed for microalbuminuria.

Before examinations, participants were instructed to be abstinent from caffeine or food containing significant amounts of methylxanthine (coffee, tea, chocolate, cola, and bananas) for 24 h. Medication containing dipyridamole was paused for 48 h, long-lasting nitroglycerin, antihypertensive and anti-ischemic medication for 24 h, and short-lasting nitroglycerin 1 h before the examination. Abstinence was confirmed before commencing the examination. Measurements of vascular function by PAT were undertaken before echocardiography on the same day.

Microvascular function by PAT. Digital pulse amplitude was measured in a standardized setting (i.e., a quiet, dark, temperate environment [21°C to 24°C]) with a PAT device that comprises a pneumatic plethysmograph measuring digital pulse volume changes (EndoPAT2000, Itamar Medical, Caesarea, Israel). Patients were fasting.

Blood pressure and heart rate were recorded 3 times with 2-min intervals before the examination. The mean of the last 2 recordings was used as baseline blood pressure and heart rate. Single-use fingertip probes were placed on each index finger and inflated. Baseline pulse amplitude was measured from each fingertip for 6 min. Arterial flow was interrupted for 5 min in the nondominant arm by manually inflating a blood pressure cuff placed on the proximal forearm at an occlusion pressure of 60 mm Hg above baseline systolic blood pressure. The cuff was deflated and pulse amplitude readings were continued for 5 min. Measurements from the contra-lateral arm were used to control for changes in vascular tone.

The digital pulse amplitude was acquired continually during the examination and recorded digitally

to a laptop. Data was analyzed by a computerized algorithm (Itamar Medical), which automatically and operator-independently calculates RHI.

Echocardiographic examination. Echocardiographic examinations were performed using a GE Healthcare Vivid E9 cardiovascular ultrasound system (GE Healthcare, Horten, Norway) with a 1.3 to 4.0 MHz transducer (GE Vivid 5S probe) for the standard echocardiography and a 2.7 to 8 MHz transducer (GE Vivid 6S probe) for the CFVR examination. The participants were studied in the left lateral decubitus position. All examinations were performed in the same setting by 3 experienced echocardiographers. Images were stored for off-line analysis in software designed for echocardiographic analysis (GE EchoPac v.112; GE HealthCare, Oslo, Norway).

For the measurement of CFVR, the octave was set at 3.1/6.2 MHz and the frequency at 8 MHz for B-mode (2-dimensional [2D]). The baseline color scale was chosen according to low- or high-flow velocities, respectively, and set between 1.00 to 2.50 KHz (velocity range ± 10 to 24 cm/s). Color gain was adjusted to provide optimal 2D imaging quality. The left anterior descending artery (LAD) was visualized by color Doppler in an apical modified foreshortened 2- or 4-chamber view or in a modified short-axis view of the left ventricle. Coronary flow velocities were measured by pulsed-wave Doppler as a laminar flow towards the transducer. Probe position was adjusted to align the ultrasound beam as parallel to the LAD flow as possible. The probe was maintained in the same position during recording of 2D and pulse wave images. In case of difficulty in visualization of the LAD contrast (SonoVue, Bracco Imaging Courcouronnes, France) was used. Acquisitions of coronary flow velocities during high-dose dipyridamole infusion (0.84 mg/kg over 6 min) were obtained throughout the infusion or up to 3 min after the infusion had terminated until flow had reached peak velocity. After the examination, intravenous theophylline (maximum dose, 220 mg) was administered to relieve potential side effects to dipyridamole.

For the analysis of CFVR, diastolic peak flow velocities were measured at rest and at peak hyperemia. CFVR was calculated as the ratio between peak velocities during stress and during rest. Two experienced echocardiographers, blinded to participant data, analyzed every CFVR examination independently. If estimates differed by more than 0.2 the 2 analyzers re-analyzed the CFVR examination and reached agreement. In our previous validation study with repeated CFVR examinations in 10 young, healthy individuals by the same observer we found an intraclass correlation coefficient of 0.97 (95% confidence interval [CI]: 0.92 to 1.00) and coefficient of variation (95% CI) for repeat examinations of 7% (3% to 10%). In a sub-sample of 50 participants from the iPOWER study, CFVR readings for the 2 observers were highly reproducible (13).

All CFVR measurements were assigned a quality score from 0 to 3, and thus categorized as nonfeasible (score 0), low quality (score 1), medium quality (score 2), and high quality (score 3), based on a semiquantitative assessment.

Left ventricular ejection fraction was analyzed by an automated biplane calculation with an automated ejection fraction tool (GE EchoPac v.112, Norway). Left ventricular wall dimensions and left ventricle mass index were analyzed according to guidelines (14).

STATISTICAL ANALYSES. Spearman's rank correlation coefficient was used to examine whether CFVR and RHI were associated. Participants were stratified using established cutoff points: RHI cutoff points were 1.67 and 2.0, and CFVR cutoff points were 2.0 and 2.5 (15). Trend tests by logistic or linear regression analysis for dichotomous and continuous variables, respectively, were used to evaluate the distribution of variables between the 3 CFVR and RHI groups. For outcome parameters with non-Gaussian distribution, natural logarithmic transformation was performed.

CIs refer to 95% intervals. A 2-sided p value <0.05 was considered significant. All analyses were performed using STATA/IC version 13.1 (StataCorp LP, College Station, Texas).

ETHICS. This study was performed in accordance with the Helsinki Declaration and was approved by the Danish Regional Committee on Biomedical Research Ethics (H-3-2012-005). All participants gave written informed consent after receiving oral and written information about the study.

RESULTS

STUDY POPULATION. Among 623 participants included between March 2012 and September 2013, 339 were chosen randomly for PAT examination (54%). Participants with an unsuccessful CFVR measurement or a PAT examination with an error signal and therefore an incomplete examination were excluded (n = 17). Median CFVR was 2.3 (interquartile range [IQR]: 2.0 to 2.8) and median RHI (IQR) was 2.1 (IQR: 1.6 to 2.6). Table 1 displays baseline data. PAT examination gave a warning signal for 86 examinations due to minor differences in occlusion time, incomplete occlusion, or a noisy signal. Quality of CFVR examination was low in 38 participants. To ensure that the results were not affected by the quality of the examinations, we repeated analyses

TABLE 1 Characteristics of Included Participants (n = 322)

Age, yrs	62.1 ± 9.5
Body mass index, kg/m^2	27.5 ± 5.4
Hypertension	168 (52)
Hyperlipidemia	206 (65)
Diabetes mellitus	43 (13)
Family history of ischemic heart disease	177 (56)
Smoking (current)	53 (16)
Peripheral arterial disease (claudication)	20 (6)
Atherosclerosis at coronary angiography	112 (35)
Post-menopausal	261 (83)

Values are mean ± SD or n (%).

after excluding participants with a low-quality CFVR examination or a PAT examination with a warning signal. Results were similar with no correlation between RHI and CFVR and similar correlations with cardiovascular factors.

CARDIOVASCULAR CHARACTERIZATION OF PARTICIPANTS WITH REDUCED CFVR AND RHI. A total of 80 (25%) participants had a CFVR ≤ 2 and 87 (27%) had a RHI ≤ 1.67. Table 2 displays characteristics of the study population divided into 3 groups according to CFVR and RHI level. Participants with low CFVR were significantly older, had a greater burden of hypertension and a slightly higher left ventricular ejection fraction. Participants with low RHI were more likely to have visually assessed nonsignificant atherosclerosis at CAG, diabetes, a higher body mass index, a higher left ventricle mass index, a lower HDL cholesterol level, and to be current smokers.

ASSOCIATION BETWEEN VASCULAR FUNCTION MEASURED BY CFVR AND RHI. There was no statistically significant correlation between CFVR and RHI (Spearman's rho = -0.067, p = 0.23), nor when adjusting for age (Figure 1). There was also no difference in RHI between CFVR categories (p = 0.39). A subgroup analysis including only participants with normal appearing coronary angiograms (n = 210) showed no correlation between CFVR and RHI (Spearman's rho = -0.094, p = 0.17). Moreover, in a sub-group analysis excluding participants with suspected peripheral arterial disease due to claudication

TABLE 2 Participant Characteristics According to Coronary Flow Velocity Reserve and Reactive Hyperemia Level

	CFVR				RHI			
	CFVR≤2.0 (n = 80)	2<CFVR≤2.5 (n = 113)	CFVR>2.5 (n = 129)	p Value*	RHI≤1.67 (n = 87)	1.67<RHI≤2 (n = 58)	RHI>2 (n = 177)	p Value*
Age, yrs	**64.6 ± 8.9**	**62.3 ± 10.3**	**60.3 ± 8.9**	**0.001**	60.9 ± 9.7	63.1 ± 10.8	62.3 ± 9.1	0.37
Hypertension	**48 (60)**	**64 (57)**	**56 (43)**	**0.014**	45 (52)	34 (59)	89 (50)	0.70
Hyperlipidemia	53 (67)	74 (66)	79 (62)	0.45	55 (64)	45 (78)	106 (61)	0.41
Diabetes mellitus	17 (22)	11 (10)	15 (12)	0.08	**18 (21)**	**9 (16)**	**16 (9)**	**0.009**
Family history of IHD	41 (52)	64 (58)	72 (57)	0.56	41 (48)	38 (68)	98 (56)	0.39
Smoking (current)	15 (19)	22 (19)	16 (12)	0.18	**21 (24)**	**9 (16)**	**23 (13)**	**0.027**
Peripheral arterial disease (claudication)	4 (5)	10 (9)	6 (5)	0.73	4 (5)	6 (11)	10 (6)	0.99
Non-significant atherosclerosis at CAG	31 (39)	41 (36)	40 (31)	0.24	**35 (40)**	**28 (48)**	**49 (28)**	**0.019**
Post-menopausal	67 (86)	94 (85)	100 (79)	0.20	67 (80)	44 (79)	150 (86)	0.19
Clinical assessment								
CFVR					2.39 (2.0–2.9)	2.38 (2.1–2.8)	2.29 (2.0–2.7)	0.08
RHI	2.22 (1.7–2.7)	2.14 (1.6–2.7)	1.99 (1.6–2.4)	0.39				
Body mass index, kg/m^2	26.9 ± 5.2	27.3 ± 5.4	27.9 ± 5.4	0.16	**28.7 ± 5.8**	**28.2 ± 5.2**	**26.6 ± 4.9**	**0.002**
Systolic blood pressure, mm Hg	136 ± 24	136 ± 21	134 ± 21	0.59	132 ± 22	138 ± 24	137 ± 21	0.11
Heart rate at rest, beat/min	71 ± 13	73 ± 11	68 ± 10	0.07	71 ± 12	69 ± 10	71 ± 12	0.62
Ejection fraction	**61.0 ± 6.3**	**61.0 ± 5.6**	**59.2 ± 6.2**	**0.021**	59.4 ± 5.6	60.4 ± 6.7	60.6 ± 6.1	0.14
Left ventricular mass index	68.7 ± 14.1	68.1 ± 13.1	70.6 ± 14.0	0.26	**72.3 ± 14.9**	**68.3 ± 13.3**	**68.1 ± 13.1**	**0.029**
Laboratory tests								
HbA1c†, mmol/l	42.7 ± 10.8	39.9 ± 8.1	40.5 ± 7.0	0.56	41.9 ± 8.8	42.7 ± 10.2	39.7 ± 7.6	0.31
Total cholesterol, mg/dl	192.8 ± 37.7	191.6 ± 43.3	197.6 ± 47.7	0.39	189.4 ± 43.8	197.4 ± 51.2	195.7 ± 41.2	0.33
HDL cholesterol, mg/dl	59.4 ± 16.3	60.2 ± 20.2	60.3 ± 21.6	0.76	**56.3 ± 16.8**	**56.9 ± 21.2**	**62.9 ± 20.4**	**0.007**
LDL cholesterol, mg/dl	108.3 ± 37.9	109.0 ± (38.9)	116.2 ± 46.2	0.16	108.3 ± 43.5	114.9 ± 49.1	112.4 ± 38.3	0.52
Non-HDL cholesterol, mg/dl	133.4 ± 41.7	131.4 ± (41.9)	137.3 ± 51.1	0.49	133.1 ± 44.6	140.5 ± 53.5	132.8 ± 43.5	0.82
Triglycerides, mg/dl	124.3 ± 66.6	117.7 ± (68.1)	115.6 ± 57.7	0.36	123.7 ± 58.3	133.5 ± 73.4	111.0 ± 62.0	0.08
Urine albumin/creatinine, g/mol	5.28 (16.2)	4.90 (22.8)	7.14 (25.9)	0.52	4.68 (16.7)	8.42 (31.8)	5.70 (21.9)	0.84

Values are mean ± SD, n (%), or median (interquartile range). *p value from trend test (linear regression and logistic regression). †Trend test adjusted for diabetes. **Bold** values indicate p < 0.05.

CAG = coronary angiography; CFVR = coronary flow velocity reserve; HbA1c = glycated hemoglobin, adjusted for diabetes; HDL = high-density lipoprotein; IHD = ischemic heart disease; LDL = low-density lipoprotein; RHI = reactive hyperemia index.

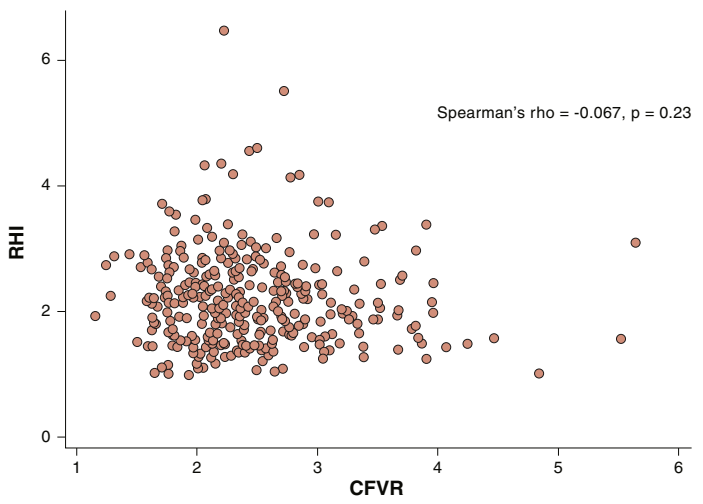
(n = 20) the Spearman correlation coefficient investigating the association between RHI and CFVR did not change (Spearman's rho = -0.070, p = 0.22).

DISCUSSION

In this comparative study investigating the association between coronary and peripheral microvascular function assessed by CFVR and RHI, we found no correlation between the 2 measures. Moreover, CFVR and RHI were not associated with the same cardiovascular risk factors.

Previous studies have reported that peripheral vascular function can be used as an indicator of microvascular function in patients without obstructive CAD (10,12). These studies focused mainly on endothelium-dependent coronary vascular function assessed by a lack of dilatation or a paradoxical vasoconstriction of coronary epicardial and microvessels in response to intracoronary administration of acetylcholine during invasive CAG. Matsuzawa et al. (10) showed that patients with CMD and no obstructive CAD have impaired RHI compared with patients with normal coronary microvascular function. However, the majority of patients had acetylcholine-induced epicardial and coronary microvascular spasms (n = 38) and only few patients were examined for (n = 34) and found to have an impaired CFVR (n = 4) (10). CFVR is regarded as a measure of mainly endothelium-independent function of the coronary microvasculature. Dipyridamole, used in this study, inhibits adenosine reuptake and catabolism, and thereby has a direct effect on smooth muscle cells relaxation (16). Impaired CFVR is therefore a measure of inadequate vasodilator capacity, which is mainly independent of endothelial signal substances. RHI measured by PAT reflects changes in digital blood flow and microvascular dilation. The response to reactive hyperemia is in part mediated by endogenous nitric oxide (11,17). Therefore, the lack of correlation could be explained by different pathophysiologic mechanisms with endothelial factors regulating digital vascular dilation (endothelin and nitric oxide) and microvascular arterial stiffness due to atherosclerosis, fibrosis, and calcification. This corresponds to the different associations of each of the methods with cardiovascular risk factors. Thus, our study adds to the current knowledge on microvascular coronary function in patients with suspected ischemic heart disease without obstructive coronary artery disease suggesting that RHI measured by PAT is able to identify the endothelial-dependent aspect of CMD, as found by Matsuzawa et al. (10), and not the endothelial-independent part of the syndrome.

FIGURE 1 Scatter Plot



Coronary flow velocity reserve versus reactive hyperemia index. CFVR = coronary flow velocity reserve; RHI = reactive hyperemia index.

Interestingly, in this present study we found that coronary atherosclerosis was significantly more frequent in patients with reduced RHI, whereas no significant relation between nonsignificant atherosclerosis and CFVR was detected. Nonetheless, we did show a trend towards a higher degree of atherosclerosis for patients with impaired CFVR. Only a few studies exist investigating the relation between CFVR and nonsignificant atherosclerosis in patients with no obstructive CAD (stenosis <50%). In a small study by Reis et al. (5) there was likewise not sufficient power to detect an association between invasively measured CFVR and the degree of coronary artery stenosis. The evaluation of no atherosclerosis versus nonobstructive CAD based on angiography is imprecise with epicardial remodeling not being detected by the angiography. Thus, the lack of association is presumably due to lack of power. Endothelial function is impaired in atherosclerotic disease. Because RHI is a marker partly related to peripheral endothelial function, it is not surprising that we find an association with epicardial atherosclerosis. Moreover, studies show that low RHI detects obstructive CAD (18,19), and in patients without known CAD and diabetes, RHI predicts coronary atherosclerosis defined by a coronary calcium score ≥400. Nevertheless, studies have failed to show any meaningful association between RHI and other vascular measures, such as brachial flow-mediated dilation and carotid artery intima-media thickness, also related to atherosclerosis (20–23).

Importantly, both CFVR and RHI are markers of cardiovascular disease. CFVR has proven to be a strong predictor of cardiovascular prognosis in various populations with study sizes from 111 to 4,313 (4,24-30). Smaller studies (n = 111 to n = 528) have found RHI to be predictive of prognosis (2,17,31-34), but evidence is not as solid as for CMD.

STUDY LIMITATIONS. For this large comparison study, participants represented women with clinically assessed angina pectoris and no obstructive CAD in a region covering almost 3.0 million inhabitants. All women referred to CAG for angina were systematically screened and randomly assigned to examination of RHI and CFVR.

It is a limitation of the study that we did not additionally assess coronary endothelial, epicardial, or microvascular dysfunction by acetylcholine provocation testing. However, this must be assessed invasively and is only routinely performed in few centers in the world, partly due to safety concerns. Moreover, we measured vascular function only once in every individual, which does not account for intraindividual variability and circadian rhythms. Both pathological and nonpathological conditions may interfere with the measurement of RHI. However, we did control for environmental factors by performing PAT in a standardized settings (i.e., a quiet, dark, temperate room [21°C to 24°C]). None of the participants had been diagnosed with Raynaud syndrome, vasculitis, or other vascular diseases; but we did not perform supplementary assessments to rule out such conditions.

CONCLUSIONS

RHI does not identify impaired CFVR in women with angina pectoris and no obstructive CAD. The 2 methods are likely to identify different aspects of vascular pathology, as indicated by the different association with cardiovascular risk factors.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: RHI and CFVR are not associated in women with angina pectoris and no obstructive CAD, implicating that RHI does not identify the endothelial-independent component of CMD.

TRANSLATIONAL OUTLOOK: RHI cannot identify all aspects of CMD. Therefore, CFVR, which assesses mainly the endothelial-independent vasodilation capability of resistance vessels, is important in the work-up of participants with no obstructive CAD and possible CMD. Additional studies that focus on the pathophysiology and the development of clinical applicable noninvasive diagnostic tests of CMD are warranted.

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