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ORIGINAL RESEARCH

Coronary Microvascular Function in Asymptomatic Middle-Aged Individuals With Cardiometabolic Risk Factors

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ABSTRACT

BACKGROUND In patients with ischemic heart disease, coronary microvascular dysfunction is associated with cardiovascular risk factors and poor prognosis; however, data from healthy individuals are scarce.

OBJECTIVES The purpose of this study was to assess the impact of cardiovascular risk factors and subclinical atherosclerosis on coronary microvascular function in middle-aged asymptomatic individuals.

METHODS Myocardial perfusion was measured at rest and under stress using cardiac magnetic resonance in 453 individuals and used to generate myocardial blood flow (MBF) maps and calculate myocardial perfusion reserve (MPR). Subclinical atherosclerosis was assessed using 3-dimensional vascular ultrasound of the carotid and femoral arteries and coronary artery calcium scoring at baseline and at 3-year follow-up.

RESULTS Median participant age was 52.6 years (range: 48.9-55.8 years), and 84.5% were male. After adjusting for age and sex, rest MBF was directly associated with the number of the metabolic syndrome components present (elevated waist circumference, systolic and diastolic blood pressure, fasting glucose, and triglycerides and low high-density lipoprotein cholesterol), insulin resistance (homeostatic model assessment for insulin resistance), and presence of diabetes. MPR was reduced in the presence of several metabolic syndrome components, elevated homeostatic model assessment for insulin resistance, and diabetes. Stress MBF was inversely associated with coronary artery calcium presence and with global plaque burden. Higher stress MBF and MPR were associated with less atherosclerosis progression (increase in plaque volume) at 3 years.

CONCLUSIONS In asymptomatic middle-aged individuals free of known cardiovascular disease, the presence of cardiometabolic risk factors and systemic (poly-vascular) subclinical atherosclerosis are associated with impaired coronary microvascular function. Better coronary microvascular function reduces atherosclerosis progression at follow-up. (Progression of Early Subclinical Atherosclerosis [PESA]; NCT01410318). (JACC Cardiovasc Imaging. 2024;■:■–■)

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ABBREVIATIONS AND ACRONYMS

3D = 3-dimensional

AIF = arterial input function

CAC = coronary artery calcium

CACS = coronary artery calcium scoring

CMD = coronary microvascular dysfunction

CMR = cardiac magnetic resonance

CT = computed tomography

CVRF = cardiovascular risk factors

HOMA-IR = homeostatic model assessment for insulin resistance

IHD = ischemic heart disease

MBF = myocardial blood flow

MPR = myocardial perfusion reserve

The coronary arterial microcirculation plays a critical role in the regulation of myocardial blood flow (MBF) in response to shifting metabolic demand, and appropriate microvascular function is thus essential to provide adequate coronary blood flow according to dynamic myocardial demands.[1]

In patients with ischemic heart disease (IHD), cardiovascular risk factors (CVRF) increase the risk of coronary microvascular dysfunction (CMD), a marker of poor prognosis;[2,3] indeed, coronary artery disease burden correlates with worse CMD.[4,5] Moreover, CMD is a cause of myocardial ischemia in patients without obstructive coronary artery disease and indicates a worse prognosis in these patients.[6,7] CMD also has prognostic implications in patients with nonischemic cardiomyopathies[8,9] and takotsubo syndrome,[10,11] and is an important contributor to heart failure with preserved ejection fraction, in which its presence is associated with adverse cardiovascular events.[12,13]

To date, whether CMD precedes epicardial coronary artery disease is unclear.[6,7] Previous studies have shown that the presence of coronary endothelial dysfunction is associated with the development of coronary artery disease in the long term,[14] which supports the hypothesis that there is a link between the functional and structural abnormalities present in CMD and the subsequent development of epicardial disease. CMD is also associated with microvascular dysfunction in other organs, and may be the underlying mechanism of atherosclerotic disease in multiple territories.[15]

Although the association between CVRFs, coronary atherosclerosis, and CMD in patients with IHD has been extensively studied, information is lacking about the association between these entities in apparently healthy asymptomatic individuals (free of known IHD). Changes in coronary microvascular function in response to CVRFs can occur even in the absence of symptoms,[16] similar to (and possibly in parallel with) the progress of subclinical atherosclerosis.

Cardiac magnetic resonance (CMR) can be used to derive quantitative maps of MBF, both at rest and in hyperemia.[17] Myocardial perfusion reserve (MPR) can be calculated as the ratio of stress MBF/rest MBF and correlates well with invasive angiography measurements.[18,19] MPR and stress MBF allow accurate assessment of CMD in a variety of settings,[5,8,9,20] constituting an ideal noninvasive tool for the evaluation of microvascular function in asymptomatic persons.

Here, we assessed the impact of CVRFs and multiterritorial subclinical atherosclerosis on coronary microvascular function in a large cohort of asymptomatic middle-aged individuals free of known cardiovascular disease.

METHODS

STUDY POPULATION. The study population consisted of participants in the PESA study ("Progression of Early Subclinical Atherosclerosis" - Centro Nacional de Investigaciones Cardiovasculares-Santander)[21] who underwent CMR.[22] PESA is a prospective observational cohort study of 4,184 apparently healthy asymptomatic employees at Santander Bank in Madrid. Participants were aged 40-54 years at enrollment (June 2010-February 2014). Exclusion criteria were previous cardiovascular disease, any condition reducing life expectancy or affecting study adherence, morbid obesity (body mass index ≥40 kg/m^2), or chronic kidney disease (estimated glomerular filtration rate <60 mL/min/m^2). The main goal of the PESA study is to characterize atherosclerosis initiation and progression by means of serial multiterritory, multimodality noninvasive imaging and paired biological sampling.[23] The selection criteria for CMR in PESA participants have been published before;[22] in brief, this subgroup included participants presenting subclinical atherosclerosis on arterial ultrasound and/or coronary artery calcium (CAC) at baseline. A fasting blood test included blood count and biochemistry.[21] Metabolic syndrome was defined when a participant met ≥3 of the following conditions: central obesity (waist circumference ≥88 cm in women and ≥102 cm in men);[24] elevated plasma triglycerides (≥150 mg/dL); low plasma high-density lipoprotein

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cholesterol (<40 mg/dL in men or <50 mg/dL in women); elevated fasting plasma glucose (≥100 mg/dL); and high blood pressure (systolic ≥130 mm Hg and/or diastolic ≥85 mm Hg).[25] Insulin resistance was quantified using the homeostatic model assessment for insulin resistance (HOMA-IR) method as (fasting plasma glucose × fasting plasma insulin)/405.[26]

The study protocol was approved by the Centro Nacional de Investigaciones Cardiovasculares Institutional Review Board, and all participants gave written informed consent.

CMR ACQUISITION AND ANALYSIS. The CMR protocol has been previously defined.[22] All studies were performed using a Philips Achieva 3.0-TX magnetic resonance imaging scanner (Philips Healthcare) according to a standard protocol including cine imaging, adenosine-stress and rest perfusion, and late gadolinium enhancement. Participants were asked to abstain from caffeine for 24 hours before the scan. Pharmacologic stress was achieved with adenosine infusion at 140 μg/kg/min. Contraindications for adenosine-stress CMR included adenosine allergy, systolic blood pressure <90 mm Hg, second- or third-degree atrioventricular block, chronic obstructive pulmonary disease, and bronchospasm. Participants were monitored for symptoms throughout the scan, and blood pressure and heart rate were recorded during adenosine infusion. For the measurement of stress and rest perfusion, an intravenous bolus of 0.1 mmol/L/kg gadolinium-based contrast agent (0.5 mmol/L/mL Magnevist, Bayer) was administered at an injection rate of 3 mL/s. Cardiac perfusion was measured by dynamic acquisition with dual-saturation recovery (saturation times: 28 ms for arterial input function [AIF] slice and 90 ms for high-resolution images).[27] The AIF was estimated from a low spatial resolution slice with short saturation recovery centered on the ascending aorta, whereas the long saturation-high-resolution images were acquired in short axis orientation at the basal, middle, and apical positions with an in-plane resolution of 2.6 × 2.6 × 10.0 mm^3 (repetition time [TR] = 2.1 ms, echo time [TE] = 1.0 ms, and 15° flip angle). The first dynamic was acquired without a saturation pulse to obtain proton density images that were later used for contrast concentration conversion. Low- and high-resolution images were acquired with a parallel acceleration factor of 2, resulting in shot lengths of 100 ms for high-resolution images and 40 ms for low-resolution AIF images (Supplemental Table 1). Dynamic images were acquired in free-breathing conditions.

Dynamic studies were analyzed using the QuantitativePerfusion PRIDE tool (Philips Healthcare) and 2-dimensional elastic registration was applied on dynamic images using Fast Elastic Image Registration.[28] After imaging registration, myocardial perfusion maps were generated using the generalized kinetic model described in Eq. 24 by Tofts et al.[29] Perfusion maps were visually inspected for quality and discarded if there were errors; segments including the left ventricular outflow tract or significant artifacts were excluded from the analysis. Regions of interest were analyzed with dedicated software (MR Extended WorkSpace 2.6, Philips Healthcare) by an expert blinded to clinical variables; the analysis included 16 myocardial segments (according to the 17-segment American Heart Association model, excluding the true apex), and mean MBF values were calculated under stress and at rest. MPR was calculated as the ratio of stress MBF to rest MBF.

3-DIMENSIONAL VASCULAR ULTRASOUND. The 3-dimensional (3D) vascular ultrasound protocol has been described.[30] In brief, the carotid and femoral arterial segments adjacent to the bifurcation were scanned, and the acquired images were analyzed using the Vascular Plaque Quantification tool in QLAB version 10.2 (Philips Healthcare). Global plaque burden was defined as the sum of plaque volumes (mm^3) in the right and left carotid and femoral arteries.[30] Plaque presence and the number of arterial territories affected were also recorded.

CAC BY COMPUTED TOMOGRAPHY. CAC protocol has been described.[31] CAC was detected with a 16-slice computed tomography (CT) scanner (Philips Brilliance, Philips Healthcare), and coronary artery calcium score (CACS) was calculated using the Agatston method.

3D vascular ultrasound and CT for CAC were performed at baseline and at the 3-year follow-up.

STATISTICAL ANALYSIS. Normally distributed continuous variables are expressed as mean ± SD, whereas non-normally distributed variables are expressed as median (Q1-Q3). Categorical variables are expressed as n (%). The distribution of continuous variables was assessed with graphical methods and Shapiro-Wilk test. Associations between stress MBF, rest MBF, MPR, and CVRF were evaluated with a linear regression model adjusting for age and sex. Associations between stress MBF, rest MBF, MPR, and subclinical atherosclerosis (at baseline and at follow-up), as well as comparisons between groups according to the extent of systemic atherosclerosis (1, 2, or 3 territories affected), were evaluated with a linear regression model adjusting for the SCORE-2 (Systematic COronary Risk Evaluation model 2) risk prediction algorithm.[32] Differences between absolute

TABLE 1 Baseline Characteristics (N = 453)

Age	52.6 (48.9-55.8)
Male	383 (84.5)
Metabolic syndrome and its components	
Metabolic syndrome	67 (14.8)
Number of metabolic syndrome components (0-5)	1 (0-2)
0	176 (8.9)
1-2	210 (46.4)
≥3	67 (14.8)
Central obesity	119 (26.3)
BMI, kg/m^2	26.7 ± 3.3
Waist circumference, cm	94.3 ± 10.4
Systolic blood pressure, mm Hg	119.8 ± 12.1
Diastolic blood pressure, mm Hg	74.8 ± 9.2
HDL-C, mg/dL	47.5 ± 11.8
Triglycerides, mg/dL	94 (72-133)
Fasting glucose, mg/dL	91 (85-97)
Cardiovascular risk factors	
Family history of cardiovascular disease	69 (15.2)
Hypertension	96 (21.2)
Dyslipidemia	257 (56.7)
Diabetes	20 (4.4)
Current smoking	106 (23.4)
Medications	
Statins	78 (17.2)
Antihypertensive agents	67 (14.8)
Antidiabetic drugs	18 (4.0)
Antiplatelet therapy	6 (1.3)
Biochemistry	
Total cholesterol, mg/dL	210.7 ± 37.1
LDL-C, mg/dL	141.1 ± 32.4
Hemoglobin A1c, %	5.5 (5.2-5.7)
HOMA-IR, %	1.31 (0.91-2)
Insulin, μU/mL	5.8 (4.2-8.4)
Subclinical atherosclerosis	
CAC presence	291 (65.5)
CACS	14 (0-70)
Peripheral atherosclerosis	359 (83.3)
Global plaque volume,[a] mm^3	82 (16-182)
Quantitative perfusion CMR	
Rest MBF, mL/g/min	0.92 (0.80-1.10)
Stress MBF, mL/g/min	2.74 ± 0.7
MPR	3.01 ± 0.9
Hemodynamic characteristics during index CMR	
Rest heart rate, beats/min	62 (57-71)
Rest systolic blood pressure, mm Hg	120 (110-130)
Rest diastolic blood pressure, mm Hg	75 (70-80)
Stress heart rate, beats/min	94 (85-103)
Stress systolic blood pressure, mm Hg	129 (119-137)
Stress diastolic blood pressure, mm Hg	78 (71-84)
Stress rate pressure product, mm Hg, beats/min	11,986 (10,591-13,426)

Values are n (%) or median (Q1-Q3). [a]Global plaque volume was calculated per participant as the sum of plaque volumes in each of the 4 explored vascular sites (right and left carotid and femoral arteries).

BMI = body mass index; CAC = coronary artery calcium; CACS = coronary artery calcium score; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; LDL-C = low-density lipoprotein cholesterol; MBF = myocardial blood flow; MPR = myocardial perfusion reserve.

myocardial perfusion values between groups were assessed using Student's *t*-test or Wilcoxon signed rank, as appropriate. Progression of subclinical atherosclerosis was defined as the difference between CACS at baseline and follow-up (△ CACS) and evaluated using linear regression adjusting for SCORE-2 and CACS at baseline; and as the difference in global plaque volume between baseline and follow-up (△ plaque volume) and evaluated using linear regression adjusting for SCORE-2 and global plaque volume at baseline. For all endpoints, differences were considered statistically significant at values of $P < 0.05$. Statistical analyses were performed using Stata software version 15 (StataCorp).

RESULTS

Stress and rest CMR scans were obtained from 530 PESA participants. Data from 50 participants (9.4%) were not evaluated due to limited image quality for MBF mapping. Also excluded were 11 participants (2.1%) with evidence of a subendocardial (ischemic pattern) scar, 11 (2.1%) with wall-motion abnormalities, 3 (0.6%) with visual perfusion defects, and 2 (0.4%) with imaging findings of hypertrophic cardiomyopathy. The study population thus included 453 (85.5%) participants. At a median follow-up of 3.08 years (Q1-Q3: 2.81-3.48 years), 422 participants (93.2%) underwent a 3D vascular ultrasound and 414 (91.4%) underwent a CT for CAC evaluation.

CARDIOVASCULAR RISK FACTORS AND CORONARY MICROVASCULAR FUNCTION. Median participant age was 52.6 years (Q1-Q3: 48.9-55.8 years), and 84.5% of the study participants were male. Baseline and hemodynamic characteristics are summarized in Table 1. Median rest MBF was 0.92 mL/g/min (Q1-Q3: 0.8-1.1 mL/g/min), mean stress MBF was 2.74 ± 0.7 mL/g/min, and mean MPR was 3.01 ± 0.9.

Factors associated with rest MBF. Male sex was associated with lower rest MBF (ß = −0.264; $P < 0.001$) (Table 2). After age and sex adjustments, rest MBF was directly associated with the number of the metabolic syndrome components present (ß = 2.861; $P = 0.002$) as well as with systolic and diastolic blood pressure (ß = 0.296; $P = 0.002$; ß = 0.335; $P = 0.007$; respectively). Rest MBF was also directly associated with the presence of diabetes (ß = 19.365; $P < 0.001$), fasting glucose (ß = 0.257; $P = 0.001$), HbA1c (ß = 6.215; $P = 0.007$), HOMA-IR (ß = 2.550; $P = 0.008$), and insulin levels (ß = 0.565; $P = 0.036$), and inversely associated with total cholesterol (ß = −0.083; $P = 0.005$) and low-density lipoprotein cholesterol (ß = −0.095; $P = 0.005$).

TABLE 2 Cardiovascular Risk Factors and Myocardial Blood Flow

	Rest MBF			Stress MBF			MPR		
		Beta-Coefficient (SE)	*P* Value		Beta-Coefficient (SE)	*P* Value		Beta-Coefficient (SE)	*P* Value
Age	≈	−0.346 (0.254)	0.173	≈	−0.934 (0.702)	0.184	≈	−0.005 (0.009)	0.589
Male	↓	−26.409 (3.030)	<0.001	↓	−53.549 (8.381)	<0.001	≈	0.143 (0.113)	0.205
Metabolic syndrome and its components									
Metabolic syndrome	Trend ↑	5.861 (3.140)	0.063	≈	1.555 (8.719)	0.859	≈	−0.148 (0.117)	0.205
Central obesity	≈	2.947 (2.515)	0.242	≈	−0.590 (6.967)	0.933	≈	−0.062 (0.094)	0.509
BMI, kg/m^2	≈	−0.049 (0.364)	0.893	≈	−0.944 (1.005)	0.348	≈	−0.001 (0.014)	0.967
Weight, kg	≈	−0.066 (0.106)	0.533	≈	−0.184 (0.294)	0.532	≈	0.002 (0.004)	0.535
Waist circumference, cm	≈	0.125 (0.126)	0.322	≈	−0.357 (0.349)	0.307	≈	−0.005 (0.005)	0.259
Systolic blood pressure, mm Hg	↑	0.296 (0.097)	0.002	≈	0.069 (0.271)	0.799	Trend ↓	−0.007 (0.004)	0.051
Diastolic blood pressure, mm Hg	↑	0.335 (0.123)	0.007	≈	−0.038 (0.343)	0.912	↓	−0.010 (0.005)	0.037
HDL-C, mg/dL	≈	−0.161 (0.105)	0.128	≈	−0.077 (0.292)	0.791	≈	0.003 (0.004)	0.467
Triglycerides, mg/dL	≈	−0.000 (0.020)	0.982	Trend ↓	−0.100 (0.055)	0.071	≈	−0.001 (0.001)	0.155
Fasting glucose, mg/dL	↑	0.257 (0.080)	0.001	≈	−0.243 (0.222)	0.275	↓	−0.010 (0.003)	0.001
Number of components of metabolic syndrome (0-5)	↑	2.861 (0.908)	0.002	≈	−0.607 (2.539)	0.811	↓	−0.083 (0.034)	0.015
None	↓	−7.495 (2.253)	0.001	≈	0.800 (6.307)	0.899	↑	0.202 (0.084)	0.017
1 to 2	≈	4.115 (2.190)	0.061	≈	−1.500 (6.080)	0.805	≈	−0.115 (0.081)	0.157
≥3	≈	5.861 (3.140)	0.063	≈	1.555 (8.719)	0.859	≈	−0.148 (0.117)	0.205
Cardiovascular risk factors									
Hypertension	↑	7.790 (2.698)	0.004	≈	8.200 (7.523)	0.276	≈	−0.139 (0.101)	0.171
Dyslipidemia	≈	−2.839 (2.243)	0.206	≈	−6.542 (6.207)	0.292	≈	−0.004 (0.083)	0.966
Diabetes	↑	19.365 (5.418)	<0.001	≈	13.281 (15.184)	0.382	↓	−0.423 (0.203)	0.038
Current smoking	≈	2.131 (2.593)	0.412	≈	−5.912 (7.172)	0.410	≈	−0.157 (0.096)	0.103
Family history of cardiovascular disease	≈	3.645 (3.048)	0.232	↑	18.644 (8.397)	0.027	≈	0.095 (0.113)	0.405
Biochemistry									
Total cholesterol, mg/dL	↓	−0.083 (0.029)	0.005	≈	−0.130 (0.082)	0.113	≈	0.001 (0.001)	0.556
LDL-C, mg/dL	↓	−0.095 (0.034)	0.005	≈	−0.104 (0.094)	0.269	≈	0.001 (0.001)	0.334
Hemoglobin A1c, %	↑	6.215 (2.274)	0.007	≈	−5.287 (6.336)	0.404	↓	−0.231 (0.084)	0.006
HOMA-IR, %	↑	2.550 (0.951)	0.008	≈	−1.021 (2.650)	0.700	↓	−0.074 (0.035)	0.037
Insulin, μU/mL	↑	0.565 (0.268)	0.036	≈	−0.292 (0.745)	0.695	≈	−0.017 (0.010)	0.093

"↓", "↑", and "≈" signify reduced, increased, or no change in the value of a given condition, respectively. Linear regression adjusted by age and sex.
Abbreviations as in Table 1.

Factors associated with stress MBF. Male sex was associated with lower stress MBF (ß = −53.549; $P < 0.001$) (Table 2).

After age and sex adjustments, a trend toward lower stress MBF was observed with higher triglyceride levels (ß = −0.100; $P = 0.071$).

Factors associated with MPR. MPR was inversely associated with the number of metabolic syndrome components present (ß = −0.083; $P = 0.015$), as well as with diastolic blood pressure (ß = −0.010; $P = 0.037$); a trend toward lower MPR was observed with higher systolic blood pressure levels (ß = −0.007; $P = 0.051$; Table 2). MPR was also lower in the presence of diabetes (ß = −0.423; $P = 0.038$), as well as with higher fasting plasma glucose (ß = −0.010; $P = 0.001$), HbA1c (ß = −0.231; $P = 0.006$), and HOMA-IR (ß = −0.074; $P = 0.037$). Absolute values (Table 3) showed significant differences between participants with and without diabetes (MPR 3.03 vs 2.58; $P = 0.025$) as well as between participants with 1-2 components of the metabolic syndrome and those with 0 components (MPR 2.95 vs 3.12; $P = 0.045$).

To better evaluate the associations between coronary microvascular function and CVRFs, we performed some subgroup analysis according to the presence of CAC and/or peripheral plaque. The group with peripheral plaque and without CAC (n = 134; 37% of those with peripheral plaque) showed similar association trends with coronary microvascular function to those observed in the overall cohort, although these associations did not reach statistical significance (Supplemental Table 2). The group with CAC and without peripheral plaque (n = 21; 7% of those with CAC) showed similar association trends to the observed in the global cohort and, in this subgroup, smoking showed a trend to increase rest MBF and

TABLE 3 Absolute Values for Rest MBF, Stress MBF, and MPR According to the Presence of Metabolic Syndrome and Diabetes

	Rest MBF, mL/g/min	*P* Value	Stress MBF, mL/g/min	*P* Value	MPR	*P* Value
Number of components of the metabolic syndrome						
0	0.91 (0.78-1.06)	(0) vs (1-2) 0.142	2.79 ± 0.68	(0) vs (1-2) 0.384	3.12 ± 0.87	(0) vs (1-2) 0.045
1-2	0.94 (0.80-1.13)	(1-2) vs (>2) 0.968	2.73 ± 0.67	(1-2) vs (>2) 0.586	2.95 ± 0.85	(1-2) vs (>2) 0.610
≥3	0.95 (0.80-1.12)	(0) vs (>2) 0.264	2.68 ± 0.65	(0) vs (>2) 0.247	2.89 ± 0.84	(0) vs (>2) 0.056
Diabetes						
No diabetes	0.92 (0.79-1.09)	0.009	2.74 ± 0.67	0.793	3.03 ± 0.87	0.025
Diabetes	1.12 (0.91-1.25)		2.78 ± 0.68		2.58 ± 0.61	

Values are mean ± SD or median (Q1-Q3), unless otherwise indicated.
Abbreviations as in Table 1.

decrease MPR (Supplemental Table 3). Finally, the group with both CAC and peripheral plaque (n = 261) showed that in addition to the associations observed in the overall cohort, the presence of metabolic syndrome and greater waist circumference were associated with higher rest MBF (Supplemental Table 4).

A subgroup analysis was performed for those participants receiving statins and antihypertensive agents (Supplemental Table 5); no associations were found between the use of these medications and coronary microvascular function.

SUBCLINICAL ATHEROSCLEROSIS AND CORONARY MICROVASCULAR FUNCTION. After adjusting for age, sex, and CVRF (SCORE-2), stress MBF was reduced in the presence of CAC (ß = −13.40; $P = 0.047$) and with increasing global plaque burden (ß = −0.041; $P = 0.036$) (**Table 4**). MPR showed a trend toward reduction with increasing CACS (ß = −0.000; $P = 0.064$). Absolute values are represented in Supplemental Table 6.

To tighten the analysis of the associations between systemic subclinical atherosclerosis and MBF, participants were classified according to the presence of atherosclerosis in 1, 2, or 3 vascular territories (the carotid, femoral, and coronary arteries; **Figure 1**). Compared with the presence of plaque in just 1 territory, plaque presence in 3 territories was associated with lower stress MBF (ß = −32.82; $P < 0.001$) and MPR (ß = −0.36; $P = 0.001$).

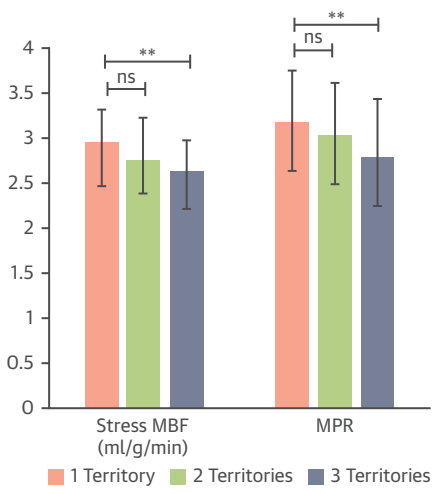
RISK OF PROGRESSION OF SUBCLINICAL ATHEROSCLEROSIS ACCORDING TO CORONARY MICROVASCULAR FUNCTION AT BASELINE. After adjusting for age, sex, and CVRF (SCORE-2), participants with higher stress MBF at baseline presented lower global plaque volume (ß = −0.248; $P = 0.036$) at the 3-year follow-up (**Table 5**); in addition, a trend toward lower CACS at the 3-year follow-up was observed in those with higher stress MBF (ß = −0.225; $P = 0.073$) as well as in those with higher MPR (ß = −18.08; $P = 0.064$). Moreover, after adjusting for global plaque volume at baseline, higher stress MBF and higher MPR were associated with less atherosclerosis progression (less increase in global plaque volume; ß = −0.233; $P = 0.018$; and ß = −14.78; $P = 0.05$, respectively) (**Table 5**).

TABLE 4 Subclinical Atherosclerosis and MBF

	Rest MBF			Stress MBF			MPR		
		Beta-Coefficient (SE)	*P* Value		Beta-Coefficient (SE)	*P* Value		Beta-Coefficient (SE)	*P* Value
Coronary atherosclerosis									
CAC presence	≈	−2.873 (2.527)	0.256	↓	−13.40 (6.72)	0.047	≈	−0.050 (0.086)	0.561
CACS	≈	0.002 (0.007)	0.767	≈	−0.032 (0.018)	0.073	Trend ↓	−0.0004 (0.0002)	0.064
Peripheral atherosclerosis									
Peripheral plaque presence	≈	−5.216 (3.302)	0.115	≈	−12.20 (8.806)	0.167	≈	−0.052 (0.114)	0.648
Global plaque volume,[a] mm^3	≈	−0.005 (0.007)	0.528	↓	−0.041 (0.020)	0.036	≈	−0.0003 (0.0003)	0.249

"↓", "↑", and "≈" signify reduced, increased, or no change in the value of a given condition, respectively. Linear regression adjusted by SCORE-2. [a]Global plaque volume was calculated per participant as the sum of plaque volumes in each of the 4 explored vascular sites (right and left carotid and femoral arteries).
Abbreviations as in Table 1.

FIGURE 1 Association Between the Systemic Extent of Atherosclerosis and Coronary Microcirculatory Function



The graph represents the median (Q1-Q3) values for stress MBF and MPR in the 3 groups (participants with plaque in 1 vascular territory, plaque in 2 territories, and plaque in 3 territories). The *P* values are calculated by linear regression adjusted for age, sex, and cardiovascular risk factors (SCORE-2). The tabulated data show the beta coefficients, CIs, and *P* values. MBF = myocardial blood flow; MPR = myocardial perfusion reserve; ns = nonsignificant; SCORE-2 = Systematic COronary Risk Evaluation model 2. *$P < 0.01$.

COMPARISON WITH A GROUP OF PESA PARTICIPANTS WITH ISCHEMIC SCAR. To evaluate the clinical relevance of the perfusion values observed in this cohort, PESA participants who were excluded from the study cohort due to the presence of ischemic scar (n = 11) were studied and compared with the study cohort. In this group, myocardial perfusion was evaluated in the remote myocardium (excluding myocardial segments with scar). Lower stress MBF and lower MPR were observed in the group with ischemic scar as compared with the study cohort (Table 6).

In addition, the group with ischemic scar presented lower stress MBF and lower MPR when compared with the subgroup of study participants with metabolic syndrome (Table 6).

DISCUSSION

Our results show that, in asymptomatic individuals with no known IHD, cardiometabolic risk factors and systemic subclinical atherosclerosis are associated with altered microvascular function. Our key findings can be summarized as follows: 1) rest MBF is directly associated with the number of components of the metabolic syndrome, with insulin resistance (HOMA-IR), and with the presence of diabetes; 2) MPR is inversely associated with the number of metabolic syndrome components present, insulin resistance, and diabetes; 3) stress MBF is decreased in the presence of subclinical atherosclerosis; the greater the burden of subclinical atherosclerosis, the greater the impact on MBF; and 4) higher stress MBF at baseline is associated with lower atherosclerotic burden at follow-up, and higher stress MBF and MPR are both associated with less progression of atherosclerotic plaque burden. To our knowledge, this is the largest cohort of asymptomatic subjects ever studied using quantitative myocardial perfusion CMR.

Technical advances in myocardial perfusion CMR now make it possible to accurately measure MBF, allowing noninvasive assessment of coronary microvascular function.[18,19] MPR is a widely used prognostic marker due to its good correlation with invasive angiography, and stress MBF has proven to be as good a prognostic marker as MPR.[5,20] In patients with IHD, reduced MPR or stress MBF is associated with an increased risk of cardiovascular events,[5,20,33] and an increasing number of studies point to the utility of these markers in nonischemic cardiomyopathies.[8,9]

Because of the prognostic implications of coronary microvascular function, there is growing interest in understanding the factors that influence it.[1] In patients with IHD, CVRF burden increases the risk of CMD;[2,34-36] however, there is a lack of data from asymptomatic subjects without IHD. Previous small studies suggested that CVRFs may alter coronary microvascular function even before the onset of symptoms.[37-39] Consistent with this view, a population-based study of ~200 individuals reported

TABLE 5 Coronary Microvascular Function and Progression of Subclinical Atherosclerosis at Follow-Up

	CACS[a]	*P* Value	△ CACS[b]	*P* Value	Global Plaque Volume[a]	*P* Value	△ Plaque Volume[c]	*P* Value
Rest MBF	0.099 (0.334)	0.767	0.106 (0.143)	0.460	−0.199 (0.315)	0.528	−0.104 (0.256)	0.684
Stress MBF	−0.225 (0.125)	0.073	−0.027 (0.056)	0.633	−0.248 (0.118)	0.036	−0.233 (0.098)	0.018
MPR	−18.08 (9.75)	0.064	−5.313 (4.302)	0.217	−10.58 (9.17)	0.249	−14.78 (7.52)	0.050

Values are Beta (SE), unless otherwise indicated. [a]Adjusted for SCORE-2. [b]Adjusted for SCORE-2 and CACS at baseline. [c]Adjusted for SCORE-2 and global plaque volume at baseline.
Abbreviations as in Table 1.

TABLE 6 Absolute Values for Rest MBF, Stress MBF, and MPR in the Study Cohort, in a Subgroup of the Study Cohort With Metabolic Syndrome, and in a Group of PESA Participants With Ischemic Scar

	Study Cohort (n = 453)	Participants With Metabolic Syndrome (n = 67)	Group With Ischemic Scar (Remote Myocardium) (n = 11)	*P* Value (Ischemic Scar vs Study Cohort)	*P* Value (Ischemic Scar vs Participants With Metabolic Syndrome)
Rest MBF, mL/g/min	0.92 (0.80-1.10)	0.95 (0.80-1.12)	0.99 ± 0.20	0.516	0.630
Stress MBF, mL/g/min	2.74 ± 0.70	2.68 ± 0.65	2.66 ± 0.32	<0.001	<0.001
MPR	3.01 ± 0.90	2.89 ± 0.84	2.82 ± 0.72	<0.001	<0.001

Values are n (%) or median (Q1-Q3).
Abbreviations as in Table 1.

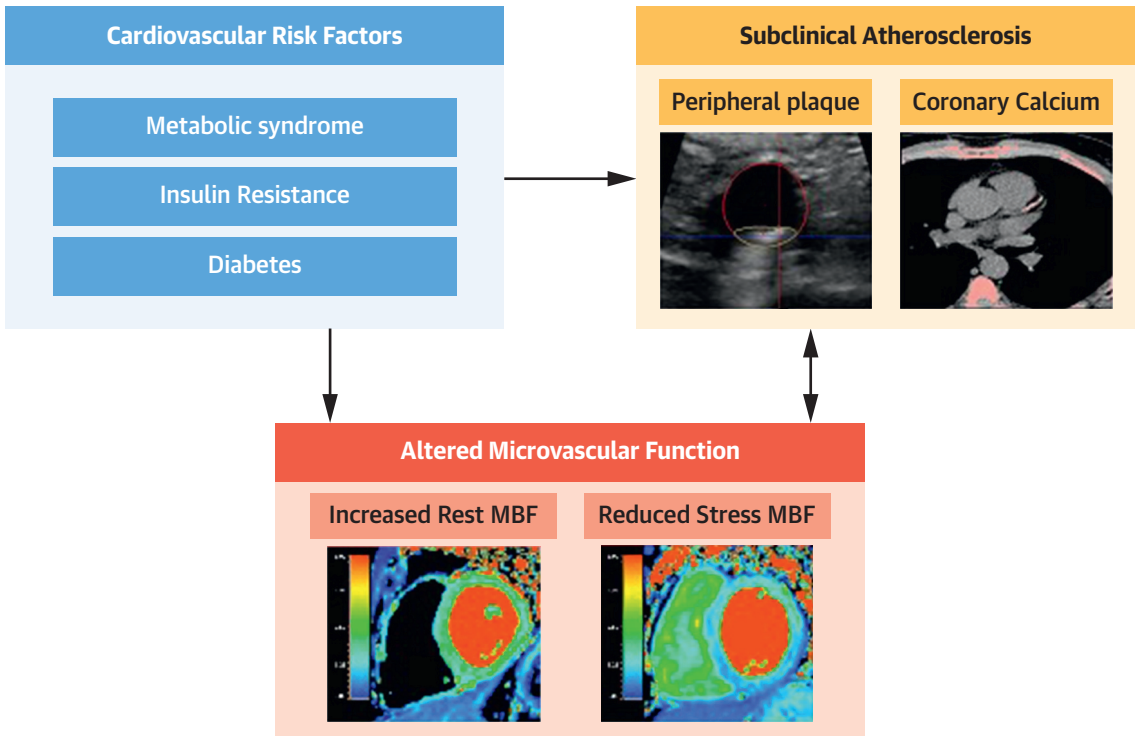
that changes in MBF and MPR were associated with elevated blood pressure, total cholesterol, and low-density lipoprotein cholesterol.[16] Our findings in more than 450 asymptomatic participants confirm these associations and further demonstrate that microvascular function is affected in diverse ways by other CVRFs, highlighting the impact on MBF of metabolic syndrome components, insulin resistance, and diabetes. Consistent with previous findings,[40] our analysis also shows that male sex was associated with lower stress and rest MBF. Furthermore, the effect size of the impact of CVRFs on coronary microvascular function (ie, absolute differences in MBF and MPR) is similar to that observed in other studies with prognostic value in future events.[5]

Our results show that cardiometabolic risk factors principally affect coronary microvascular function by increasing rest MBF. Potential mechanisms include functional abnormalities (such as impaired vasodilatation and/or vasoconstriction) and structural changes with microvascular remodeling (including microvascular obstruction with luminal narrowing) as well as capillary rarefaction with decreased density and diameter.[1,2] Particular attention should be directed at the population with type 2 diabetes, a disease that produces microvascular damage and endothelial dysfunction through several mechanisms.[34,35] In line with previous studies,[41,42] our results show an association between diabetes and elevated rest MBF, which has been linked to a higher risk of adverse cardiovascular outcomes[43] and ultimately leads to a reduction in MPR. In the diabetic heart, baseline myocardial oxygen consumption is believed to increase as a result of the switch from glucose to fatty-acid use, which leads to an increased myocardial demand at rest.[42] A link between increased myocardial energy demand at rest and diabetes is also suggested by a recent report that CVRFs and metabolic syndrome are associated with cardiac insulin resistance, thus decreasing myocardial glucose use.[44]

Changes in MBF have also been linked to the presence of CAC in asymptomatic persons.[45] Our study confirms the association between changes in microvascular function and coronary atherosclerosis (CAC) and demonstrate for the first time an association between altered microvascular function and peripheral atherosclerosis (in the carotid and femoral arteries) in a population of asymptomatic middle-aged individuals. Our results establish that the larger the atherosclerotic plaque burden and the number of affected vascular territories, the greater the impact on microvascular function, supporting the existence of a link between the microvascular and macrovascular circulatory compartments and the view of atherosclerosis as a systemic disease. Whether alterations in the microcirculation precede or parallel the development of atherosclerosis remains unclear,[6,7] but what does seem certain is the association between them. This association likely originates in cardiometabolic risk factors because these both alter coronary microvascular function and increase the risk of subclinical atherosclerosis,[31] which is in turn associated with altered microvascular function (**Central Illustration**). Moreover, peripheral atherosclerosis, which can be identified by means of noninvasive and inexpensive techniques such as a 3D vascular ultrasound, could be a useful predictive marker of altered microvascular function in asymptomatic individuals.

Lastly, a better microvascular function at baseline was associated with lower atherosclerotic burden and progression at follow-up, not only at the coronary level but also in the carotid and femoral territories. The presence of subclinical atherosclerosis has been previously defined as a strong predictor for cardiovascular events,[46-48] from what can be inferred that altered microvascular function, even in an

CENTRAL ILLUSTRATION **Cardiovascular Risk Factors and Subclinical Atherosclerosis are Associated With Altered Microvascular Function in Asymptomatic Middle-Aged Individuals**



Devesa A, et al. JACC Cardiovasc Imaging. 2024;■(■):■-■.

In asymptomatic middle-aged persons free of known cardiovascular disease, there is a link between the microvascular and the macrovascular segments of the circulation that is partly mediated by CVRF. CVRF (particularly the components of the metabolic syndrome, insulin resistance, and diabetes) alter coronary microvascular function and increase the risk of systemic subclinical atherosclerosis, which is in turn associated with changes in coronary microvascular function. Moreover, peripheral (carotid and/or femoral) and coronary subclinical atherosclerosis impact the coronary microcirculation, and this association is independent of CVRF. CVRF = cardiovascular risk factors; MBF = myocardial blood flow.

asymptomatic population, appears as a predictor of future adverse cardiovascular events.

STUDY LIMITATIONS. The selection of participants from the PESA cohort to undergo CMR was based on the detection of subclinical atherosclerosis using vascular ultrasound and/or CAC at baseline. However, the correlation we detected between plaque burden and altered MBF suggests that the inclusion of a subgroup without atherosclerosis would likely have revealed more marked differences in coronary microvascular function. Women were underrepresented, accounting for only 15.5% of the study population. Limited quality of MBF maps precluded the assessment of 9.4% of the studies; however, imaging quality was optimal in the remaining studies. Coronary angiography was not available in this cohort; however, a normal stress CMR has been linked to a high negative predictive value for coronary events.[19,49] Moreover, to compensate for the lack of coronary angiography and to the reduce the bias of any missed epicardial coronary artery stenosis, we excluded participants with an ischemic pattern on CMR, visual perfusion defects, or wall motion abnormalities. Longitudinal follow-up of participants would be desirable to compare the evolution of MBF according to the progression of CVRFs and subclinical atherosclerosis. The scheduled long-term follow-up in PESA places this study in a strong position to address this question.

CONCLUSIONS

In a large cohort of asymptomatic middle-aged individuals without IHD, the presence of cardiometabolic risk factors and systemic atherosclerosis is associated with altered coronary microvascular

function. The greater the cardiometabolic risk factor burden and the systemic extent of atherosclerosis, the larger the negative impact on coronary microvascular function. Moreover, better coronary microvascular function is associated with a lower risk of atherosclerosis progression at follow-up.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In asymptomatic middle-aged persons free of known cardiovascular disease, the presence of cardiovascular risk factors and systemic (poly-vascular) subclinical atherosclerosis is associated with altered coronary microvascular function.

TRANSLATIONAL OUTLOOK: Peripheral atherosclerosis, which can be identified by noninvasive and inexpensive techniques such as vascular ultrasound, could be a predictor of altered microvascular function in asymptomatic individuals.

REFERENCES

1. Del Buono MG, Montone RA, Camilli M, et al. Coronary microvascular dysfunction across the spectrum of cardiovascular diseases: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2021;78:1352–1371.

2. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med*. 2007;356:830–840.

3. Kelshiker MA, Seligman H, Howard JP, et al. Coronary flow reserve and cardiovascular outcomes: a systematic review and meta-analysis. *Eur Heart J*. 2022;43:1582–1593.

4. Taqueti VR, Hachamovitch R, Murthy VL, et al. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. *Circulation*. 2015;131:19–27.

5. Seraphim A, Dowsing B, Rathod KS, et al. Quantitative myocardial perfusion predicts outcomes in patients with prior surgical revascularization. *J Am Coll Cardiol*. 2022;79:1141–1151.

6. Pepine CJ, Anderson RD, Sharaf BL, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia: results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) Study. *J Am Coll Cardiol*. 2010;55:2825–2832.

7. Schroder J, Michelsen MM, Mygind ND, et al. Coronary flow velocity reserve predicts adverse prognosis in women with angina and no obstructive coronary artery disease: results from the iPOWER study. *Eur Heart J*. 2021;42:228–239.

8. Cecchi F, Olivotto I, Gistri R, Lorenzoni R, Chiriatti G, Camici PG. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. *N Engl J Med*. 2003;349:1027–1035.

9. Choi KH, Lee JM, Kim SR, et al. Prognostic value of the index of microcirculatory resistance over serum biomarkers in cardiac amyloidosis. *J Am Coll Cardiol*. 2020;75:560–561.

10. Sans-Roselló J, Fernández-Peregrina E, Duran-Cambra A, et al. Prognostic value of microvascular resistance at rest in patients with Takotsubo Syndrome. *JACC Cardiovasc Imaging*. 2022;15:1784–1795.

11. Pelliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of Takotsubo Syndrome. *Circulation*. 2017;135:2426–2441.

12. Shah SJ, Lam CSP, Svedlund S, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. *Eur Heart J*. 2018;39:3439–3450.

13. Taqueti VR, Solomon SD, Shah AM, et al. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. *Eur Heart J*. 2018;39:840–849.

14. Bugiardini R, Manfrini O, Pizzi C, Fontana F, Morgagni G. Endothelial function predicts future development of coronary artery disease. *Circulation*. 2004;109:2518–2523.

15. Mejia-Renteria H, Travieso A, Matías-Guiu JA, et al. Coronary microvascular dysfunction is associated with impaired cognitive function: the Cerebral-Coronary Connection study (C3 study). *Eur Heart J*. 2023;44:113–125.

16. Wang L, Jerosch-Herold M, Jacobs DR, Shahar E, Folsom AR. Coronary risk factors and myocardial perfusion in asymptomatic adults: the Multi-Ethnic Study of Atherosclerosis (MESA). *J Am Coll Cardiol*. 2006;47:565–572.

17. Jerosch-Herold M. Quantification of myocardial perfusion by cardiovascular magnetic resonance. *J Cardiovasc Magnet Reson*. 2010;12:57.

18. Kotecha T, Martinez-Naharro A, Boldrini M, et al. Automated pixel-wise quantitative myocardial perfusion mapping by CMR to detect obstructive coronary artery disease and coronary microvascular dysfunction: validation against invasive coronary physiology. *JACC Cardiovasc Imaging*. 2019;12:1958–1969.

19. Patel AR, Salerno M, Kwong RY, Singh A, Heydari B, Kramer CM. Stress cardiac magnetic resonance myocardial perfusion imaging: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2021;78:1655–1668.

20. Sammut EC, Villa ADM, Di Giovine G, et al. Prognostic value of quantitative stress perfusion cardiac magnetic resonance. *JACC Cardiovasc Imaging*. 2018;11:686–694.

21. Fernández-Ortiz A, Jiménez-Borreguero LJ, Peñalvo JL, et al. The progression and early

detection of subclinical atherosclerosis (PESA) study: rationale and design. *Am Heart J*. 2013;166:990–998.

22. de-la Chica JA, Gómez-Talavera S, García-Ruiz JM, et al. Association between left ventricular noncompaction and vigorous physical activity. *J Am Coll Cardiol*. 2020;76:1723–1733.

23. Ibanez B, Fernández-Ortiz A, Fernández-Friera L, García-Lunar I, Andrés V, Fuster V. Progression of Early Subclinical Atherosclerosis (PESA) study. *J Am Coll Cardiol*. 2021;78:156–179.

24. World Health Organization G 2000. Obesity: preventing and managing the global epidemic: report of a WHO Consultation.

25. Swarup S, Goyal A, Grigorova Y, Zeltser R. Metabolic syndrome. Accessed August 15, 2024. https://www.ncbi.nlm.nih.gov/books/NBK459248/

26. Pisprasert V, Ingram KH, Lopez-Davila MF, Munoz AJ, Garvey WT. Limitations in the use of indices using glucose and insulin levels to predict insulin sensitivity. *Diabetes Care*. 2013;36:845LP–853LP.

27. Sánchez-González J, Fernandez-Jiménez R, Nothnagel ND, López-Martín G, Fuster V, Ibañez B. Optimization of dual-saturation single bolus acquisition for quantitative cardiac perfusion and myocardial blood flow maps. *J Cardiovasc Magnet Reson*. 2015;17:21.

28. Kabus S, Lorenz C. Fast elastic image registration. In: *Proceedings of 13th meeting of medical image computing and computer assisted intervention (MICCAI)*. Springer; 2010:81–89.

29. Tofts PS, Brix G, Buckley DL, et al. Estimating kinetic parameters from dynamic contrast-enhanced t1-weighted MRI of a diffusible tracer: standardized quantities and symbols. *J Magnet Reson Imag*. 1999;10:223–232.

30. López-Melgar B, Fernández-Friera L, Oliva B, et al. Subclinical atherosclerosis burden by 3D ultrasound in mid-life: the PESA Study. *J Am Coll Cardiol*. 2017;70:301–313.

31. Fernández-Friera L, Peñalvo JL, Fernández-Ortiz A, et al. Prevalence, vascular distribution, and multiterritorial extent of subclinical atherosclerosis in a middle-aged cohort. *Circulation*. 2015;131:2104–2113.

32. Anon. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J*. 2021;42:2439–2454.

33. Knott KD, Seraphim A, Augusto JB, et al. The prognostic significance of quantitative myocardial perfusion. *Circulation*. 2020;141:1282–1291.

34. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. *Eur Heart J*. 2013;34:2436–2443.

35. Hinkel R, Howe A, Renner S, et al. Diabetes mellitus-induced microvascular destabilization in the myocardium. *J Am Coll Cardiol*. 2017;69:131–143.

36. Osborne M, Baja j N, Taqueti V, et al. Coronary microvascular dysfunction identifies patients at high risk of adverse events across cardiometabolic diseases. *J Am Coll Cardiol*. 2017;70:2835–2837.

37. Dayanikli F, Grambow D, Muzik O, Mosca L, Rubenfire M, Schwaiger M. Early detection of abnormal coronary flow reserve in asymptomatic men at high risk for coronary artery disease using positron emission tomography. *Circulation*. 1994;90:808–817.

38. Kaufmann PA, Gnecchi-Ruscone T, Schäfers KP, Lüscher TF, Camici PG. Low density lipoprotein cholesterol and coronary microvascular dysfunction in hypercholesterolemia. *J Am Coll Cardiol*. 2000;36:103–109.

39. Yokoyama I, Momomura S, Ohtake T, et al. Reduced myocardial flow reserve in non-insulin-dependent diabetes mellitus. *J Am Coll Cardiol*. 1997;30:1472–1477.

40. Brown LAE, Gulsin GS, Onciul SC, et al. Sex- and age-specific normal values for automated quantitative pixel-wise myocardial perfusion cardiovascular magnetic resonance. *Eur Heart J Cardiovasc Imag*. 2023;24:426–434.

41. Picchi A, Limbruno U, Focardi M, et al. Increased basal coronary blood flow as a cause of reduced coronary flow reserve in diabetic patients. *Am J Physiol Heart Circulatory Physiol*. 2011;301:H2279–H2284.

42. Sørensen MH, Bojer AS, Pontoppidan JRN, et al. Reduced myocardial perfusion reserve in type 2 diabetes is caused by increased perfusion at rest and decreased maximal perfusion during stress. *Diabetes Care*. 2020;43:1285–1292.

43. Guerraty MA, Rao HS, Anjan VY, et al. The role of resting myocardial blood flow and myocardial blood flow reserve as a predictor of major adverse cardiovascular outcomes. *PLoS One*. 2020;15:e0228931.

44. Devesa A, Fuster V, Vazirani R, et al. Cardiac insulin resistance in subjects with metabolic syndrome traits and early subclinical atherosclerosis. *Diabetes Care*. 2023;46(11):2050–2057.

45. Wang L, Jerosch-Herold M, Jacobs DR, Shahar E, Detrano R, Folsom AR. Coronary artery calcification and myocardial perfusion in asymptomatic adults: the MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2006;48:1018–1026.

46. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med*. 2008;358:1336–1345.

47. Baber U, Mehran R, Sartori S, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage Study. *J Am Coll Cardiol*. 2015;65:1065–1074.

48. Budoff MJ, Young R, Burke G, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the Multi-Ethnic Study of Atherosclerosis (MESA). *Eur Heart J*. 2018;39:2401–2408.

49. Gargiulo P, Dellegrottaglie S, Bruzzese D, et al. The prognostic value of normal stress cardiac magnetic resonance in patients with known or suspected coronary artery disease. *Circ Cardiovasc Imag*. 2013;6:574–582.

KEY WORDS cardiovascular risk factors, coronary microvascular function, quantitative cardiac magnetic resonance myocardial perfusion, subclinical atherosclerosis

APPENDIX For supplemental tables, please see the online version of this paper.