Coronary Circulatory Function in Patients with the Metabolic Syndrome

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The metabolic syndrome affects 25% of the U.S. population and greatly increases the risk of diabetes and coronary artery disease (CAD). We tested the hypothesis that the metabolic syndrome is associated with impaired coronary vasodilator function, a marker of atherosclerotic disease activity. **Methods:** Four hundred sixty-two patients at risk for CAD, as defined by a low-density lipoprotein cholesterol $\geq$ 160 mg/dL with fewer than 2 coronary risk factors, a low-density lipoprotein cholesterol $\geq$ 130 mg/dL with 2 or more coronary risk factors, or with documented CAD were included. A subset of 234 individuals underwent repeated PET at 1 y. Myocardial blood flow (MBF) and vasodilator reserve were assessed by PET. Modified criteria of the National Cholesterol Education Program, Adult Treatment Panel III were used to characterize the metabolic syndrome. **Results:** Adenosine- and cold-stimulated MBF were similar in patients with and without metabolic syndrome, whereas baseline MBF showed a stepwise increase with increasing features of the syndrome. Consequently, patients with metabolic syndrome showed a lower coronary flow reserve (CFR) (2.5 $\pm$ 1.0) than those without metabolic syndrome (3.0 $\pm$ 0.9, P = 0.004). Differences in CFR were no longer present after correcting rest flows for the rate–pressure product. Change in MBF and CFR at 1 y were not different across groups of patients with increasing features of the metabolic syndrome. **Conclusion:** Patients with metabolic syndrome demonstrate impaired CFR, which is related to the augmentation in resting coronary blood flow caused by hypertension. In high-risk individuals, peak adenosine- and cold-stimulated blood flows are impaired even in the absence of the metabolic syndrome.

Key Words: cardiology (clinical); PET/CT; other; coronary blood flow; metabolic syndrome

In 1988, Reaven demonstrated that a cluster of risk factors, including abdominal obesity, hypertension, impaired fasting glucose, and dyslipidemia, was strongly associated with the risk of coronary artery disease (CAD) (*1*). The term *metabolic syndrome* emerged to describe this clustering, and metabolic syndrome is now recognized to have a prevalence of 25% of the adult population of the United States (*2*).

Vascular dysfunction, including that caused by endothelial dysfunction, is an early abnormality in the metabolic syndrome that may contribute to premature atherosclerosis (*3*). Each of the components of the metabolic syndrome has been independently associated with vascular dysfunction (*4–8*). In addition to insulin resistance, release of proinflammatory cytokines (e.g., interleukin-6, tumor necrosis factor-α) by visceral adipose tissue or other as yet undefined factors may also contribute to vascular dysfunction (*9*) or adverse clinical outcomes (*10,11*) in patients with the metabolic syndrome. However, they do not together fully explain the 2.6-fold increased risk of coronary death among those with the metabolic syndrome (*12*), suggesting that other mechanisms may contribute to the association between the metabolic syndrome and the increased risk of CAD. One such mechanism may involve the potential adverse effect of features of the metabolic syndrome on vascular function and, in particular, endothelial function, thereby increasing the potential for atherothrombotic complications (*13*).

We tested the hypothesis that the metabolic syndrome is associated with impaired coronary vascular function in a large cohort of high-risk patients with diverse risk factors, including the metabolic syndrome and established CAD.

MATERIALS AND METHODS

Patient Population

We included men and women (18–75 y) at risk for or with documented CAD, who completed the screening phase of the RAMPART (Relative and Absolute Myocardial Perfusion changes as measured by Positron Emission Tomography to Assess the Effects of ACAT Inhibition: A Double-Blind, Randomized, Con-

trolled, Multicenter Trial). The RAMPART was a phase II clinical trial designed to determine the effects of avasimibe (Acyl coenzyme A: cholesterol acyltransferase inhibitor) on myocardial blood flow (MBF) in patients with documented or at risk for CAD. Patients were considered to have CAD if they had a history of stable angina, a positive stress electrocardiogram, an abnormal stress myocardial perfusion or stress echocardiography study, an abnormal coronary angiogram, or prior revascularization. Patients with a low-density lipoprotein cholesterol (LDL-C) $\geq$ 160 mg/dL with fewer than 2 coronary risk factors or an LDL-C $\geq$ 130 mg/dL with 2 or more coronary risk factors were considered to be at risk for CAD. Women of childbearing potential were excluded, as were patients with known diabetes, advanced renal dysfunction, active liver disease or hepatic dysfunction, skeletal myopathy, uncontrolled hypertension, valvular heart disease, symptomatic heart failure, historical or diagnostic evidence of left ventricular hypertrophy, unstable angina pectoris, or dilated cardiomyopathy (left ventricular ejection fraction < 40%).

Individuals with a coronary flow reserve less than 2.5 in at least 1 arterial territory or a stress defect occupying $\geq$ 15% of at least 1 coronary territory received a low-cholesterol diet for 4 wk. Individuals with a low-density lipoprotein (LDL) $\geq$ 100 mg/dL after 4 wk on this diet were randomized to 1 y of therapy with avasimibe plus atorvastatin (10 mg/d) or atorvastatin plus placebo. Two hundred thirty-four patients who met these criteria were randomized and underwent repeated scanning at 1 y.

Definition of Metabolic Syndrome

A battery of risk factors and other demographic variables were assessed at baseline, allowing classification of the patients in the study according to the number of components of the metabolic syndrome, on the basis of the modified criteria of the National Cholesterol Education Program (NCEP) (14), with body mass index (BMI) in place of waist circumference (10,15,16). Accordingly, the 5 thresholds used were triglycerides level $\geq$ 150 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL in men and < 50 mg/dL in women, systolic blood pressure $\geq$ 130 mm Hg or diastolic blood pressure $\geq$ 85 mm Hg, fasting glucose $\geq$ 110 mg/dL, and BMI > 28.8 kg/m^2 (16). According to the NCEP, patients were considered as having metabolic syndrome if they fulfilled 3 or more of these criteria.

Measurements of MBF

Patients underwent PET for assessment of MBF using whole-body PET tomographs (Siemens/CTI) at 12 U.S. sites. All subjects refrained from caffeine-containing beverages or theophylline-containing medications for 24 h before the PET study. Patients using calcium channel blockers or β-blockers were instructed to withhold the medications for 24 h before the PET study. All subjects were studied in the fasting state.

MBF was measured at rest and during peak hyperemia as described previously (17) using ^{13}N-ammonia. A 10- to 15-min transmission scan was acquired for correction of photon attenuation. Beginning with the intravenous bolus administration of ^{13}N-ammonia (10.582 MBq/kg [0.286 mCi/kg]), serial images were acquired for 19 min. Thirty minutes later, adenosine (0.14 mg/kg/min) was infused intravenously for 6 min. Three minutes into the adenosine infusion, a second dose of ^{13}N-ammonia was injected, and images were recorded in the same acquisition sequence. In a subgroup of patients ($n = 109$), cold pressor testing was also performed as previously described (17). Briefly, cold stimulation was performed by immersing the patient's hand and forearm in ice water (equal parts of ice and water at

0°C–2°C) for 3 min. Ninety seconds into the cold stimulus, a third dose of ^{13}N-ammonia (10.582 MBq/kg [0.286 mCi/kg]) was injected, and images were recorded in the same manner. The heart rate, blood pressure, and 12-lead electrocardiogram were recorded at baseline and throughout the infusion of adenosine and the cold pressor test. Imaging equipment used in the trial was validated for quality control and measurement of reproducibility by a core laboratory (UCLA School of Medicine). Image acquisition protocols were standardized at each site, and MBF was measured at the core laboratory.

Data Analysis

The serially acquired transaxial images were reoriented into short-axis slices of the heart and assembled into serial polar maps. Regions of interest were assigned to coronary vascular territories on the last 15-min polar map and copied to the serial polar maps acquired during the initial 2 min after intravenous ^{13}N-ammonia injection. An additional small, circular region of interest was assigned to the center of the left ventricular blood pool. Regional myocardial and blood-pool time–activity curves were then generated. In each coronary territory, MBF was calculated by fitting the ^{13}N-ammonia time–activity curves with a 2-compartment tracer kinetic model. The coronary flow reserve (primary study endpoint) was defined as the ratio between hyperemic and basal MBF. An index of coronary vascular resistance was calculated by dividing the mean arterial blood pressure by MBF. Coronary flow reserve and resistance values are the average of the entire left ventricular myocardium, except for patients with perfusion defects, for whom the values derived from the regional perfusion defect are reported. To account for differences in cardiac work, resting MBF values were normalized to the corresponding rate–pressure product by dividing the resting blood flow value by the rate–pressure product (an index of cardiac work), multiplied by a linear factor of 10,000 in each individual patient. Corrected coronary flow reserve was also calculated as the ratio between hyperemic and normalized basal MBF.

Laboratory Analyses

A central laboratory (Medical Research Laboratories) performed all clinical and lipid analyses as specified by the standardization program of the Centers for Disease Control and Prevention and the National Heart, Lung and Blood Institute (18). Venous plasma and serum samples were taken after an overnight fast. Plasma glucose was measured by the glucose oxidase method. Plasma total cholesterol and total triglycerides were determined enzymatically with the Hitachi 747 analyzer (19). Plasma HDL-C was determined enzymatically after LDL-C and very-low-density lipoprotein cholesterol were selectively removed from the plasma sample by heparin and magnesium chloride precipitation (20). LDL-C was calculated using the Friedewald formula (21), except in situations in which triglycerides were greater than 400 mg/dL, at which time LDL-C was derived using the β-Quant method. C-reactive protein (CRP) was measured using a latex-enhanced immunonephelometric assay on a BN II analyzer (Dade Behring) (22). Plasminogen activator inhibitor type 1 (PAI-1) levels were measured using a commercially available sandwich enzyme-linked immunosorbent assay (R&D Systems and American Diagnostics). Serum creatinine and BUN were also obtained.

Statistical Analysis

Data are presented as mean ± SD. Differences in baseline characteristics of patients, coronary blood flow, coronary vascular resistance, and coronary flow reserve between groups were compared using single-factor ANOVA. Significant main effects for

group were followed with Tukey post hoc tests to identify differences between groups. A MANCOVA design was used to investigate differences in adjusted MBF, coronary vascular resistance, and flow reserve between groups. Independent predictors of changes in coronary flow reserve in response to adenosine at baseline and the change in vasodilator reserve over time were investigated using multiple-regression analysis. The SPSS statistical package (version 18; SPSS Software) was used for analyses. For all analyses, an α of 0.05 was used to define statistical significance.

RESULTS

Baseline Characteristics

Table 1 summarizes the baseline characteristics of the study population. Sex distribution and the proportion of active smokers and patients with CAD were similar in the 3 groups studied. As expected, there was a stepwise increase in BMI, total cholesterol, triglycerides, triglyceride/HDL-C ratio (a close correlate of insulin resistance/hyperinsulinemia) (23,24), plasma glucose, and blood pressure, with the characteristic stepwise reduction in HDL-C with increasing number of features of the metabolic syndrome. There was no difference in LDL-C between the groups.

Differences in CRP and PAI-1 Levels

CRP and PAI-1 levels were available for 293 patients. Figure 1 demonstrates stepwise increases in both CRP and PAI-1 levels with increasing features of the metabolic syndrome, confirming the correct characterization of patients in the study (25).

MBF, Coronary Vascular Resistance, and Flow Reserve in Patients with Metabolic Syndrome

Table 2 summarizes the differences in MBF and coronary vascular resistance in the study groups. There was a stepwise increase in baseline MBF with increasing features of the metabolic syndrome, reflecting the increase in blood pressure and, consequently, cardiac work and myocardial oxygen demand in patients with metabolic syndrome. In fact, these differences were no longer present after normalization of resting blood flow by the rate–pressure product, as an index of cardiac work.

During peak hyperemia, MBF increased and coronary vascular resistance decreased significantly in the 3 groups. However, peak adenosine-stimulated MBF was similar in the 3 groups (Fig. 2). Similar results were observed when only patients without CAD were analyzed (Table 3).

Consequently, there was a reduction in coronary flow reserve with increasing features of the metabolic syndrome (Fig. 3). Patients with 3 or more features of the syndrome showed a 17% relative reduction in coronary flow reserve compared with those without metabolic syndrome (Fig. 3, top), even after adjusting for age, sex, and a history of prior CAD. However, the difference in flow reserve was no longer seen after correcting the rest flows for the rate–pressure product (Fig. 3, bottom).

In the subgroup of patients who underwent cold pressor testing ($n = 109$), MBF increased significantly in the 3 groups studied (Table 2). However, the magnitude of flow increase was similar in the 3 groups (Fig. 4). Comparable results were observed when only patients without CAD were analyzed (Table 3).

### Predictors of Abnormalities in Coronary Flow Reserve in Patients with Metabolic Syndrome

Multivariable modeling including age, sex, a history of prior CAD, a history of active smoking, and the modified NCEP diagnostic criteria for metabolic syndrome (fasting

TABLE 1
Baseline Characteristics of Patients

Variable	All patients	Patients with features of metabolic syndrome			P
		No features	1 or 2 features	3 or more features	
Age (y)	58 ± 10	56 ± 11	59 ± 10	56 ± 10	0.01
Female sex	129 (28)	9 (24)	74 (30)	46 (25)	0.46
Smokers	87 (19)	9 (24)	36 (15)	42 (23)	0.06
Prior CAD	115 (25)	4 (11)	60 (25)	51 (28)	0.07
BMI	30 ± 6	25 ± 2	28 ± 4	33 ± 7	<0.001
Total cholesterol (mg/dL)	241 ± 46	228 ± 36	240 ± 46	245 ± 48	0.09
HDL-C (mg/dL)	46 ± 13	52 ± 9	51 ± 13	39 ± 9	<0.001
LDL-C (mg/dL)	152 ± 41	152 ± 33	153 ± 38	152 ± 46	0.97
Triglycerides (mg/dL)	220 ± 162	114 ± 23	186 ± 132	288 ± 187	<0.001
Triglyceride/HDL-C	5.6 ± 6.3	2.3 ± 0.7	4.2 ± 4.7	8.3 ± 7.7	<0.001
Plasma glucose (mg/dL)	98 ± 19	88 ± 10	94 ± 11	105 ± 25	<0.001
Blood urea nitrogen (mg/dL)	16 ± 4	16 ± 3	16 ± 4	16 ± 4	0.69
Creatinine (mg/dL)	1.15 ± 0.17	1.15 ± 0.14	1.13 ± 0.18	1.18 ± 0.17	0.02
Rest heart rate (bpm)	62 ± 11	59 ± 9	61 ± 10	63 ± 11	0.09
Systolic blood pressure (mm Hg)	132 ± 21	112 ± 10	132 ± 21	135 ± 19	<0.001
Diastolic blood pressure (mm Hg)	71 ± 10	65 ± 9	72 ± 10	73 ± 10	<0.001
Rest rate–pressure product	8,158 ± 2,072	6,623 ± 1,089	8,111 ± 2,048	8,146 ± 2,112	<0.001

bpm = beats per minute.

$n = 462$ for all patients; 37 for patients with no features of metabolic syndrome, 244 for patients with 1 or 2 features, and 181 for patients with 3 or more features. Data are mean ± SD, or n with percentage in parentheses.
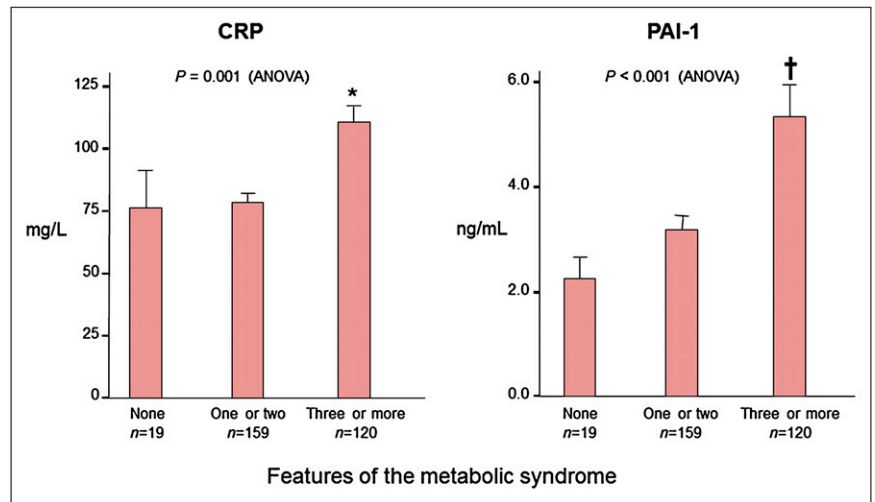
FIGURE 1. Relationship between mean CRP and PAI-1 levels and features of metabolic syndrome. *$P = 0.03$ vs. none, and $P = 0.001$ vs. 1 or 2. †$P = 0.05$ vs. none, and $P < 0.001$ vs. 1 or 2.

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glucose, triglycerides, blood pressure, HDL-C, and BMI) was performed to identify factors associated with coronary flow reserve. In the final model ($R = 0.35$, $P < 0.001$), variables associated with an impaired coronary flow reserve were hypertension (R^2 change = 0.04, $F_{460} = 20$, $P < 0.001$), male sex (R^2 change = 0.03, F_{459} change = 13, $P < 0.001$), a history of prior CAD (R^2 change = 0.03, $F_{458} = 15$, $P < 0.001$), age (R^2 change = 0.01, F_{457} change = 7, $P = 0.01$), and active smoking (R^2 change = 0.008, $F_{456} = 4$, $P = 0.04$). A similar model in patients without CAD revealed ($R = 0.37$, $P < 0.001$) that impaired coronary flow reserve was associated with male sex (R^2 change = 0.07, $F_{340} = 24$, $P < 0.001$), age (R^2 change = 0.04, F_{339} change = 16, $P < 0.001$), a history of hypertension (R^2 change = 0.02, $F_{338} = 6$, $P = 0.012$), and active smoking (R^2 change = 0.01, $F_{337} = 4$, $P = 0.04$).

To determine the relative contribution of systemic inflammation and PAI-1 levels to the impaired coronary flow reserve, a separate multivariable analysis was per-

formed in the subgroup of patients with CRP and PAI-1 data. In addition to the variables included in the original model, CRP and PAI-1 were also considered in this analysis. In this model ($R = 0.31$, $P < 0.001$), impaired coronary flow reserve was associated with active smoking (R^2 change = 0.03, F_{291} change = 10, $P = 0.002$), a history of prior CAD (R^2 change = 0.02, F_{290} change = 6, $P = 0.011$), male sex (R^2 change = 0.03, F_{289} change = 8, $P = 0.006$), and the PAI-1 level (R^2 change = 0.02, F_{288} change = 6, $P = 0.017$). The CRP level was not a predictor of impaired coronary flow reserve ($P = 0.95$).

Change in MBF and Coronary Vascular Resistance over Time

MBF was measured in a subset of 234 patients after 1 y of randomized therapy. Associations between the metabolic syndrome and the change in indices of MBF over time are summarized in Table 4. Within this subset, there were non-

TABLE 2
MBF and Coronary Vascular Resistance in All Study Patients

Variable	All patients	Patients with features of metabolic syndrome		
		No features	1 or 2 features	3 or more features
MBF (mL/min/g)				
Baseline	0.78 ± 0.25	0.65 ± 0.15	0.78 ± 0.26	0.80 ± 0.25
Baseline-corrected	0.97 ± 0.23	0.99 ± 0.21	0.98 ± 0.24	0.94 ± 0.22
Adenosine	1.88 ± 0.68	1.90 ± 0.59	1.83 ± 0.64	1.94 ± 0.75
Coronary vasodilator reserve	2.6 ± 1.0	3.0 ± 0.9	2.5 ± 0.9	2.5 ± 1.0
Coronary vasodilator–reserve corrected	1.96 ± 0.7	2.0 ± 0.6	1.9 ± 0.7	2.03 ± 0.7
Coronary vascular resistance (mL/min/g/mm Hg)				
Baseline	127 ± 37	131 ± 33	126 ± 37	127 ± 38
Adenosine	54 ± 23	50 ± 22	54 ± 21	55 ± 25
Cold pressor test* (mL/min/g)	0.90 ± 0.31	0.72 ± 0.25	0.94 ± 0.32	0.87 ± 0.29
Increase from baseline* (%)	17 ± 30	13 ± 12	21 ± 30	12 ± 30

*Cold pressor testing was performed on only a subgroup of patients ($n = 109$), of whom 7 had no features of metabolic syndrome, 54 had 1 or 2 features, and 48 had 3 or more features. Rest of table contains data for entire group of patients ($n = 462$), of whom 37 had no features of metabolic syndrome, 244 had 1 or 2 features, and 181 had 3 or more features.
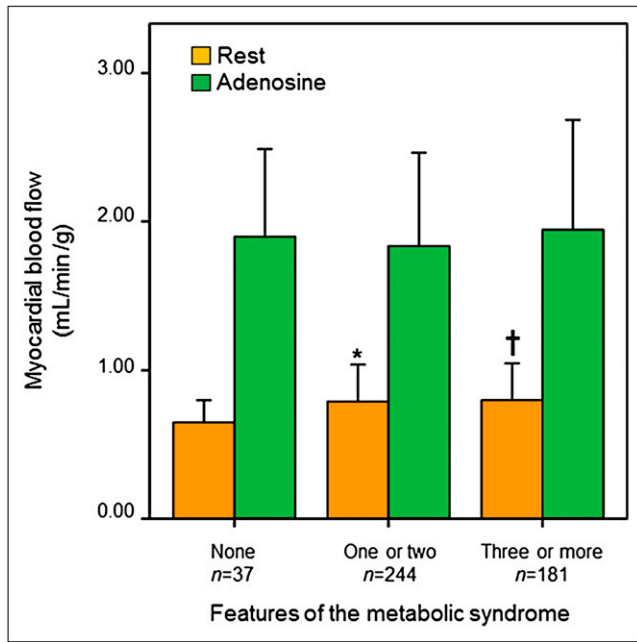
Data are mean ± SD.

FIGURE 2. Relationship between mean rest and adenosine-stimulated coronary blood flow and features of metabolic syndrome. *P = 0.007 vs. none. †P = 0.003 vs. none.

significant trends toward a stepwise increase in resting MBF at baseline ($P = 0.07$) and a decrease in baseline coronary vascular resistance ($P = 0.07$) with increasing features of the metabolic syndrome. Conversely, there was a significant decrease in coronary vasodilator reserve with increasing features of the metabolic syndrome ($P = 0.01$). In unadjusted analyses, there were no significant differences in the change in MBF or vascular resistance between individuals with 0, 1–2, or 3 or more parameters of the metabolic syndrome (Table 3). In multivariable anal-

yses adjusted for randomized therapy, only age of 40–60 y ($R = -0\ 0.79$, $P = 0.03$) and more than 60 y ($R = -1.04$, $P = 0.006$), compared with age less than 40 y, were significant predictors of an increased loss in vasodilator reserve over time. The number of components of the metabolic syndrome was not associated with the change in vasodilator reserve at 1 y in models incorporating indicator variables for the components of the syndrome.

DISCUSSION

This study demonstrates in a large cohort of patients that coronary flow reserve, as a measure of vascular health, is impaired in high-risk patients with the metabolic syndrome. Subjects with metabolic syndrome, based on the presence of 3 or more NCEP diagnostic criteria, showed a significant 17% relative reduction in coronary flow reserve, compared with subjects without the syndrome. This difference persisted after adjusting for age, sex, and a history of prior CAD. This reduction in coronary flow reserve appeared to be related to an increase in resting MBF rather than reduced peak adenosine-stimulated blood flow. Indeed, coronary flow reserve was similar in all groups studied when corrected rest blood flow (for rate–pressure product) was used in the calculation of flow reserve. Likewise, in subgroup analysis all 3 groups showed similar increases in MBF in response to cold pressor testing. These results were consistent in patients with and without overt CAD.

Patients in the RAMPART study were recruited on the basis of the presence of either dyslipidemia (LDL > 130 mg/dL) or documented CAD and did not include healthy controls. However, all 3 groups in our study had a peak adenosine-stimulated MBF that was approximately 20% lower than that reported among age-matched healthy controls using the same methodology (8,26). Similarly, the increase in

TABLE 3
MBF and Coronary Vascular Resistance in Only Patients Without CAD

Variable	All patients	Patients with features of metabolic syndrome			P
		No features	1 or 2 features	3 or more features	
MBF (mL/min/g)					
Baseline	0.78 ± 0.25	0.66 ± 0.15	0.80 ± 0.26	0.80 ± 0.24	0.008
Baseline-corrected	0.97 ± 0.23	1.0 ± 0.21	0.98 ± 0.24	0.94 ± 0.22	0.221
Adenosine	1.95 ± 0.63	1.85 ± 0.55	1.91 ± 0.62	2.03 ± 0.66	0.181
Coronary vasodilator reserve	2.6 ± 0.9	2.9 ± 0.9	2.6 ± 0.9	2.7 ± 1.0	0.133
Coronary vasodilator reserve–corrected	2.0 ± 0.6	1.9 ± 0.5	1.99 ± 0.6	2.13 ± 0.7	0.105
Coronary vascular resistance (mL/min/g/mm Hg)					
Baseline	127 ± 38	130 ± 34	125 ± 39	127 ± 37	0.747
Adenosine	51 ± 18	51 ± 22	51 ± 18	50 ± 17	0.836
Cold pressor test (mL/min/g)	0.91 ± 0.31	0.74 ± 0.27	0.97 ± 0.34	0.87 ± 0.27	0.179
Increase from baseline (%)	21 ± 30	14 ± 12	23 ± 32	18 ± 29	0.705

*Cold pressor testing was performed on only a subgroup of patients ($n = 79$), of whom 5 had no features of metabolic syndrome, 41 had 1 or 2 features, and 33 had 3 or more features. Rest of table contains data for entire group of patients ($n = 349$), of whom 34 had no features of metabolic syndrome, 185 had 1 or 2 features, and 130 had 3 or more features.
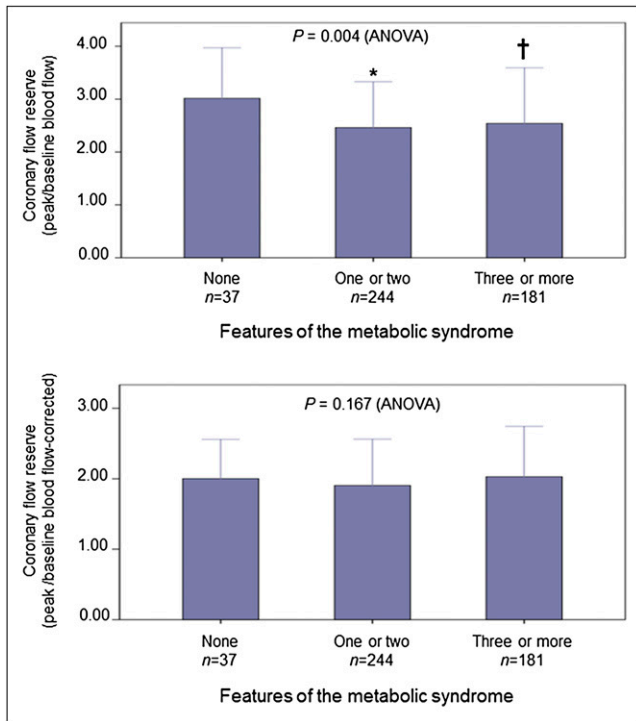
Data are mean ± SD.

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FIGURE 3. Relationship between mean coronary flow reserve (ratio between adenosine-stimulated and baseline coronary blood flow) (top) and corrected coronary flow reserve (bottom) and features of metabolic syndrome. *$P = 0.003$ vs. none. †$P = 0.015$ vs. none.

blood flow during cold pressor testing was approximately 60% lower than that reported in nonobese healthy subjects (8,17). Therefore, our findings are consistent with the presence of impaired vasodilator responses to both adenosine and cold pressor testing in at-risk individuals, such as those included in the study, and provide further evidence for the early presence of impaired endothelium-independent and endothelium-dependent coronary vasodilator function in patients with coronary risk factors. Importantly, our study
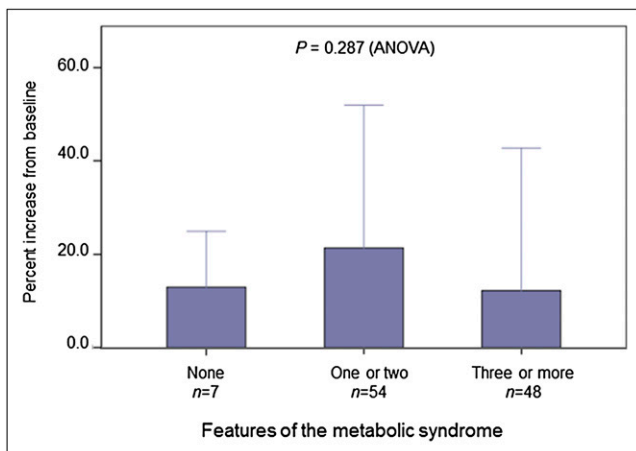

FIGURE 4. Subgroup analysis demonstrating relationship between coronary blood flow response to cold pressor testing and features of metabolic syndrome.

suggests that these abnormalities in coronary vasodilator function are not worsened by the combined presence of high-risk features that define the metabolic syndrome.

The vasodilator response to adenosine reflects the integrated effects of both vascular smooth muscle and endothelial cell function (27), whereas the corresponding increase in blood flow in response to cold reflects primarily endothelium-mediated vasodilation (28). The finding that peak adenosine- and cold-stimulated MBF was similar in patients with and without the metabolic syndrome suggests a rather weak contribution of insulin resistance per se to coronary microvascular dysfunction, beyond that caused by already-established cardiovascular risk factors (i.e., dyslipidemia, smoking, and CAD). These findings are new and potentially important and consistent with a recent analysis of an 8-y follow-up of 3,323 Framingham offspring (29). In this analysis, Framingham investigators examined whether the cardiovascular risk of metabolic syndrome is greater than the sum of its component risk factors. The results of this analysis suggest that most of the risk associated with the metabolic syndrome is captured by age, blood pressure, total cholesterol, diabetes, and HDL-C. Beyond these, abdominal obesity, triglycerides, and fasting glucose levels (in the absence of diabetes) added little to the power of prediction.

In asymptomatic subjects without clinical CAD, coronary flow reserve shows a modest inverse relationship with estimated 10-y Framingham coronary heart disease risk (30). Although the metabolic syndrome is related to an increased risk of CAD events, individuals with metabolic syndrome encompass a wide range of risk levels (31). The findings of this study suggest that the addition of higher risk patients with metabolic syndrome does not contribute significantly to the identification of patients with abnormal microvascular function beyond the information provided by individual risk factors in lower risk individuals. A quarter of the patients in this study had documented CAD. Although the metabolic syndrome has been used as an educational target to decrease the risk of diabetes and CAD in the general population, its presence has clinical importance even after CAD develops. Indeed, in the EUROPA trial including more than 8,000 patients with established CAD, the metabolic syndrome was associated with greater than a 2-fold increase in cardiovascular death, and a 50% increase in the frequency of myocardial infarction, even after adjustment for conventional risk factors (10). The effect of the metabolic syndrome on cardiovascular events was independent of its association with diabetes, and the risks associated with diabetes and the metabolic syndrome were incremental to each other. Similar findings have been reported in the WIZARD study (11). Our findings suggest that the increased risk associated with the metabolic syndrome in high-risk individuals may be related to the effect of insulin resistance on atherosclerosis burden (32) rather than coronary microvascular function (33).

In multivariable analysis, factors that were independently associated with an impaired coronary vasodilator reserve

TABLE 4
Change in MBF and Coronary Vascular Resistance over Time in Patients with Baseline and Follow-up Scanning

| Variable | All patients | Patients with features of metabolic syndrome | | | P |
		No features	1 or 2 features	3 or more features	
Rest MBF (mL/min/g)					
Baseline	0.83 ± 0.24	0.70 ± 0.16	0.82 ± 0.26	0.87 ± 0.24	0.07
Follow-up	0.79 ± 0.26	0.74 ± 0.20	0.79 ± 0.2	0.81 ± 0.27	0.23
Change at 1 y	−0.04 ± 0.07	0.03 ± 0.26	−0.02 ± 0.25	−0.06 ± 0.28	0.84
Hyperemic MBF (mL/min/g of tissue)					
Baseline	1.69 ± 0.57	1.80 ± 0.58	1.66 ± 0.51	1.72 ± 0.65	0.19
Follow-up	1.78 ± 0.68	1.71 ± 0.57	1.78 ± 0.69	1.79 ± 0.69	0.95
Change at 1 y	0.08 ± 0.68	−0.09 ± 0.82	0.12 ± 0.66	0.07 ± 0.69	0.82
Coronary vasodilator reserve					
Baseline	2.13 ± 0.75	2.60 ± 0.84	2.11 ± 0.66	2.09 ± 0.84	0.01
Follow-up	2.37 ± 0.98	2.34 ± 0.70	2.35 ± 1.00	2.40 ± 1.01	0.91
Change at 1 y	0.24 ± 1.00	−0.26 ± 1.06	0.24 ± 1.00	0.32 ± 0.98	0.96
Rest coronary vascular resistance (mL/min/g/mm Hg)					
Baseline	120.1 ± 33.2	121.5 ± 24.7	121.3 ± 34.3	118.3 ± 33.3	0.07
Follow-up	125.9 ± 40.2	124.8 ± 37.5	123.4 ± 38.6	129.4 ± 42.8	0.33
Change at 1 y	5.75 ± 40.9	3.38 ± 47.7	2.12 ± 39.4	11.1 ± 41.6	0.46
Hyperemic coronary vascular resistance (mL/min/g/mm Hg)					
Baseline	59.3 ± 24.3	51.2 ± 16.8	58.7 ± 20.7	61.5 ± 29.4	0.34
Follow-up	58.4 ± 25.6	56.4 ± 20.6	57.5 ± 26.1	59.9 ± 26.0	0.99
Change at 1 y	−0.93 ± 27.1	5.29 ± 28.8	−1.26 ± 24.5	−1.56 ± 30.2	0.89

n = 234 for all patients, 16 for patients with no features of metabolic syndrome, 125 for patients with 1 or 2 features, and 93 for patients with 3 or more features. Data are mean ± SD.

included a history of hypertension, a history of prior CAD, age, and active smoking. No other features of the metabolic syndrome contributed significantly to the prediction of the impaired coronary vasodilator reserve in this high-risk population. The results of multivariable modeling were similar in the subgroup of patients without overt CAD, suggesting a dynamic contribution of different risk factors at various stages in the development of atherosclerosis. It is recognized that dyslipidemia (5,6), diabetes (7), and hypertension (34) contribute to impaired coronary flow reserve when each is present in isolation. However, as these factors coalesce and the metabolic syndrome develops, hypertension, age, smoking, and, ultimately, obstructive CAD predominate in determining the health of the coronary vasculature. Indeed, by the time these patients become high-risk, as in this study, the constellation of risk factors associated with the metabolic syndrome per se appears to have a less substantive effect in determining vascular health.

A novel feature of our study design is that it allowed us to analyze the association of the metabolic syndrome with changes in perfusion, vascular resistance, and flow reserve after 1 y of follow-up. To our knowledge, ours is the first study to examine the effects of the metabolic syndrome on longitudinal changes in indices of myocardial perfusion. Interestingly, we did not find any significant associations between the metabolic syndrome and the change in these indices over time. These data should be interpreted within the context of the relatively small sample size, relatively short duration of follow-up, and requirement for a baseline reduced flow reserve in the cohort undergoing repeated imaging. Nevertheless, our finding that the presence of the metabolic syndrome is not associated with accelerated losses of MBF and flow reserve or greater increases in vascular resistance at 1 y lends supports to the concept that insulin resistance may not substantively affect endothelial function in individuals with preexisting cardiovascular disease, advanced age, hypertension, or smoking.

Our results contrast with a previous study reporting an association between obesity and insulin resistance and endothelial dysfunction (35). Steinberg et al. reported a blunted increase in leg blood flow in response to methacholine in a small group of young obese and insulin-resistant subjects, compared with a group of lean controls (35). In the study by Steinberg et al., however, there were important differences in lipids (HDL-C, LDL-C, and triglycerides) and blood pressure between the obese and insulin-resistant subjects and the controls. Thus, it is difficult to ascertain the relative contribution of the differences in lipids and blood pressure between the patients and controls and insulin resistance per se to the observed abnormalities in endothe-

lium-dependent blood flow increase in response to metha-
choline.

Several factors should be considered when interpreting the
results of this study. Although the data were collected on a
prospective cohort, the analysis is retrospective. The study
substituted BMI over waist circumference in calculating the
number of components of the metabolic syndrome. Although
waist circumference is a preferable measure of abdominal
obesity, as explained it is closely related to BMI (*15,16*) and
predictive of cardiovascular events (*10,16*).

CONCLUSION

This study demonstrates that in high-risk patients, the
cluster of metabolic and hemodynamic abnormalities
present with the metabolic syndrome are associated with
impaired coronary vasodilator reserve, even in the absence
of obstructive CAD. This abnormality appears to be related
to an augmentation in resting MBF, likely reflecting the
increased blood pressure in patients with metabolic syn-
drome. Our finding that peak adenosine- and cold-stimu-
lated blood flows are impaired in patients with established
cardiovascular risk factors, even in the absence of the
metabolic syndrome, suggests that by the time patients
develop high-risk characteristics, the contribution of the
metabolic syndrome to coronary microvascular health is
diminished.

DISCLOSURE STATEMENT

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