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Invasive Evaluation of Patients with Angina in the Absence of Obstructive Coronary Artery Disease

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Abstract

Background—More than 20% of patients presenting to the cardiac catheterization laboratory with angina have no angiographic evidence of coronary artery disease (CAD). Despite a “normal” angiogram, these patients often have persistent symptoms, recurrent hospitalizations, a poor functional status, and adverse cardiovascular outcomes, without a clear diagnosis.

Methods and Results—In 139 patients with angina in the absence of obstructive CAD (no diameter stenosis >50%), endothelial function was assessed, the index of microcirculatory resistance (IMR), coronary flow reserve (CFR), and fractional flow reserve (FFR) were measured, and intravascular ultrasound (IVUS) was performed. There were no complications. The average age was 54.0±11.4 years and 107 (77%) were women. All patients had at least some evidence of atherosclerosis based on IVUS examination of the LAD. Endothelial dysfunction (a decrease in luminal diameter of >20% after intracoronary acetylcholine) was present in 61 patients (44%). Microvascular impairment (an IMR ≥25) was present in 29 patients (21%). Seven patients (5%) had an FFR ≤0.80. A myocardial bridge was present in 70 patients (58%). Overall, only 32 patients (23%) had no coronary explanation for their angina, with normal endothelial function, normal coronary physiologic assessment, and no myocardial bridging.

Conclusions—The majority of patients with angina in the absence of obstructive CAD have occult coronary abnormalities. A comprehensive invasive assessment of these patients at the time of coronary angiography can be performed safely and provides important diagnostic information which may affect treatment and outcomes.

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Keywords

Chest pain; Non-obstructive coronary artery disease; Fractional flow reserve; Index of microcirculatory resistance; Endothelial dysfunction; Myocardial bridging

Angina and myocardial ischemia are usually caused by flow-limiting lesions within epicardial coronary arteries. However, several studies report that more than 20% of patients undergoing coronary angiography have no significant obstructive coronary artery disease (CAD) despite angina symptoms and/or noninvasive testing suggestive of myocardial ischemia.[1–3] Other potential causes of angina have been identified in these patients, including focal epicardial coronary spasm and epicardial endothelial dysfunction,[4] microvascular dysfunction,[5,6] occult diffuse epicardial coronary disease,[7] and the presence of myocardial bridging.[8] The prevalence of these etiologies in the same population is poorly defined, and the percentage of patients without any of these abnormalities and presumably non-cardiac symptoms is also unknown.

Accordingly, the aim of this study was to investigate the potential underlying causes of angina in symptomatic patients with non-obstructive CAD by using a comprehensive combination of invasive investigations. Specifically, we tested for endothelial dysfunction with intracoronary acetylcholine (Ach), coronary microvascular dysfunction with the index of microcirculatory resistance (IMR) and coronary flow reserve (CFR), occult diffuse epicardial coronary disease with fractional flow reserve (FFR), and myocardial bridging with intravascular ultrasound (IVUS).

Methods

Study population

We evaluated adult patients who were electively referred to the cardiac catheterization laboratory for coronary angiography because of a clinical suspicion of coronary ischemia based on the presence of angina with or without an abnormal stress test. Typical angina was defined as having three characteristics: 1) substernal chest discomfort, 2) provoked by exertion or emotional stress, and 3) relieved by rest and/or nitroglycerin. Atypical angina was defined as meeting two of the above characteristics. Exclusion criteria included the presence of an acute coronary syndrome, prior heart transplantation, prior percutaneous coronary intervention or coronary artery bypass grafting, renal insufficiency (creatinine>1.5mg/dL), abnormal ejection fraction (EF<55%), or presence of another likely explanation of angina such as pulmonary hypertension, hypertrophic cardiomyopathy, or valvular heart disease. All coronary vasodilating drugs were discontinued more than 48 hours before the examination, except for sublingual nitroglycerin as needed. Patients had an overnight fast and peripheral blood samples were obtained for fasting lipids, serum glucose, insulin, and glycosylated hemoglobin. HOMA (homeostasis model assessment) index was calculated to evaluate for insulin resistance.[9] A baseline coronary angiogram was performed via the femoral artery to rule out obstructive CAD (>50% diameter stenosis) in the right and left coronary arteries. In patients with non-obstructive CAD, the comprehensive invasive

evaluation was conducted. The study was approved by Stanford's institutional review board and informed, written consent was obtained from all patients.

Coronary Endothelial Function Testing

Intravenous heparin (50–70 units/kg) was administered and a 6F guiding catheter without side-holes was used to engage the left main coronary artery. To test the endothelial function, 50 μg Ach was slowly injected directly into the left coronary artery over 2–3 minutes. Unless there was significant bradycardia or severe vasoconstriction, 100 μg of Ach was subsequently administered. After each injection, coronary angiography was performed. Offline, quantitative coronary angiography (QCA) was performed and endothelial dysfunction was diagnosed if the epicardial coronary artery diameter decreased by >20% compared to baseline.[10] Finally, a 200 μg bolus of intracoronary nitroglycerin was administered and a coronary angiogram was obtained to document endothelium-independent vasodilation of the epicardial artery.

Quantitative Coronary Angiography

The Stanford QCA Core Laboratory, blinded to the clinical, physiologic, and IVUS results, performed QCA on the left anterior descending artery (LAD) using the computer-assisted method QAngio XA7.3 (Medis) to determine the lumen diameter at baseline, after intracoronary Ach injection, and after intracoronary nitroglycerin administration. QCA was performed on the first 50-mm of length from the LAD ostium.

Coronary physiology measurements

Within 10 minutes after endothelial function testing, CFR, IMR, and FFR were measured by methods described previously.[11,12] In brief, a pressure-temperature sensor guidewire (Certus Pressure Wire, St. Jude, St. Paul, Minnesota) was used for physiology measurements. With the sensor positioned at the tip of the catheter, the pressure measurement from the wire was equalized with that of the guiding catheter. The sensor was then positioned in the distal third of the LAD. Three injections of 3 mL of room temperature saline were made down the coronary artery, and the transit time was measured after each and averaged to calculate the resting mean transit time (Tmn). An intravenous infusion of adenosine (140 μg/kg/min) was then administered via a large peripheral or central vein to induce steady state maximal hyperemia, and 3 more injections of 3 mL of room temperature saline were made. The transit time was measured after each and averaged to calculate the hyperemic Tmn. Simultaneous measurements of mean aortic pressure (Pa, by guiding catheter) and mean distal coronary pressure (Pd, by pressure wire) were also made during maximal hyperemia. IMR was calculated as the Pd at maximal hyperemia divided by the inverse of the hyperemic Tmn;[11] CFR was calculated as resting Tmn divided by hyperemic Tmn; and FFR was calculated by the ratio of mean Pd/mean Pa at maximal hyperemia.[12] Microvascular dysfunction was defined as an IMR ≥25.[13,14] An abnormal FFR was defined as ≤0.80.

Intravascular Ultrasound

IVUS was performed with a 40-MHz mechanical transducer ultrasound catheter (Atlantis SR Pro2, Boston Scientific Corp, Natick, Massachusetts) advanced down the LAD so that

the IVUS transducer was positioned as close as possible to the pressure transducer mounted on the pressure wire. An automated pullback at 0.5 mm/s was performed, and the IVUS images were stored onto DVD for offline analysis. Standard 2-dimensional and 3-dimensional measurements were performed as previously described.[12] All measurements were performed by the Stanford IVUS Core Laboratory, blinded to clinical, physiologic, and angiographic information.

The presence of a myocardial bridge (MB) was defined either by the identification of an echolucent half-moon sign and/or evidence of systolic compression (≥10% systolic compression during the cardiac cycle).[15] Maximum percent systolic compression was calculated by echoPlaque software (Indec Systems, Inc) and was defined as the change in vessel area during the cardiac cycle divided by vessel area during diastole.

Statistical Analysis

Normality of the data was determined using the Kolmogorov–Smirnov test and verified using histogram plots. Results are expressed as mean ± standard deviation for data following a normal distribution and median (25^{th} percentile to 75^{th} percentile) for data that were not normally distributed. Pearson's correlation test was performed to test association between normally distributed variables and Spearman's correlation test was used to test association between non-normally distributed variables. Chi-square tests were used to assess for difference between categorical variables. Student's T-tests or Mann-Whitney rank-sum tests were used to assess for difference between groups of continuous variables. Variables were tested for their ability to predict endothelial dysfunction, microvascular dysfunction, a low FFR, and myocardial bridging using univariable binary logistic regression analyses. Variables with a p value of <0.2 were considered for inclusion into multivariable forward stepwise models to determine independent correlates. Less significant univariables correlating significantly (R >0.6) with other variables in the model were removed to avoid multicollinearity. A two-sided p value of <0.05 was considered significant. Statistical analyses were performed using the SPSS 15.0 (SPSS, Chicago, IL).

Results

Between August 2007 and November 2012, a total of 139 patients completed endothelial function testing, 137 coronary physiology assessment, and 120 IVUS examination. There were no significant procedure-related complications, such as coronary dissection, myocardial infarction, life-threatening arrhythmia, major bleeding, or death.

Baseline characteristics of the study participants are shown in Table 1. The mean age was 54.0±11.4 years (range 28 to 77 years) and 107 patients (77.0%) were female. Seventy four patients (53.2%) had hypertension, 32 (23.0%) had diabetes, 87 (62.6%) had dyslipidemia, 11 (7.9%) were current smokers, and 45 (32.4%) had a family history of CAD. All patients had stable angina, with approximately half (56%) having typical symptoms and the remainder having atypical symptoms. The majority of patients (72%) had an abnormal stress test prior to coronary angiography. Thirty-three patients (24%) had at least one normal stress test, but were still referred for coronary angiography because of persistent and concerning symptoms. Five patients were referred directly to angiography without stress testing.

QCA, coronary physiology, and IVUS findings are shown in Table 2, while examples of each abnormality are shown in Figure 1. Endothelial dysfunction was present in 61 patients (43.9%). The mean change in coronary artery diameter in response to acetylcholine [ΔCAD (Ach)] was −17.1±20.7%. Any degree of vasoconstriction was found in 106 patients (76.3%). There were no cases of patients without vasoconstriction at 50 ug, who then developed vasoconstriction at 100 ug. Transient bradycardia occurred occasionally, but the exact incidence was not recorded. There were no cases of persistent or clinically relevant bradycardia. When we compared patients with and without endothelial dysfunction, there was a significant difference in serum high density lipoprotein (HDL) levels (47.7±13.7 vs. 54.1±13.7 mg/dL, p=0.007), low density lipoprotein (LDL) / HDL ratio (2.25±0.93 vs. 2.10±0.67, p=0.03), and insulin levels (12.9±11.7 vs. 8.82±6.53 μU/mL, p=0.005).

The mean IMR value was 19.6±9.1 (range 8.3 to 52.0), while the mean CFR was 4.11±1.70 (range 1.30 to 9.90). Microvascular dysfunction (IMR ≥25) was present in 29 patients (21.2%). Patients with microvascular dysfunction were significantly older (58.8±12.3 vs. 52.4±10.7 years, p=0.007), had more hypertension (79.3 vs. 47.2 %, p=0.003), a higher fasting glucose (median 101.0 [interquartile range (IQR): 92.0 to 109.5] vs. 91.0 [IQR:85.0 to 101.0] mg/dL, p=0.005), higher insulin levels (14.6±14.2 vs. 9.9±7.2μU/mL, p=0.02), a higher HOMA index (62.4±64.7 vs. 43.6±35.2, p=0.04), more diabetes (39.3 vs. 19.4%, p=0.04), and a lower CFR (3.3±1.0 vs. 4.4±1.8, p=0.002). No QCA or IVUS variables were significantly different between patients with and without microvascular dysfunction.

While no patients had >50% angiographic epicardial disease, FFR was ≤0.80 in 5.1%, with mild-moderate diffuse atherosclerosis seen on IVUS in most cases, a myocardial bridge noted in two, and marked tortuosity in another. Myocardial bridging was present in 57.9% when defined by the presence of either an echolucent half-moon sign or ≥10% systolic compression on IVUS imaging, while the prevalence was 43.2% when defined by the presence of both of these IVUS parameters. All patients had at least some evidence of atherosclerosis based on IVUS examination of the LAD. There were no significant differences in clinical, laboratory, QCA or coronary physiologic variables between those with and without myocardial bridging.

While most patients had only one occult coronary abnormality, many had more than one abnormality, with the combination of endothelial dysfunction and myocardial bridging being the most common (Figure 2A). Thirty two patients (23.0%) had no coronary explanation for their angina, with normal endothelial function, normal coronary physiologic assessment (IMR, CFR, and FFR), and no myocardial bridging (Figure 2B). These patients tended to have less atherosclerotic burden based on IVUS examination of the LAD compared to the other 107 patients (maximum plaque burden, defined as the cross-section with the maximum plaque area divided by the vessel area times 100%: 33 ±20% vs. 39 ±19%, p=0.18). There was no correlation between the stress echocardiographic findings and each of the assessed coronary abnormalities. However, 77% of the patients with at least one coronary circulatory abnormality had an abnormal stress test, while 44% of the patients without any coronary circulatory abnormality had a normal stress test (p=0.10).

Univariable correlates of endothelial dysfunction, microvascular dysfunction, low FFR, and myocardial bridging are shown in Table 3A. In a multivariable logistic regression model, diabetes was the only independent predictor of endothelial dysfunction, age was the only independent predictor of microvascular dysfunction, and homocysteine level was the only independent predictor of low FFR. There were no independent correlates of myocardial bridging (Table 3B).

Discussion

The salient findings of this study are: 1) many patients with angina in the absence of obstructive CAD have occult coronary abnormalities; 2) on the other hand, a significant minority have no coronary etiology to explain their symptoms; and 3) a comprehensive invasive functional, physiologic, and anatomic coronary assessment allows safe stratification of patients without angiographic disease into specific potential etiologies for their chest pain. Angina and myocardial ischemia are typically caused by flow-limiting lesions in the epicardial coronary arteries. When coronary angiography fails to reveal obstructive epicardial atherosclerosis, a diagnosis of non-cardiac chest pain is often given. Alternatively, in some cases, microvascular dysfunction is the presumptive diagnosis and anti-anginal therapy is instituted or escalated. In the former scenario, effective therapy and a potentially improved outcome may be withheld from a patient, while in the latter case, over-treatment causing unnecessary expense, side effects, and anxiety may occur. The lack of a clear diagnosis in the face of ongoing anginal symptoms can result in recurrent emergency room evaluations, hospitalizations, and repeat cardiac catheterizations, with adverse effects on quality of life, employment, and health care costs.[16,17,18] Moreover, patients who do have occult coronary abnormalities have higher cardiac event rates and may benefit from more aggressive treatment and follow-up.[4, 5, 19, 20,21] Therefore, the precise assessment and diagnosis of angina in patients without angiographic evidence of CAD has important clinical implications.

In the current study, we found that 76.3% of patients had evidence of epicardial endothelial dysfunction, abnormal microvascular function, occult diffuse epicardial atherosclerosis, or myocardial bridging as potential causes for their angina. This high rate of occult coronary abnormalities highlights the relevance of investigating for these entities. Prior studies in this patient population have generally focused on one entity, such as microvascular dysfunction or endothelial dysfunction, but not on the entire circulation, including the epicardial vessel (functional evaluation with Ach, physiologic assessment with FFR, and anatomic abnormalities with IVUS) and the microvasculature (IMR and CFR).[7,8,22–25,26,27] This is the first study to thoroughly delineate the prevalence of each of these entities in the same population of patients. Of note, however, is the fact that we did not see any cases of focal epicardial spasm, another potential cause of angina in the absence of obstructive CAD. Likewise, microvascular spasm or endothelial dysfunction was not specifically evaluated, although this is challenging to do in vivo.

A second important finding in this study is the 23% rate of normal invasive findings. Presumably these patients will do well without any specific cardiac medical therapy and alternative non-cardiac etiologies for their symptoms should be pursued. If long-term

follow-up in this cohort demonstrates low event rates, it will further emphasize the need to distinguish this group from those with abnormal coronary circulation. Still, it is noteworthy that all patients had at least some evidence of atherosclerosis based on IVUS examination of the LAD, which may alter prevention management.

Although performing invasive coronary assessment with Ach administration, a coronary pressure wire, and IVUS does add time and expense to the procedure, a third main finding is that this assessment was completed on a routine basis and there were no significant procedural complications. Previous studies have provided information on safety, as well as low additional radiation and contrast exposure, in patients undergoing invasive functional studies to reveal occult coronary problems.[27–29] The extra time and expense may be offset by a reduction in further unnecessary testing or treatment, as well as a decrease in recurrent hospital visits and an improvement in quality of life. However, a dedicated study is ultimately needed to determine if the performance of a comprehensive invasive assessment in patients with angina in the absence of obstructive CAD is cost-effective.

Other interesting findings in this study include the correlation between microvascular dysfunction and metabolic parameters, such as serum glucose, insulin, and HOMA index, as well as between microvascular dysfunction and cardiac risk factors, such as age, BMI, hypertension, and diabetes. Whether or not modifying these risk factors results in improved microvascular function and outcomes requires future investigation. We found the only independent predictor of microvascular dysfunction was patient age, which is consistent with results from the WISE study.[22] In addition, 5.1% of patients without obvious angiographic stenosis had an abnormal FFR, suggesting significant occult epicardial atherosclerosis as the cause for their symptoms and/or ischemia.[7] Identifying this group is important because they will likely benefit from aggressive medical therapy and potentially from revascularization. Finally, depending on the definition one chooses to diagnose myocardial bridging based on IVUS, it may be a prevalent finding in this patient population and may contribute to symptoms, either directly or as a result of its association with endothelial dysfunction.

Limitations

This is a relatively small, single center study. The complexity and expense of this strategy may limit its clinical application. Outcome data and whether or not outcomes can be modified with medical or interventional therapy are necessary to validate the importance of these findings. We performed invasive assessment only in the LAD; we may have neglected circulatory abnormalities in other coronary perfusion territories. There is no conclusive evidence that the occult coronary abnormalities identified in these patients are the cause of their symptoms. However, previous studies in asymptomatic, “normal” controls have found that the normal mean FFR value is 0.97, the normal IMR is < 25, and the normal response to acetylcholine is vasodilation.[30–32] That the mean FFR in this study was 0.87, that 21% of patients had an IMR ≥ 25, and that any degree of vasoconstriction related to acetylcholine occurred in 76% all suggests these abnormalities may be related to symptoms.

Unfortunately, symptom occurrence and electrocardiographic changes were not systematically recorded during Ach administration. Finally, endothelial dysfunction or spasm isolated to the microvasculature was not specifically assessed.

Conclusions

On the basis of our findings, over three-quarters of patients with angina in the absence of obstructive CAD have occult coronary abnormalities, which may be causing their symptoms. At the same time, nearly a quarter of patients have normal invasive findings for which reassurance can be given. A comprehensive invasive assessment of these patients at the time of coronary angiography provides important diagnostic information which may affect treatment and outcomes.

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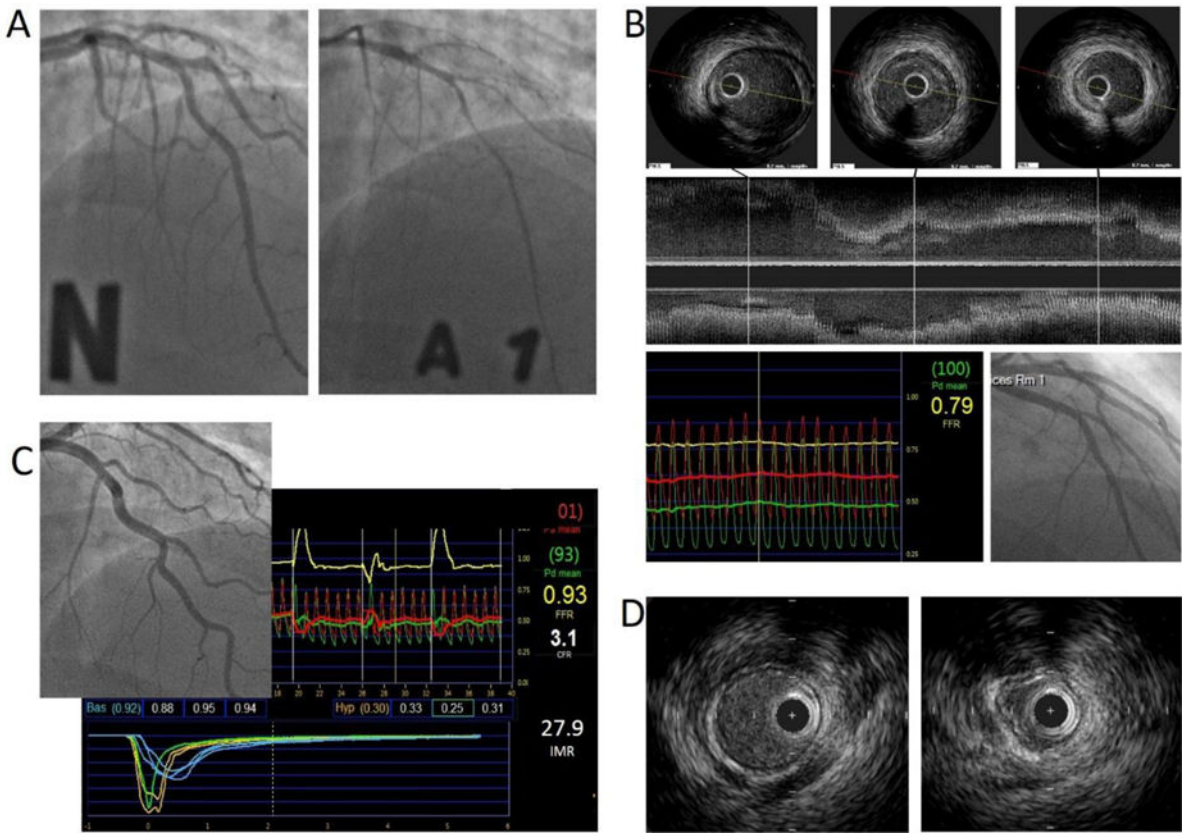

Figure 1.

Demonstrative cases of (A) epicardial endothelial dysfunction, (B) low FFR with occult diffuse epicardial disease, (C) microvascular dysfunction, and (D) myocardial bridging **A.** Paradoxical vasoconstriction after intracoronary acetylcholine injection. **B.** This angiographically non-obstructive LAD showed diffuse atherosclerosis on IVUS and low FFR. **C.** There was no significant angiographic stenosis in the LAD, but the IMR was high. **D.** An IVUS image of myocardial bridging during diastole and systole. An echolucent area surrounding the coronary artery is seen during the entire cardiac cycle.

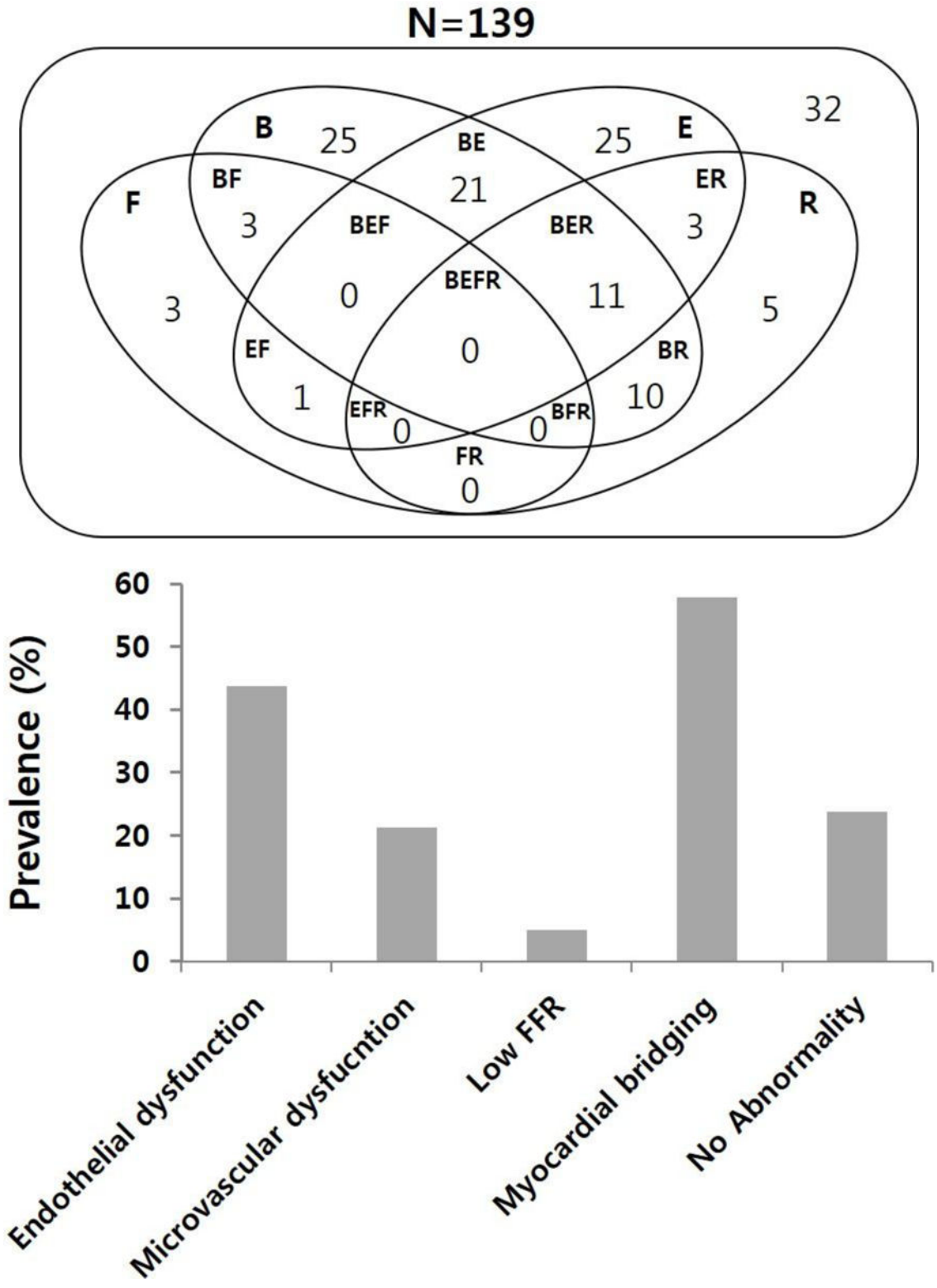

Figure 2.

A. Results of Invasive Assessment for Coronary Circulation. **B**=myocardial bridging; **E**=endothelial dysfunction; **F**=low fractional flow reserve (<0.80); **R**= high index of

microcirculatory resistance (≥25). **B**. Prevalence of occult coronary abnormalities on invasive assessment in patients with angina and angiographically non-obstructive coronary arteries. Endothelial dysfunction = a decrease in luminal diameter of ≥ 20% with intracoronary acetylcholine; Microvascular dysfunction = index of microcirculatory resistance ≥25; Low FFR = fractional flow reserve ≤0.80; Myocardial bridging = an echolucent half-moon sign and/or ≥10% systolic compression on intravascular ultrasound.

Table 1

Clinical Characteristics

Variable	N=139
Age, years	54.0±11.4
Female sex	107 (77.0)
Hypertension	74 (53.2)
Diabetes mellitus	32 (23.0)
Dyslipidemia	87 (62.6)
Current Smoking	11 (7.9)
Family history of CAD	45 (32.4)
Height, cm	167.4±10.3
Weight, kg	81.5±20.5
Body-mass index, kg/m^2	29.1±7.0
Medications	
Aspirin	93 (66.9)
Beta blockers	57 (41.0)
ACEI/ARB	19 (13.7)
Diuretics	18 (2.9)
Statins	82 (59.0)
Nitrates	53 (38.4)
Total cholesterol, mg/dL	167.8±36.3
Triglycerides, mg/dL	75.0 (45.8–110.0)
LDL, mg/dL	99.8±31.7
HDL, mg/dL	51.1±15.3
LDL/HDL ratio	2.11±0.84
Lipoprotein(a), mg/dL	16.7 (7.5–34.3)
Fasting glucose, mg/dL	92.0 (85.0–104.0)
HgA1c, %	5.7 (5.4–6.1)
Insulin, μU/mL	10.7±9.1
HOMA index *	2.61±2.39
hs-CRP, mg/L	1.60 (0.70–4.10)
Homocysteine, μmol/L	8.0 (6.6–10.0)

Variable are mean ±SD, n (%) or median (25th percentile-75th percentile) depending on normality criteria.

CAD = coronary artery disease; ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers.

* HOMA (Homeostasis model assessment) index = Insulin (μU/m) × [glucose (mg/dl)/405]

Table 2

QCA, physiologic, and IVUS findings

Variable	N=139
QCA findings	
Mean diameter (mm)	
Baseline	1.89±0.43
After acetylcholine	1.56±0.49
After nitroglycerin	1.99±0.50
Mean degree of vasoconstriction (%)	17.1±20.7
Endothelial dysfunction (%)	61 (43.9)
Physiologic findings	
IMR (mean)	19.6±9.1
IMR ≥25	29 (21.2)
CFR (mean)	4.11±1.70
CFR <2.0	9 (6.6)
FFR (mean)	0.87±0.05
FFR ≤0.80	7 (5.1)
IVUS findings	
Minimum lumen area, mm^2	5.15±1.96
Mean lumen area, mm^2	9.42±2.60
Mean EEM area, mm^2	12.7±3.1
Mean plaque thickness, mm	0.24 (0.20–0.31)
Mean plaque area, mm^2	2.85 (2.39–4.04)
EEM volume, mm^3	624.5±156.9
Lumen volume, mm^3	463.0±131.0
Plaque volume, mm^3	140.6 (115.5–201.2)
Mean plaque burden, %	25.8±8.9
Myocardial bridging, n (%)	70 (57.9)

Variables are mean±SD, n (%) or median (25^{th} percentile-75^{th} percentile) depending on normality criteria.

IVUS = intravascular ultrasound; EEM = external elastic membrane; FFR = fractional flow reserve; CFR = coronary flow reserve; IMR = index of microcirculatory resistance.

Table 3A

Univariable logistic regression analysis of various correlates for each coronary abnormality

Abnormality	Variables	OR	Lower CI	Upper CI	P value
Endothelial dysfunction	FHx	1.67	0.80	3.46	0.17
	Diabetes	2.23	1.00	4.99	0.05
Microvascular dysfunction	Age	1.05	1.01	1.10	0.01
	Diabetes	2.68	1.10	6.57	0.03
	Hypertension	4.28	1.62	11.36	0.003
	BMI	1.07	1.01	1.13	0.03
Low FFR	Homocysteine	1.69	1.01	2.83	0.05
	LDL	1.02	0.99	1.05	0.19
	Glucose	1.03	1.00	1.06	0.05
Myocardial bridging	Hypertension	1.95	0.99	3.84	0.06
	BMI	1.05	0.99	1.11	0.08

OR = odds ratio; CI = confidence interval; BMI = body mass index; FHx = Family history of coronary heart disease; FFR = fractional flow reserve; LDL = low-density lipoprotein.

Table 3B

Independent correlates for various coronary abnormalities verified by multivariable logistic regression analysis

Abnormality	Independent Correlates	OR	Lower CI	Upper CI	P value
Endothelial dysfunction	Diabetes	2.35	1.04	5.32	0.04
Microvascular dysfunction	Age	1.06	1.01	1.11	0.02
Low FFR	Homocysteine	2.30	1.14	4.63	0.02
Myocardial bridging	–	–	–	–	–

OR = odds ratio; CI = confidence interval; FFR = fractional flow reserve.