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

Background—More than 20% of patients presenting to the cardiac catheterization laboratory with angina have no angiographic evidence of coronary artery disease. 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 coronary artery disease (no diameter stenosis >50%), endothelial function was assessed; the index of microcirculatory resistance, coronary flow reserve, and fractional flow reserve were measured; and intravascular ultrasound 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 an intravascular ultrasound examination of the left anterior descending artery. Endothelial dysfunction (a decrease in luminal diameter of >20% after intracoronary acetylcholine) was present in 61 patients (44%). Microvascular impairment (an index of microcirculatory resistance ≥25) was present in 29 patients (21%). Seven patients (5%) had a fractional flow reserve ≤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 physiological assessment, and no myocardial bridging.

Conclusions—The majority of patients with angina in the absence of obstructive coronary artery disease 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 that may affect treatment and outcomes. (Circulation. 2015;131:1054-1060. DOI: 10.1161/CIRCULATIONAHA.114.012636.)

Key Words: chest pain ■ endothelium ■ fractional flow reserve, myocardial ■ myocardial bridging

Accordingly, the aim of this study was to investigate the potential underlying causes of angina in symptomatic patients with nonobstructive CAD with a comprehensive combination of invasive investigations. Specifically, we tested for endothelial dysfunction with intracoronary acetylcholine, 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 3 characteristics: It had substernal chest discomfort, was provoked by exertion or emotional stress, and was relieved by rest or nitroglycerin. Atypical angina was defined as meeting 2 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 >1.5 mg/dL), abnormal ejection fraction (<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 >48 hours before the examination, except for sublingual nitroglycerin as needed. Patients fasted overnight, and peripheral blood samples were obtained for fasting lipids, serum glucose, insulin, and glycosylated hemoglobin. Homeostasis model assessment index was calculated to evaluate for insulin resistance. 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 nonobstructive CAD, a comprehensive invasive evaluation was conducted. The study was approved by the Stanford institutional review board, and written informed consent was obtained from all patients.

Coronary Endothelial Function Testing

Intravenous heparin (50-70 U/kg) was administered, and a 6F guiding catheter without side holes was used to engage the left main coronary artery. To test endothelial function, 50 μg acetylcholine was slowly injected directly into the left coronary artery over 2 to 3 minutes. Unless there was significant bradycardia or severe vasoconstriction, 100 μg acetylcholine was subsequently administered. After each injection, coronary angiography was performed. Quantitative coronary angiography (QCA) was performed offline, and endothelial dysfunction was diagnosed if the epicardial coronary artery diameter decreased by >20% compared with baseline. 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

Researchers at the Stanford QCA Core Laboratory who were blinded to the clinical, physiological, 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 acetylcholine injection, and after intracoronary nitroglycerin administration. QCA was performed on the first 50 mm of length from the LAD ostium.

Intravascular Ultrasound

IVUS was performed with a 40-MHz mechanical transducer ultrasound catheter (Atlantis SR Pro2, Boston Scientific Corp, Natick, MA) 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. All measurements were performed by Stanford IVUS Core Laboratory researchers blinded to clinical, physiological, and angiographic information.

The presence of a myocardial bridge was defined as either the identification of an echoluent half-moon sign or evidence of systolic compression (≥10% systolic compression during the cardiac cycle). Maximum percent systolic compression was calculated by echo-Plaque 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 with the Kolmogorov-Smirnov test and verified with histogram plots. Results are expressed as mean±SD for data following a normal distribution and median (25th–75th percentiles) for data that were not normally distributed. The Pearson correlation test was performed to test association between normally distributed variables, and the Spearman correlation test was used to test the association between nonnormally distributed variables. χ² Tests were used to assess for differences between categorical variables. Student t tests or Mann-Whitney rank-sum tests were used to assess for differences between groups of continuous variables. Variables were tested for their ability to predict endothelial dysfunction, microvascular dysfunction, a low FFR, and myocardial bridging in univariable binary logistic regression analyses. Variables with a value of P<0.2 were considered for inclusion in the multivariable forward stepwise models to determine independent correlates. Significant univariables correlating significantly (P>0.6) with other variables in the model were removed to avoid multicollinearity. A 2-sided value of P<0.05 was considered significant. Statistical analyses were performed with SPSS 15.0 (SPSS, Chicago, IL).

Results

Between August 2007 and November 2012, a total of 139 patients completed endothelial function testing, 137 completed coronary physiology assessments, and 120 completed IVUS examinations. 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, 28–77 years), and 107 patients (77.0%) were female. Seventy-four patients (53.2%) had hypertension, 32 (23.0%) had diabetes mellitus, 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 before coronary angiography. Thirty-three patients (24%) had at least 1 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, and 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 (acetylcholine)) 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 μg who then developed vasoconstriction at 100 μg. 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 levels (47.7±13.7 versus 54.1±13.7 mg/dL; P=0.007), ratio of low-density lipoprotein to high-density lipoprotein (2.25±0.93 versus 2.10±0.67; P=0.03), and insulin levels (14.6±14.2 versus 9.9±7.2 μU/mL; P=0.02), a higher homeostasis model assessment index (62.4±35.2; P=0.04), more diabetes mellitus (39.3% versus 19.4%; P=0.04), and a lower CFR (3.3±1.0 versus 4.4±1.8; P=0.002). No QCA or IVUS variables were significantly different between patients with and without microvascular dysfunction.

Although no patients had >50% angiographic epicardial disease, FFR was ≤0.80 in 5.1%, with mild to moderate diffuse atherosclerosis seen on IVUS in most patients, a
myocardial bridge noted in 3 patients, and marked tortuosity was seen 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; 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 physiological variables between those with and without myocardial bridging.

Although most patients had only 1 occult coronary abnormality, many had >1 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 physiological 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 with 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% versus 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 1 coronary circulatory abnormality had an abnormal stress test, whereas 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 3. In a multivariable logistic regression model, diabetes mellitus 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 4).

**Discussion**

The salient findings of this study are the following: (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 reason to explain their symptoms; and (3) a comprehensive invasive functional, physiological, and anatomic coronary assessment allows safe stratification of patients without angiographic disease into specific potential causes 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 noncardiac chest pain is often given. Alternatively, in some cases, microvascular dysfunction is the presumptive diagnosis, and antianginal therapy is instituted or escalated. In the former scenario, effective therapy and a potentially improved outcome may be withheld from a patient, whereas in the latter case, overtreatment 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 healthcare costs. Moreover, patients who do have occult coronary abnormalities have higher cardiac event rates and may benefit from more aggressive treatment and follow-up. Therefore, the precise assessment and diagnosis of angina in patients without angiographic evidence of CAD has important clinical implications.

In the present 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 a potential cause 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 1 entity such as microvascular dysfunction or endothelial dysfunction, not on the entire circulation, including the epicardial vessel (functional evaluation with acetylcholine, physiological assessment with FFR, and anatomic abnormalities with IVUS) and the microvasculature (IMR and CFR). 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 noncardiac causes of 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

| Table 3. 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 mellitus                                |         | 2.23   | 1.00    | 4.99    | 0.05   |
| Microvascular dysfunction                        | Age     | 1.05   | 1.01    | 1.10    | 0.01   |
| Diabetes mellitus                                |         | 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   |

| BMI indicates body mass index; CI, confidence interval; FHx, family history of coronary heart disease; FFR, fractional flow reserve; LDL, low-density lipoprotein; and OR, odds ratio. |

| Table 4. 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 mellitus | 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                              | …      | …      | …      | …      | …      |

CI indicates confidence interval; FFR, fractional flow reserve; and OR, odds ratio.
of atherosclerosis based on IVUS examination of the LAD, which may alter prevention management.

Although performing invasive coronary assessment with acetylcholine administration, a coronary pressure wire, and IVUS adds time and expense to the procedure, a third main finding is that this assessment was completed on a routine basis with no significant procedural complications. Previous studies have provided information on safety and low additional radiation and contrast exposure in patients undergoing invasive functional studies to reveal occult coronary problems. 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 whether 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 homeostasis model assessment index and between microvascular dysfunction and cardiac risk factors such as age, body mass, hypertension, and diabetes mellitus. Whether modifying these risk factors results in improved microvascular function and outcomes requires future investigation. We found that the only independent predictor of microvascular dysfunction was patient age, which is consistent with results from the Women’s Ischemia Syndrome Evaluation (WISE) study. 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 or ischemia. Identifying this group is important because they will likely benefit from aggressive medical therapy and potentially will benefit from revascularization. Finally, depending on the definition one chooses to diagnose myocardial bridging on the basis of 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. Having outcome data and knowing whether 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 control subjects have found that the normal mean FFR value is 0.97, the normal IMR is <25, and the normal response to acetylcholine is vasodilatation.

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 suggest that these abnormalities may be related to symptoms. Unfortunately, symptom occurrence and electrocardiographic changes were not systematically recorded during acetylcholine administration. Finally, endothelial dysfunction or spasm isolated to the microvascular lature was not specifically assessed.

Conclusions

On the basis of our findings, more than 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 revascularization can be given. A comprehensive invasive assessment of these patients at the time of coronary angiography provides important diagnostic information that may affect treatment and outcomes.

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Disclosures

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