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Prevalence of Coronary Microvascular Dysfunction Among Patients With Chest Pain and Nonobstructive Coronary Artery Disease

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ABSTRACT

OBJECTIVES This study assessed the prevalence of coronary microvascular abnormalities in patients presenting with chest pain and nonobstructive coronary artery disease (CAD).

BACKGROUND Coronary microvascular abnormalities mediate ischemia and can lead to an increased risk of cardiovascular events.

METHODS Using an intracoronary Doppler guidewire, endothelial-dependent microvascular function was examined by evaluating changes in coronary blood flow in response to acetylcholine, whereas endothelial-independent microvascular function was examined by evaluating changes in coronary flow velocity reserve in response to intracoronary adenosine. Patients were divided into 4 groups depending on whether they had a normal (+) or abnormal (−) coronary blood flow (CBF) in response to acetylcholine (Ach) and a normal (+) or abnormal (−) coronary flow velocity reserve (CFR) in response to adenosine (Adn): CBFAch+, CFRAdn+ (n = 520); CBFAch−, CFRAdn+ (n = 478); CBFAch+, CFRAdn− (n = 173); and CBFAch−, CFRAdn− (n = 268).

RESULTS Two-thirds of all patients had some sort of microvascular dysfunction. Women were more prevalent in each group (56% to 82%). Diabetes was uncommon in all groups (7% to 12%), whereas hypertension and hyperlipidemia were relatively more prevalent in each group, although rates for most conventional cardiovascular risk factors did not differ significantly between groups. There were no significant differences in the findings of noninvasive functional testing between groups. In a multivariable analysis, age was the only variable that independently predicted abnormal microvascular function.

CONCLUSIONS Patients with chest pain and nonobstructive CAD have a high prevalence of coronary microvascular abnormalities. These abnormalities correlate poorly with conventional cardiovascular risk factors and are dissociated from the findings of noninvasive functional testing. (J Am Coll Cardiol Intv 2015;8:1445–53) © 2015 by the American College of Cardiology Foundation.

The prevalence of nonobstructive coronary artery disease (CAD) determined at coronary angiography has been reported to be 20% to 30%, (1,2) and even up to 50% (3). Despite the absence of obstructive CAD, these patients experience adverse cardiovascular events (3,4) including cardiovascular death and myocardial infarction (MI). These patients also experience recurrent chest pain resulting in ongoing anxiety, limited exercise tolerance, and lower quality of life, making them more likely to

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
CBF = coronary blood flow
CFR = coronary flow reserve
MI = myocardial infarction

present to health care services for repeat medical assessments and procedures (5,6). Thus, the diagnostic coronary angiogram alone may not suffice in the management of these patients.

Under normal physiological conditions, the coronary microcirculation regulates myocardial perfusion in response to increased demand by endothelial-dependent and -independent mechanisms (7,8). This "coronary flow reserve" may be compromised in pathological states. The inability of the vascular smooth muscle to relax adequately at the microcirculation level denotes an endothelial-independent reduction in coronary flow reserve (CFR) (8). At the same time, an attenuated increase or a decrease in coronary blood flow (CBF) in response to endothelial-dependent vasodilators such as acetylcholine or substance P denotes an impairment in microvascular endothelial-dependent CFR, also known as microvessel "endothelial dysfunction" (9–13). These coronary microvascular abnormalities are functionally meaningful, as they mediate ischemia and cause angina in patients with obstructed and angiographically unobstructed coronary arteries (14,15). This "microvascular angina" often resembles classical stable angina caused by physiologically significant narrowing of epicardial vessels.

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Previous studies have evaluated the prevalence of coronary microvascular abnormalities in patients referred for physiological testing. However, these studies examined relatively small samples (16) or focused exclusively on female subjects (17), characterized microvascular endothelial dysfunction indirectly as a reproduction of the patient's symptoms and ischemic electrocardiographic (ECG) changes in response to intracoronary infusions of acetylcholine (18) (as opposed to using direct measurements of changes in CBF), and focused on endothelial dysfunction in the epicardial vessels rather than within the microcirculation (19) where endothelial dysfunction typically resides. The current study examines the prevalence and clinical profile of coronary microvascular abnormalities in a large cohort of patients presenting with chest pain and nonobstructive CAD who underwent an invasive and comprehensive microvascular functional assessment.

METHODS

The study protocol has been described in detail elsewhere (12,16,20,21). In brief, patients presenting to the catheterization laboratory with nonobstructive CAD (<40% stenosis) underwent invasive coronary microvascular functional testing using an intracoronary Doppler guidewire. Endothelial-dependent microvascular function was examined by evaluating changes in CBF in response to acetylcholine, whereas endothelial-independent microvascular function was examined by evaluating changes in coronary flow velocity reserve in response to intracoronary adenosine. Impaired endothelial-independent microvascular function was defined as a coronary flow velocity reserve ratio in response to adenosine of ≤2.5 (22). Impaired endothelial-dependent microvascular function was defined as a maximal percentage increase in CBF in response to any dose of acetylcholine compared with baseline of ≤50% (16,17,21). A decrease in coronary artery diameter of ≥20% in response to acetylcholine compared with baseline was in keeping with epicardial endothelial dysfunction (16,17,21).

PATIENT INFORMATION. Data was collected on conventional cardiovascular risk factors including hypertension, diabetes mellitus, hyperlipidemia, smoking status, and body mass index; biochemical parameters including serum total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, creatinine, and glucose; and whether patients were investigated with noninvasive functional stress testing and, if so, the results of these tests. Smoking was categorized as a history of current, former, or never smoking. Hypertension was defined as a history of hypertension treated with antihypertensive agents, diabetes was defined as a history of diabetes treated with medication or insulin, and hyperlipidemia was defined as a history of total cholesterol levels >240 mg/dl or treatment with lipid-lowering therapy. All blood levels documented had been drawn within 2 weeks of the index procedure. Information was also collected on a previous history of MI (defined as a history of previous MI documented in the patients' clinical record or on patient self-report); other vasospasm disorders (defined as a history of Raynaud's phenomenon or migraine headaches documented in the patients' clinical record or on self-report), and other vascular diseases (defined as a history of peripheral vascular disease, stroke, or transient ischemic attack documented in the patient's clinical record or on self-report).

STATISTICAL ANALYSIS. Continuous variables are presented as the mean ± SD where data is normally distributed and as the median (quartile [Q] 1, Q3) for skewed data. Categorical variables are presented as frequencies (percentages). Differences between groups were analyzed using the 1-way ANOVA for continuous variables and chi-square test for