JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 70, NO. 19, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.09.016

Sex-Related Differences in Vasomotor Function in Patients With Angina and Unobstructed Coronary Arteries

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ABSTRACT

BACKGROUND Coronary vasomotor dysfunction is an important mechanism for angina in patients with unobstructed coronary arteries.

OBJECTIVES The purpose of this study was to determine sex differences in the prevalence and clinical presentation of vasomotor dysfunction in a European population and to examine sex differences in the dose of acetylcholine leading to a positive acetylcholine provocation test (ACH test).

METHODS Between 2007 and 2014, we included 1,379 consecutive patients with stable angina, unobstructed coronaries and ACH test performed for epicardial vasospasm or coronary microvascular dysfunction (CMD) due to microvascular spasm. The predictive value of sex, risk factors, symptoms, and noninvasive test results was analyzed by means of logistic regression.

RESULTS The mean patient age was 62 years, and 42% were male. There were 813 patients (59%) with a pathological ACH test, 33% for CMD and 26% for epicardial vasospasm. A pathological test was more common in females (70% vs. 43%; $p < 0.001$). In a multivariable logistic regression model the sex difference was statistically significant with a female-male odds ratio for CMD and epicardial vasospasm of 4.2 (95% confidence interval: 3.1 to 5.5; $p < 0.001$) and 2.3 (95% confidence interval: 1.7 to 3.1; $p < 0.001$), respectively. Effort-related symptoms, but neither risk factors nor noninvasive stress tests, contributed to predicting a pathological test. Female patients were more sensitive to acetylcholine with vasomotor dysfunction occurring at lower ACH doses compared with male patients.

CONCLUSIONS Vasomotor dysfunction is frequent in patients with angina and unobstructed coronaries in a European population. Female patients have a higher prevalence of vasomotor dysfunction (especially CMD) compared with male patients. A pathological ACH test was observed at lower ACH doses in women compared with men.
(J Am Coll Cardiol 2017;70:2349–58) © 2017 by the American College of Cardiology Foundation.

The majority of patients with angina pectoris without obstructive coronary artery disease (CAD) might still have myocardial ischemia as the cause of their symptoms (1–4). Coronary vasomotor disorders comprising both epicardial and microvascular dysfunction have been proposed as important pathophysiological mechanisms causing symptoms of myocardial ischemia (2). Moreover, an association between stable angina pectoris with nonobstructive CAD and major adverse cardiovascular events is well-demonstrated (2,5), and it is likely that patients with vasomotor disorders carry the major part of this adverse prognosis (2,6–8).

Angina pectoris without obstructive CAD is more common in female compared with male patients (5,9–11). The importance of recognizing sex differences is enhanced by the fact that angina pectoris in female patients can present differently from the symptoms among male patients (12). This distinction may lead to an underestimation of cardiac causes of chest-related symptoms in female patients, in particular if coronary angiography (CAG) is normal,

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Manuscript received July 9, 2017; revised manuscript received September 4, 2017, accepted September 6, 2017.

ABBREVIATIONS AND ACRONYMS

ACH = acetylcholine
AUC = area under the curve
CAD = coronary artery disease
CAG = coronary angiography
CMD = coronary microvascular dysfunction
ECG = electrocardiograph
EV = epicardial vasospasm

the symptoms are atypical and further investigations beyond the CAG are not performed (13). Female patients are also reported to differ in the result of noninvasive tests compared with male patients with a much greater proportion of female patients diagnosed with the now abandoned term cardiac syndrome X, a syndrome of exertional angina pectoris and no obstructive CAD (14). Conversely, some recent studies indicate that the sex difference in coronary microvascular dysfunction (CMD) is not as great as indicated in prior studies (15).

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Several studies have indicated that epicardial vasospasm (EV) and CMD according to acetylcholine (ACH) test are much more frequent in Asian than in European patients (16–18). However, we have previously shown that the prevalence in European patients might be underestimated (3). The Japanese population is well-described, and ACH tests are done routinely at many Japanese centers (19–21). In contrast, ACH tests are rarely performed in Europe and the United States. In Japanese studies, coronary vasomotor disorders are a frequent finding among patients with angina pectoris without obstructive CAD (21,22). In Japan, CMD seems to be more frequent in female patients, and EV more frequent in male patients (6,17,22). Furthermore, vasomotor dysfunction is correlated with a prior history of obstructive CAD and, in most studies, patients with CAD have been part of the study population (3,16,19,22,23).

We sought to determine prevalence of epicardial and microvascular vasomotor dysfunction in a large European population with neither prior history nor present evidence of obstructive epicardial CAD (no epicardial stenosis >50%) or other cardiac reasons for their symptoms. Furthermore, we sought to compare the prevalence of vasomotor dysfunction in male and female patients and whether sex differences were related to the clinical presentation, presence of cardiovascular risk factors, or results of noninvasive stress tests. In addition, we investigated whether there was a sex difference in the dose needed to achieve a pathological ACH test.

METHODS

STUDY POPULATION. This retrospective study included consecutive patients with angina pectoris undergoing an ACH test at Robert-Bosch-Krankenhaus in Stuttgart, Germany, from September 2007 to December 2014 (**Figure 1**). Patients undergoing CAG for suspected or progression of known CAD who were found to have unobstructed coronary arteries (no epicardial stenosis >50% by visual assessment) underwent an ACH test. The test was not performed in patients with severe chronic obstructive pulmonary disease or impaired renal function. Patients undergoing an ACH test between 2007 and June 2010 were also included in our prior study (3).

A total of 2,690 ACH tests were performed in the study period. To ensure a homogeneous population, 191 patients with non-ST-segment elevation myocardial infarction and ST- segment elevation myocardial infarction were excluded. There were 566 patients with a prior history of obstructive CAD and 404 patients with other symptoms (n = 316) such as palpitations, syncope, or another reason (n = 88) leading to the invasive assessment. All these patients were excluded from the final population, as were 139 patients with nonischemic cardiac disease such as cardiomyopathies or severe valvular disorders. Furthermore, another 11 patients were excluded due to a missing electrocardiograph (ECG) or a lack of description of the symptoms during the ACH test. Our final population thus consisted of 1,379 patients with either angina pectoris or unexplained dyspnea considered to be an angina equivalent (**Figure 1**).

CLINICAL DATA. The previous medical history was derived from patient charts and included the classical risk factors hypertension, family history of cardiovascular disease, diabetes mellitus, hypercholesterolemia, and a history of smoking. A history of smoking was considered positive if the patient had a history of habitual smoking of at least 5 years in the past or was an active smoker. Patients on statin treatment or with a clinical indication for statin treatment based on serum lipids at admission were defined as having hypercholesterolemia. Family history was considered positive if at least 1 first- or second-degree relative had a cardiovascular event at a margin of <10 years from the age of the patient. If a noninvasive stress test was performed before the ACH test, the result was recorded. Furthermore, it was recorded whether the patient had symptoms at rest, during exercise, or a combination of resting and effort-related symptoms. Dyspnea, which could not be explained by known lung disease, was considered as an angina equivalent.

ACH TESTING. The ACH test was performed immediately after the CAG if no coronary artery stenosis of