# Epicardial Coronary Spasm in Women With Angina Pectoris and Unobstructed Coronary Arteries Is Linked With a Positive Family History: An Observational Study

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## ABSTRACT

**Purpose:** Coronary spasm is frequently found in patients with angina and unobstructed coronaries. The pathophysiology is incompletely understood, although sex differences have been described. Often a positive family history (PFH) is encountered. We assessed the relationship between sex, coronary spasm, and a PFH for cardiovascular disease.

**Methods:** This single-center observational study recruited 415 stable angina patients with unobstructed coronaries (no stenosis >50%) between 2008 and 2011 (mean [SD] age, 62 [10] years; 38% men). Patients were referred for angiography because of signs and symptoms of myocardial ischemia. Intracoronary acetylcholine (ACh) testing was performed in all patients according to a standardized protocol. Risk factor assessment included hypertension, hypercholesterolemia, diabetes, smoking, and a PFH. The latter was defined as a first-degree relative with myocardial infarction or stroke. Statistical analysis involved comparison of categorical and continuous variables. Multivariable analysis aimed at identifying predictors for a pathologic ACh testing, microvascular spasm, and a PFH.

**Findings:** Epicardial spasm was found in 33% of patients and microvascular spasm in 30% of patients. A pathologic ACh test was more frequent in women than in men (72% vs 49%; $P < 0.0005$). A PFH was found in 55% of patients with significantly more women than men (61% vs 45%; $P = 0.001$). Among patients with epicardial spasm, women had a PFH significantly more often than men (66% vs 43%; $P = 0.006$). The latter difference was not found when comparing women and men with microvascular spasm.

**Implications:** There is a female preponderance among patients with angina and unobstructed coronaries. ACh testing enables detection of coronary spasm. Epicardial spasm in women is associated with a PFH. (*Clin Ther*. 2018;■:1–7) © 2018 Elsevier Inc. All rights reserved.

**Key words:** acetylcholine, coronary spasm, family history, sex.

## INTRODUCTION

The clinical scenario of patients with signs and symptoms of myocardial ischemia yet unobstructed epicardial coronary arteries continues to be a challenge for the clinical cardiologist. Studies have reported that invasive coronary angiography in such patients reveals significant epicardial stenoses in <50% of cases.[1] Frequent and important differential diagnoses in this setting are coronary vasomotion abnormalities such as coronary spasm and/or microvascular dysfunction which can be diagnosed with intracoronary acetylcholine (ACh) testing in ~60% of cases.[2] Although this scenario is encountered more often in female than male patients, the pathophysiology is still incompletely understood.[3,4] However, frequently a positive family history is found in these patients. Large studies from Japan have reported that a positive family history for cardiovascular disease is more frequently found in patients with vasospastic angina than in patients without.[5,6] Moreover, a positive family history was an independent predictor for an abnormal spasm provocation test result. In one of our studies, we were able to reproduce these findings in German patients.[2] However, data about a comparison of sex and a positive family history in patients with coronary spasm are scarce.

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One study from Japan described that a positive family history was more often found in women with vasospastic angina than in men,[7] but this has not been assessed in other patient cohorts. Thus, the aim of this study was to assess a large cohort of European patients with angina pectoris and unobstructed coronary arteries for the potential associations of sex, a positive family history for cardiovascular disease, and ACh-induced coronary spasm.

## PATIENTS AND METHODS

### Patients

Over a period of 3 years (ie, between January 2008 and December 2011) a total of 415 consecutive patients (mean [SD] age, 62 [11] years; 62% women) with stable angina and unobstructed coronary arteries (no stenosis >50%) was recruited. All patients were referred for invasive coronary angiography because of signs and symptoms suggestive of myocardial ischemia. Patients with previous coronary revascularisation procedures were excluded. The patients reported in this study have been reported in part in a previous study.[8] However, different inclusion and exclusion criteria were applied for the previous study, and the detailed results about the family history are reported in the present study for the first time. Of all patients, 313 patients (75%) had undergone noninvasive stress testing for myocardial ischemia before being selected for angiography. Exercise stress testing was performed in 250 patients, stress echocardiography in 11 patients, stress cardiac magnetic resonance imaging in 10 patients, and myocardial scintigraphy in 42 patients. In 183 of the 313 patients (58%) who underwent noninvasive stress testing for myocardial ischemia an abnormal test result was noted.

Apart from demographic data and the clinical presentation, the following information was recorded in every patient: left ventricular ejection fraction and cardiovascular risk factors, including hypertension, diabetes, hypercholesterolemia, a history of smoking, and a positive family history for cardiovascular events. The latter was defined as a first-degree relative with myocardial infarction or stroke. In patients with a positive family history it was recorded whether the relative had the event within a margin of more than or fewer than 10 years of the current age of the respective patient.

### Study Protocol

This single-center study was conducted at the Robert-Bosch-Krankenhaus, Department of Cardiology, Stuttgart, Germany. All patients gave written informed consent before the study, and the study protocol was approved by the local ethics committee. All patients underwent intracoronary ACh testing immediately after diagnostic coronary angiography according to a standardized protocol as described previously.[2] Patients were excluded and the provocation test was not performed if patients had severe chronic obstructive pulmonary disease or impaired renal function (glomerular filtration rate <30 mL/min/1.73 $m^2$) or a left ventricular ejection fraction of <30%. All patients received standardized treatment with secondary prevention medication according to the current guidelines from the European Society of Cardiology. In addition, in the presence of a pathologic ACh test, calcium channel blockers and short-acting nitrates were prescribed.

### ACh Testing

During ACh testing heart rate, blood pressure, and the 12-lead ECG were continuously monitored. Ischemic ECG shifts were defined as transient ST-segment depression or elevation ≥0.1 mV in at least 2 contiguous leads. In all patients the left coronary artery was the first vessel used for ACh injections. Manual infusions over 3 minutes each were performed with incremental doses of 2, 20, 100, and 200 $\mu$g through the diagnostic catheter. The right coronary artery was challenged with a single dose of 80 $\mu$g in patients who remained asymptomatic, and no diagnostic ST-segment changes were found during provocation testing of the left coronary artery[2]. Glyceryl trinitrate (0.2 mg; Pohl-Boskamp, Hohenlockstedt, Germany) was injected into the left and right coronary artery to relieve coronary spasm or severe anginal symptoms during ACh infusion. Nitrates were also infused routinely at the end of the ACh testing into the right and left coronary artery.

### ACh Test Assessment

A positive (ie, pathologic) test result for epicardial spasm was defined as (1) reproduction of the patient's symptoms, (2) ischemic ECG shifts on the 12-lead ECG, and (3) focal or diffuse epicardial coronary diameter reduction ≥75% compared with the relaxed state after intracoronary nitroglycerin infusion in any epicardial coronary artery segment. Moreover, diffuse