Clinical Usefulness, Angiographic Characteristics, and Safety Evaluation of Intracoronary Acetylcholine Provocation Testing Among 921 Consecutive White Patients With Unobstructed Coronary Arteries

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Background—Coronary spasm can cause myocardial ischemia and angina in patients with and those without obstructive coronary artery disease. However, provocation tests using intracoronary acetylcholine administration are rarely performed in clinical routine in the United States and Europe. Thus, we assessed the clinical usefulness, angiographic characteristics, and safety of intracoronary acetylcholine provocation testing in white patients with unobstructed coronary arteries.

Methods and Results—From September 2007 to June 2010, a total of 921 consecutive patients (362 men, mean age 62±12 years) who underwent diagnostic angiography for suspected myocardial ischemia and were found to have unobstructed coronary arteries (no stenosis ≥50%) were enrolled. The intracoronary acetylcholine provocation testing was performed directly after angiography according to a standardized protocol. Three hundred forty-six patients (35%) reported chest pain at rest, 222 (22%) reported chest pain on exertion, 238 (24%) reported a combination of effort and resting chest pain, and 41 (4%) presented with troponin-positive acute coronary syndrome. The overall frequency of epicardial spasm (>75% diameter reduction with angina and ischemic ECG shifts) was 33.4%, and the overall frequency of microvascular spasm (angina and ischemic ECG shifts without epicardial spasm) was 24.2%. Epicardial spasm was most often diffuse and located in the distal coronary segments (P<0.01). No fatal or irreversible nonfatal complications occurred. However, 9 patients (1%) had minor complications (nonsustained ventricular tachycardia [n=1], fast paroxysmal atrial fibrillation [n=1], symptomatic bradycardia [n=6], and catheter-induced spasm [n=1]).

Conclusions—Epicardial and microvascular spasm are frequently found in white patients with unobstructed coronary arteries. Epicardial spasm is most often diffuse and located in the distal coronary segments. The intracoronary acetylcholine provocation test is a safe technique to assess coronary vasomotor function. (Circulation. 2014;129:1723-1730.)

Key Words: acetylcholine ◼ complications ◼ coronary vasospasm ◼ microvascular angina.

Since its inaugural description in 1959,1 coronary artery spasm has been recognized as an important cardiac condition that can lead to myocardial ischemia and angina pectoris in patients with obstructive coronary artery disease and in those without, as well.2 Coronary spasm can be the cause for myocardial infarction3 and ventricular arrhythmias,4 and coronary spasm has also been shown to occur on the level of the microcirculation.5 It has been suggested that coronary spasm is more prevalent among Asian in comparison with white populations6,7 and that whites more often have focal coronary spasm associated with an atherosclerotic plaque rather than diffuse spasm in the distal parts of the epicardial vessels.8 Moreover, it has been hypothesized that the frequency of coronary spasm is on the decrease in the Western world.9 However, provocation testing using intracoronary acetylcholine administration in search of coronary spasm is rarely performed in daily clinical routine in the United States and Europe. In this study, we sought to assess the frequency of epicardial and microvascular coronary spasm, the angiographic characteristics, and the safety of intracoronary acetylcholine (ACH) provocation testing (ACH test) in a contemporary cohort of 921 consecutive white patients with unobstructed coronary arteries.

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Methods

Patients
From September 2007 to June 2010, a total of 921 consecutive patients (362 men, mean age 62±12 years) who underwent diagnostic coronary angiography for suspected myocardial ischemia and were found to have unobstructed coronary arteries (no epicardial stenosis ≥50%) were included in the study. ACH test was performed directly after diagnostic coronary angiography. Subjects were excluded and the provocation test was not performed if patients had severe chronic obstructive pulmonary disease or impaired renal function (creatinine ≥2.0 mg/dL), or if spontaneous spasm was observed. The following information was recorded for every patient: clinical presentation (chest pain at rest, chest pain on exertion, or a combination of both); previous history of obstructive coronary artery disease including previous coronary stent implantation or coronary artery bypass surgery; cardiovascular risk factors including hypertension, diabetes mellitus, hypercholesterolemia, a history of smoking, and a positive family history for cardiovascular events (myocardial infarction or stroke in a parent or sibling); presentation with troponin-positive acute coronary syndrome (ST-segment elevation myocardial infarction or non–ST-segment myocardial infarction); results of noninvasive stress tests for myocardial ischemia (a positive response was defined as transient ischemic ECG changes ≥0.1 mV in at least 2 contiguous leads, 80 ms after the J point, and reproduction of angina during the stress test). Furthermore, the degree of narrowing along the epicardial vessels was quantified and categorized (0%–20% and 21%–49% narrowing). Patients with a previous history of obstructive coronary artery disease had all undergone revascularization and were eligible because repeated coronary angiography owing to recurrent symptoms and the suspicion of progress of coronary artery disease did not reveal any relevant epicardial stenosis.

Study Protocol
The study protocol complied with the Declaration of Helsinki and the study was approved by the institutional review committee. All patients gave written informed consent before angiography. All patients in the study underwent intracoronary provocation with ACH in accordance to a standardized protocol[9,10] immediately after diagnostic angiography. Cardiovascular medications (β-blockers, calcium channel blockers, and nitrates) were discontinued 48 hours before coronary angiography. Sublingual glyceryl trinitrate administration was permitted for the relief of chest pain at all times. However, none of the patients required this treatment <4 hours before angiography. Heart rate, blood pressure, and the 12-lead ECG were continuously monitored during ACH testing. Ischemic ECG changes were defined as transient ST-segment depression or elevation ≥0.1 mV in at least 2 contiguous leads.

ACH Testing
Incremental doses of 2, 20, 100, and 200 μg of ACH were manually infused over a period of 3 minutes into the left coronary artery (LCA) via the angiographic catheter. In patients who remained asymptomatic and showed no diagnostic ST-segment changes during LCA ACH infusion, 80 μg of ACH were injected into the right coronary artery (RCA).[9] The ACH doses used in our protocol were derived from the multicenter Evaluation of Nifedipine and Cerivastatin on Recovery of Cardial coronary constriction ≥2 contiguous leads. Both the location and type of epicardial coronary spasm had all undergone revascularization and were eligible because repeated coronary angiography owing to recurrent symptoms and the suspicion of progress of coronary artery disease did not reveal any relevant epicardial stenosis.

Constriction. Nitrates were also infused routinely at the end of the ACH test into the RCA and LCA.

ACH Test Assessment
Angiographic responses during the ACH test were analyzed by using computerized quantitative coronary angiography (QCA-CMS, Version 6.0, Medis-Software, Leiden, The Netherlands). The ACH test was considered positive for epicardial coronary spasm in the presence of focal or diffuse epicardial coronary diameter reduction ≥75% in comparison with the relaxed state following intracoronary nitroglycerine infusion in any epicardial coronary artery segment together with the reproduction of the patient’s symptoms and ischemic ECG shifts. Both the location and type of epicardial coronary spasm (ie, focal versus diffuse) were also assessed.[11] Focal constriction was defined as a circumscribed transient vessel narrowing within the borders of 1 isolated or 2 neighboring coronary segments as defined by the American Heart Association. Diffuse constriction was diagnosed when the vessel narrowing was observed in ≥22 adjacent coronary segments. Proximal spasm was defined as vasoconstriction occurring in segments 1, 5, 6, or 11. Midvessel spasm was recorded when occurring in segments 2, 3, or 7, whereas distal spasm was defined as that occurring in segments 4, 8, 9, 10, 12, 13, 14, or 15.

Microvascular spasm was diagnosed when typical ischemic ST-segment changes and angina developed in the absence of epicardial coronary constriction ≥75% diameter reduction.[7] Patients who experienced no angina, constriction, or ST-segment shifts were considered to have a negative ACH-test response (normal coronary vasoreactivity). The ACH test was judged inconclusive in patients who only experienced angina without ECG changes. The same was true for those who had ST-segment shifts without reproduction of their symptoms. Finally, tests with angiographic vasospasm and ST-segment shifts but no angina were also defined to be inconclusive.

Statistical Analysis
Data analysis was conducted with the use of SPSS 17.0 (SPSS Inc, Chicago, IL). Results are expressed as mean±standard deviation. The t test was used to compare continuous variables. The Fisher exact test was used for categorical variables. Multiple logistic regression analysis was performed by using forward variable selection based on likelihood ratios to identify predictors for a pathological ACH test and for identification of patients with epicardial spasm in comparison with those who have microvascular spasm. A 2-tailed P value of <0.05 was considered significant.

Results
Overall Results
The summary of the results of all patients is shown in Table 1. In 74 of the 921 patients, the ACH test could not be performed owing to logistic reasons or patient refusal. Among the remaining 847 patients, the ACH test revealed epicardial coronary spasm in 283 patients (33.4%), and microvascular spasm was seen in another 205 (24.2%; Figures 1 and 2). In 117 patients, the ACH test was negative (no symptoms, no ECG changes, no epicardial spasm). In the remaining 242 patients, the test was inconclusive because patients had reproduction of symptoms (n=87), ischemic ECG changes (n=81), and epicardial spasm (n=74; 40 with associated ischemic ECG changes but no reproduction of symptoms, 1 with reproduction of symptoms but without ECG shifts, and 33 with neither of the latter) as the only abnormal finding, respectively.

Clinical Characteristics
Overall, patients with a positive ACH test were older, they were more often female, and they more often presented with
exertional chest pain. In addition, they more often had a positive family history for cardiovascular disease and they more often showed a pathological response to noninvasive stress testing. Interestingly, there were also fewer smokers in the group with an abnormal ACH test than in the group with a negative ACH test.

In comparison with patients with microvascular spasm, those with epicardial spasm were more often male, were smokers, and had a previous history of obstructive coronary artery disease. They more often presented with resting chest pain and a clinical presentation of acute coronary syndrome in comparison with the microvascular spasm group. The detailed results are shown in Table 2.

Multivariable analysis revealed that female sex, a previous history of coronary artery disease, and a clinical presentation with effort angina or mixed angina were independent predictors for a pathological ACH-test response (Table 3). Moreover, male sex, older age, cigarette smoking, a previous history of coronary artery disease, resting angina, lower left ventricular ejection fraction, and a clinical presentation with acute coronary syndrome were identified as independent predictors for epicardial spasm in comparison with patients with microvascular spasm.

**Angiographic Characteristics of Epicardial Coronary Spasm**

Epicardial coronary spasm occurred in 378 vessels in 282 patients, including 190 (67%) with 1-vessel spasm, 88 (31%) with 2-vessel spasm, and 4 (1.4%) with 3-vessel spasm. The most frequent type and location of spasm was distal and diffuse (40%, \( P<0.01 \); Figures 2 and 3), mainly in segment 8 (distal left anterior descending artery). Only 9 patients (3.2%) had a proximal and focal epicardial spasm. Patients with epicardial plaques between 21% and 49% had epicardial spasm more often (ie, 45%) than patients with only minor coronary artery narrowings between 0% and 20% (ie, 30%, \( P<0.01 \)). However, spasm was found to be focally superimposed on insignificant atherosclerotic lesions in only 13 cases (4.6%).

Table 1. Patient Characteristics – All Patients

<table>
<thead>
<tr>
<th>All Patients</th>
<th>ACH Pathological</th>
<th>ACH Negative</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>847</td>
<td>488 (58)</td>
<td>359 (42)</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

Sex (male), n (%) 362 (43) 164 (34) 198 (55) <0.0005
Age, y, mean±SD 61.8±11.6 62.8±11.1 60.5±12.1 0.006
Previous history of obstructive coronary artery disease 164 (19) 105 (22) 59 (16) 0.065
Admissions for chest pain before ACH test 242 (28.6) 136 (28) 106 (29.5) 0.64
Diagnostic angiography before ACH test 274 (32.3) 167 (34) 107 (29.8) 0.18
Noninvasive test for ischemia performed 565 (66.7) 340 (70) 225 (62.7) 0.039
Positive response to noninvasive test for ischemia 328 (38.7) 210 (43) 118 (32.9) 0.023

Clinical presentation

Predominantly resting chest pain 346 (41) 168 (34) 178 (50) <0.0005
Predominantly exertional chest pain 222 (26) 145 (30) 77 (21) 0.007
Effort and resting chest pain 238 (28) 154 (32) 84 (23) 0.011
Troponin-positive ACS 41 (5) 21 (4) 20 (6) 0.421

ACH test

LCA only 556 (65.6) 395 (81) 161 (45) <0.0005
RCA only 2 (0.02) 1 (0.2) 1 (0.3) 1.0
LCA+RCA 289 (34) 92 (19) 197 (55) <0.0005
LVEF %, mean±SD 72±11 72±10 71±11 0.31

Risk factors

Hypertension 609 (72) 346 (71) 263 (73) 0.49
Diabetes mellitus 142 (17) 84 (17.2) 58 (16) 0.71
Hypercholesterolemia 460 (54) 275 (56.3) 185 (52) 0.19
Smoking 307 (36) 161 (33) 146 (41) 0.025
Positive family history for CVD 441 (52) 271 (55.5) 170 (47.4) 0.022

Values shown are n (%), unless stated otherwise. ACH indicates acetylcholine; ACH test, intracoronary acetylcholine provocation testing; ACS indicates acute coronary syndrome; CVD, cardiovascular disease; LCA, left coronary artery; LVEF, left ventricular ejection fraction; RCA, right coronary artery; and SD, standard deviation.
Complications
We did not observe any fatal or serious nonfatal complications (e.g., sustained ventricular tachycardia, ventricular fibrillation, or myocardial infarction due to prolonged coronary spasm). However, 9 patients (1%) experienced minor complications. One patient developed nonsustained

Table 2. Patient Characteristics According to ACH-Test Result

<table>
<thead>
<tr>
<th></th>
<th>Epicardial Spasm</th>
<th>Microvascular Spasm</th>
<th>ACH Test Inconclusive</th>
<th>ACH Test Normal</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=</td>
<td>283 (33.4)</td>
<td>205 (24.2)</td>
<td>242 (28.6)</td>
<td>117 (13.8)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>128 (45)</td>
<td>36 (18)</td>
<td>123 (51)</td>
<td>75 (64)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>63±11</td>
<td>62±11</td>
<td>61±12</td>
<td>60±12</td>
<td>0.025</td>
</tr>
<tr>
<td>Previous history of obstructive coronary artery disease</td>
<td>79 (28)</td>
<td>26 (13)</td>
<td>45 (19)</td>
<td>14 (12)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Admissions for chest pain before ACH test</td>
<td>86 (30)</td>
<td>50 (24)</td>
<td>73 (30)</td>
<td>33 (28)</td>
<td>0.469</td>
</tr>
<tr>
<td>Diagnostic angiography before ACH test</td>
<td>105 (37)</td>
<td>62 (30)</td>
<td>75 (31)</td>
<td>32 (27)</td>
<td>0.188</td>
</tr>
<tr>
<td>Noninvasive test for ischemia performed</td>
<td>193 (68)</td>
<td>147 (72)</td>
<td>155 (64)</td>
<td>70 (60)</td>
<td>0.119</td>
</tr>
<tr>
<td>Positive response to noninvasive test for ischemia</td>
<td>118 (42)</td>
<td>92 (45)</td>
<td>84 (35)</td>
<td>34 (29)</td>
<td>0.103</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Predominantly resting chest pain</td>
<td>112 (40)</td>
<td>56 (27)</td>
<td>111 (46)</td>
<td>67 (57)</td>
</tr>
<tr>
<td>Predominantly exertional chest pain</td>
<td>72 (25)</td>
<td>73 (36)</td>
<td>55 (23)</td>
<td>22 (19)</td>
<td>0.003</td>
</tr>
<tr>
<td>Effort and resting chest pain</td>
<td>82 (29)</td>
<td>72 (35)</td>
<td>62 (26)</td>
<td>22 (19)</td>
<td>0.012</td>
</tr>
<tr>
<td>Troponin-positive ACS</td>
<td>17 (6)</td>
<td>4 (2)</td>
<td>14 (6)</td>
<td>6 (5)</td>
<td>0.128</td>
</tr>
<tr>
<td>ACH test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCA only</td>
<td>240 (84.8)</td>
<td>155 (76)</td>
<td>126 (52)</td>
<td>35 (30)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>RCA only</td>
<td>1 (0.4)</td>
<td>0</td>
<td>1 (0.3)</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>LCA+RCA</td>
<td>42 (14.8)</td>
<td>50 (24)</td>
<td>115 (8)</td>
<td>82 (70)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LVEF %, mean±SD</td>
<td>71±11</td>
<td>74±10</td>
<td>71±11</td>
<td>72±11</td>
<td>0.010</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>192 (68)</td>
<td>154 (75)</td>
<td>175 (72)</td>
<td>88 (75)</td>
<td>0.271</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>50 (18)</td>
<td>34 (17)</td>
<td>41 (17)</td>
<td>17 (15)</td>
<td>0.912</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>167 (59)</td>
<td>108 (53)</td>
<td>121 (50)</td>
<td>64 (55)</td>
<td>0.207</td>
</tr>
<tr>
<td>Smoking</td>
<td>113 (40)</td>
<td>48 (23)</td>
<td>108 (45)</td>
<td>38 (32)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Positive family history for CVD</td>
<td>163 (58)</td>
<td>108 (53)</td>
<td>117 (48)</td>
<td>53 (45)</td>
<td>0.072</td>
</tr>
</tbody>
</table>

Values shown are n (%), unless stated otherwise. ACH indicates acetylcholine; ACH test, intracoronary acetylcholine provocation testing; ACS, acute coronary syndrome; CVD, cardiovascular disease; LCA, left coronary artery; LVEF, left ventricular ejection fraction; RCA, right coronary artery; and SD, standard deviation.

*P refers to the comparison of all 4 patient groups.

Figure 2. A and B, LCA angiograms and ECGs of a patient with epicardial spasm. Note the diffuse but distally accentuated narrowing of the LAD during acetylcholine infusion (arrows) together with ischemic ECG shifts (A) and resolution of both findings after nitroglycerine i.c. (B). C and D, Example of a patient with microvascular spasm. During ACH the patient had reproduction of angina, ischemic ECG changes, but no epicardial constriction (C). After nitroglycerine i.c., chest pain and ECG changes resolved (D). ACH indicates acetylcholine; i.c., intracoronary; LAD, left anterior descending artery; and LCA, left coronary artery.
The most frequent finding was a distal and diffuse spasm combination and location (proximal, midsegment, distal, combination) of epicardial coronary artery spasm (n=283). The most frequent finding was a distal and diffuse spasm (40%, P<0.01).

Figure 3. Graphic showing the distribution of type (diffuse, focal, combination) and location (proximal, midsegment, distal, combination) of epicardial coronary artery spasm (n=283).

Table 3. Multivariable Analysis

<table>
<thead>
<tr>
<th>Pathological ACH test vs normal ACH test</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>2.501; 1.875–3.335; &lt;0.0005</td>
</tr>
<tr>
<td>Previous history of coronary artery disease</td>
<td>1.351; 1.058–1.552; 0.023</td>
</tr>
<tr>
<td>Clinical presentation without resting angina</td>
<td>1.749; 1.314–2.330; &lt;0.0005</td>
</tr>
</tbody>
</table>

Epicardial vs microvascular spasm

| Male sex                             | 1.679; 1.491–1.798; <0.0005 |
| Age                                  | 1.023; 1.003–1.042; 0.022 |
| Cigarette smoking                    | 1.463; 1.149–1.661; 0.008 |
| Previous history of coronary artery disease | 1.536; 1.209–1.728; 0.005 |
| Resting angina                       | 1.518; 1.261–1.865; 0.001 |
| Clinical presentation with acute coronary syndrome | 1.749; 1.192–1.922; 0.020 |

Left ventricular ejection fraction | 0.979; 0.960–0.998; 0.034

Values shown are odds ratio, confidence interval, and P value. ACH indicates acetylcholine; and ACH test, intracoronary acetylcholine provocation testing.

ventricular tachycardia during ACH provocation and 1 patient had fast paroxysmal atrial fibrillation that resolved spontaneously after discontinuing the injection. Six patients developed symptomatic bradycardia and transient hypotension that resolved spontaneously after stopping the ACH injection in 5 patients; in 1 patient, the intravenous injection of atropine was necessary to stabilize heart rate and blood pressure. The remaining patient had catheter-induced coronary spasm of the proximal right coronary artery associated with ST-segment elevation that resolved after removing the catheter. Apart from that, no other catheter-induced spasms were observed. Statistical comparison of patients with and those without a complication did not reveal any significant differences (data not shown).

Figure 3. Graphic showing the distribution of type (diffuse, focal, combination) and location (proximal, midsegment, distal, combination) of epicardial coronary artery spasm (n=283). The most frequent finding was a distal and diffuse spasm (40%, P<0.01).

Discussion

This is the largest study to assess the safety of ACH testing in white patients showing that the ACH test is a safe method for the assessment of coronary vasomotor function when performed with an appropriate protocol. Moreover, we report a high frequency of coronary microvascular spasm in a large contemporary cohort of white patients with anginal symptoms and unobstructed coronary arteries. In addition, we could show that epicardial coronary spasm is most often diffuse and located in the distal parts of the epicardial vessels, probably as a sign of concomitant microvascular disease.

Clinical Characterization

Comparison of the clinical characteristics between patients with and those without coronary spasm revealed that female sex, a previous history of coronary artery disease, and a clinical presentation with effort angina or mixed angina were independent predictors for a pathological ACH-test response. In contrast to expectations, resting angina, male sex, and cigarette smoking were not identified as significant predictors for the entire group. However, these variables were identified as predictors for epicardial spasm.

Our study extends previous data in so far that we also found a previous history of coronary artery disease, a lower left ventricular ejection fraction, and a clinical presentation with acute coronary syndrome as independent predictors for the observation of epicardial spasm in response to ACH testing. Therefore the results of our study provide a comprehensive clinical characterization of white patients with angina despite unobstructed coronary arteries with a high likelihood for epicardial spasm.

Microvascular spasm was also found to be frequent in our patients. Interestingly, hypertension and diabetes mellitus were not found to be predictors of microvascular spasm, although both conditions are well known to impair microvascular function. However, diabetes mellitus was rather infrequent in our cohort, and our data show that microvascular disease is also common in patients without a history of hypertension indicating that the feature hypertension has a good sensitivity (ie, 80%), but it does not have a high positive predictive value (ie, 70%) for the presence of ACH-induced coronary spasm. Moreover, all cardiovascular risk factors may have substantial and deleterious effects on the microcirculation as recently reported by Granger et al. 15 The fact that epicardial spasm was often distal and diffuse suggests that patients with microvascular spasm may also experience distal epicardial spasm as previously shown in smaller cohorts. 16,17 Larger studies are needed to elucidate the relationship between epicardial and microvascular coronary vasomotor disorders.

Angiographic Characteristics

The detailed analysis of the angiographic characteristics of our patients revealed that diffuse and distal epicardial coronary spasm was the most frequent finding. Our results contrast with a report on white patients by Bertrand et al who most often found focal epicardial spasm in their patients. This difference is most probably due to
the different substance used for provocation of spasm (ie, ergonovine in the study of Bertrand) and the different route of administration (intravenous versus intracoronary). A study by Goto et al$^{18}$ showed that coronary spasm can often be elicited by ACH even if ergonovine did not reveal any spasm. Moreover, our results are comparable to a more recent study by COMA-Canella et al$^{19}$, suggesting that distal and diffuse spasm is a frequent observation in whites who have angina and unobstructed coronary arteries. In addition, the prevalence of coronary spasm of 32.3% reported in an Asian cohort of 685 Japanese patients appears to be similar to our findings.$^7$

Recently, Sato et al$^{20}$ reported their findings from 1877 patients who underwent ACH testing with the use of similar criteria as in our study. They found a pathological ACH-test response in 53% with 511 patients having focal spasm and 362 with diffuse spasm. Diffuse spasm was associated with a better prognosis after 5 years in comparison with focal spasm. In both studies, a positive family history for cardiovascular disease was more often found in patients with a spastic ACH-test response, albeit in our study with a higher frequency (ie, 55.5% in comparison with only 17% in the study by Sato et al). Complication rates were similarly low in both studies. The main difference in comparison with our study is the inclusion of patients with an epicardial stenosis $>75\%$. This probably explains the high number of patients with focal spasm (ie, 59% of all patients with spasm) in comparison with only 18% in our study. This is supported by a study from Okumura et al$^{21}$ showing that diffuse spasm is frequently found in patients without advanced organic stenotic lesions. In addition, Saito et al$^{22}$ showed that the presence of epicardial plaque is likely to be related to the occurrence of focal spasm. It should, however, be noted that there is currently no consensus definition for diffuse or focal coronary spasm. Clearly, comparative studies between Asian and white patients with stringent inclusion criteria and similar provocation test protocols should be performed to ultimately answer the question of whether there are differences in the prevalence and type of coronary spasm in ethnically diverse groups.

Safety
Because of its invasive nature, there has been a lot of skepticism regarding intracoronary provocation testing for coronary spasm because of the potential complications associated with the test. Interestingly, it is not the fact that coronary angiography is required for performing the test that raises concern, but the fear of irreversible spasm leading to arrhythmia and death due to the provocative testing itself.$^7$ However, previous studies in Asian, and white patients, as well, have demonstrated that the test is reasonably safe. Bertrand et al$^8$, using intravenous ergonovine, had no serious irreversible complications among their 1088 patients, and Harding et al$^9$, reporting some 3447 intracoronary ergonovine tests in American patients, only had a single patient with serious complications such as myocardial infarction or ventricular tachycardia/fibrillation, corresponding to a complication rate of 0.03%. A higher complication rate was reported by Sueda et al$^7$, who used intracoronary ACH in 685 patients and experienced sustained ventricular tachycardia, shock, or cardiac tamponade in 1.3% of patients. In addition, Wei et al$^{24}$ have recently reported their experience with 293 US patients who underwent coronary reactivity testing reporting a complication rate of 0.7% for serious adverse events such as coronary artery dissection (1 patient) and myocardial infarction (1 patient). These complication rates are comparable to our rate of 1%. Thus, there is compelling evidence that the ACH test using a stepwise approach with increasing doses as reported in our study is a safe procedure that can routinely be performed in the catheterization laboratory. One has to view these complication rates in context with current complication rates for diagnostic coronary angiography, which are similar to those reported for ACH testing.$^{25,26}$

Clinical Implications
The detection of abnormal coronary vasomotion in patients with anginal symptoms but angiographically unobstructed coronary arteries not only leads to the reassurance of the patient that a cause for the symptoms is found, but also enables the physician to initiate appropriate medical therapy (ie, calcium channel blockers and nitrates)$^{27}$ aimed at reducing morbidity and mortality.$^{28,29}$ This may also have important implications on healthcare systems because most health care–related costs in patients with unobstructed coronary arteries are due to recurrent or ongoing angina pectoris.$^{30}$ Moreover, despite treatment with calcium channel blockers, patients with coronary spasm may experience persistent or recurrent episodes of angina at follow-up,$^{31}$ underpinning the need for the development of new drugs for treatment of vasospastic angina. This report should also encourage interventionists to add the ACH test to their portfolio in the search of functional causes for angina in patients with unobstructed coronary arteries.$^{32}$ In patients presenting with symptoms other than angina pectoris (eg, syncope or heart failure), ACH testing may also be useful because these conditions can also be caused by coronary spasm.$^{33,34}$

Limitations
Because we did not challenge the RCA when coronary spasm was provoked in the LCA, the frequency of multivessel spasm may be underestimated.

We used a slightly different definition for epicardial coronary spasm than other investigators, especially from Asia$^{35}$ (ie, $\geq 75\%$ in comparison with subtotal vasoconstriction and a maximum dose of 200 $\mu$g in comparison with 100 $\mu$g of ACH as in the Asian protocols). Thus, the frequency of coronary spasm may be higher than with the use of other definitions.

The ACH test was not performed in the early morning in all patients. Because a circadian variation of coronary spasm$^{36}$ has been described, the frequency of spasm might have been higher, if early morning examinations had been conducted consistently.

Conclusions
Epicardial and microvascular coronary spasm are frequently found in white patients with anginal symptoms and
unobstructed coronary arteries. Epicardial spasm is most often diffuse and located in the distal parts of the epicardial vessels. The ACH test is a safe technique to assess coronary vasomotor function.

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Disclosures

None.

References

Coronary spasm can cause myocardial ischemia and angina in patients with and those without obstructive coronary artery disease. However, provocation tests using intracoronary acetylcholine provocation testing (ACH test) are rarely performed in clinical routine in the United States and Europe. In this study, we assessed the clinical usefulness, angiographic characteristics, and safety of the ACH test in white patients with unobstructed coronary arteries. Our study shows that the ACH test is a safe method for the assessment of coronary vasomotor function and that patients with angina and angiographically unobstructed coronary arteries often experience coronary spasm of the epicardial and microvascular coronary vessels. If such an abnormality is diagnosed (eg, with intracoronary acetylcholine provocation testing), this not only leads to reassurance of the patient that a cause for the symptoms is found, but also enables the physician to initiate the appropriate medical therapy (eg, calcium channel blockers and nitrates aimed at reducing morbidity and mortality). Moreover, this may also have important implications on our healthcare systems, because most health care–related costs in patients with unobstructed coronary arteries are due to recurrent or ongoing angina pectoris. However, consistent definitions for coronary vasomotor disorders are needed to be able to compare the frequency of such disorders between different ethnic groups (eg, whites versus Asians). In addition, based on the favorable safety profile of the ACH test as shown in this study, we hope to encourage interventionalists to add the ACH test to their portfolio in search of functional causes for angina, especially in patients with unobstructed coronary arteries.

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Clinical Usefulness, Angiographic Characteristics, and Safety Evaluation of Intracoronary Acetylcholine Provocation Testing Among 921 Consecutive White Patients With Unobstructed Coronary Arteries

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