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Real-World Positivity, Procedural Events, and Management Changes After Intravenous Methylergometrine Provocation Testing for Coronary Vasospasm: A Single-Center Study of 139 Patients

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Abstract

Background: Intracoronary acetylcholine is the reference agent for coronary spasm provocation, but intravenous ergot derivatives remain in use in several European centres, with limited contemporary data on their positivity rate in current clinical practice.

Aims: To assess the operator-defined positivity rate, procedural events, and associated changes in medical management following intravenous methylergometrine provocation.

Methods: All coronary angiograms performed at a single centre between January 2025 and July 2026 were screened through a mandatory regional registry. Provocation consisted of a single 0.20-mg intravenous bolus of methylergometrine, with vasodilator therapy withdrawn 72 hours beforehand. The primary analysis was restricted to the first test performed in each patient. Medical treatment before and after provocation was compared using exact tests for paired data.

Results: Among 2168 coronary angiograms screened, 152 provocation tests were performed in 139 patients. Among the 139 first tests, 28 were considered positive by the operator (20.1%; 95% confidence interval, 13.8-27.8%), while 14 fulfilled all three international diagnostic criteria. Current smoking was the only characteristic nominally associated with positivity (64.3% vs. 36.9%), although this association did not remain significant after correction for multiple comparisons. Transient events occurred during seven positive tests, including three self-terminating episodes of non-sustained ventricular tachycardia; none required cardioversion or vasopressor support. Vasodilator therapy was initiated or intensified after all 28 positive tests compared with 7 of 111 negative tests (6.3%). An alternative diagnosis was retained after 75 of 111 negative tests (67.6%).

Conclusions: Intravenous methylergometrine provocation was associated with operator-defined positivity in approximately one fifth of patients undergoing a first test and was consistently followed by the initiation or intensification of vasodilator therapy. Transient events occurred during a quarter of positive tests, and all resolved without cardioversion or vasopressor support; because procedure reports were retrievable for only a subset of negative tests, no cohort-wide safety estimate can be derived.

Categories: Therapeutics, Cardiology, Internal Medicine
Keywords: coronary artery angiography, coronary artery vasospasm, coronary vasospastic angina, methylergometrine, provocation testing

Introduction

Coronary vasospasm is an established mechanism of myocardial ischaemia in patients with angiographically normal or non-obstructive coronary arteries, accounting for a substantial share of angina and of myocardial infarction with non-obstructive coronary arteries and associated with ventricular arrhythmia and sudden death [1,2]. Because coronary tone fluctuates and spontaneous episodes are rarely captured, diagnosis usually relies on invasive provocation testing, for which the Coronary Vasomotion Disorders International Study Group (COVADIS) has proposed standardised criteria combining a reduction of at least 90% in luminal diameter, reproduction of the usual chest pain, and ischaemic electrocardiographic changes [1].

Intracoronary acetylcholine is currently regarded as the reference agent and features in current European guidance on the invasive assessment of coronary vasomotor disorders [3-5], but ergot derivatives remain in use in several European laboratories, particularly by the intravenous route, which exposes both coronary networks within a single acquisition sequence [6,7]. Published experience with this approach is largely historical, and contemporary data describing its positivity rate, the events it provokes, and its consequences

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for management are scarce.

These consequences deserve attention in their own right. Randomised data show that the value of invasive functional assessment lies in linking the diagnosis to a stratified treatment strategy rather than in the diagnostic label itself [8]. A positive test is expected to prompt vasodilator therapy and withdrawal of beta-blockers, which may aggravate spasm; a negative test is expected to redirect the diagnostic pathway. These effects are seldom quantified, and when reported, they usually describe discharge prescriptions rather than a paired before/after comparison.

We therefore analysed all methylergometrine provocation tests performed over 18 months at a single centre. The primary objective was to determine the operator-defined positivity rate of a first test. The secondary objectives were to describe the procedural events provoked by the test, the changes in vasodilator therapy that followed, and the proportion of negative tests followed by diagnostic redirection. Analyses of the characteristics associated with a positive test and of the reassessment cohort were exploratory.

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Materials And Methods

Design and population

This was a retrospective, observational, single-centre study reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [9]. All coronary procedures performed between January 2, 2025 and July 1, 2026 were screened from CARDIO-ARSIF [10], the mandatory regional registry of invasive cardiology of the Ile-de-France region, which prospectively records demographic, clinical, procedural, and angiographic data for every coronary procedure, including a dedicated field for methylergometrine provocation. Elective percutaneous coronary interventions were excluded, as the provocation field does not apply to them.

Provocation was performed at the operator's discretion, without formal written selection criteria, in patients investigated for chest pain in whom coronary angiography did not account for the clinical presentation. It was not performed in the presence of severe left main or three-vessel obstructive disease, haemodynamic instability, or acute ST-elevation myocardial infarction.

Two cohorts were defined. The primary diagnostic cohort comprised the first provocation test of each patient during the study period, giving one observation per patient. The exploratory reassessment cohort comprised subsequent tests performed in patients already known to be positive, undertaken to assess persistence of vasospasm during treatment. All analyses of positivity rate, characteristics associated with a positive result, procedural events, and management change refer to the primary cohort.

This retrospective study was based exclusively on the reuse of data collected during routine clinical care and, under French regulations, did not require review by a Comité de Protection des Personnes (CPP). The study was conducted in compliance with the MR-004 reference methodology of the French Data Protection Authority (CNIL) [11]. Data were pseudonymised at extraction.

Provocation protocol

The protocol was uniform throughout the study period. A 12-lead electrocardiogram was systematically recorded before methylergometrine injection in the catheterisation laboratory to serve as a baseline for comparison. After diagnostic coronary angiography, a single 0.20 mg ampoule of methylergometrine was injected as an intravenous bolus by the nursing staff through a peripheral venous line. A three-minute timer was then started, during which the patient was continuously monitored for chest pain or electrocardiographic change. If either occurred before the timer elapsed, both coronary networks were reassessed angiographically immediately; otherwise, reassessment took place at three minutes, at which point a further 12-lead electrocardiogram was systematically recorded and compared with the baseline tracing. Calcium channel blockers (CCB) and nitrates were withdrawn 72 hours before diagnostic tests so as not to mask vasospasm. This washout applied to the patient's chronic oral therapy; it was distinct from the intra-arterial radial cocktail (verapamil, with or without nitroglycerin) administered at the start of most procedures for radial artery spasm prophylaxis, which was not withheld. Radial spasm prophylaxis has not been shown to materially affect coronary vasomotor responses during acetylcholine testing [12], although its effect on intravenous methylergometrine testing has not been specifically evaluated. In patients undergoing repeat testing to assess the persistence of vasospasm, the test was deliberately performed with antispastic treatment maintained. Whenever spasm was induced, intracoronary isosorbide dinitrate was administered to antagonise it, and both networks were reassessed angiographically to confirm resolution.

Definitions

Procedural events were abstracted from the catheterisation report as documented by the operator and

comprised any ventricular arrhythmia, bradycardia or atrioventricular block, symptomatic hypotension, need for electrical cardioversion, vasopressor use, or death occurring during the provocation sequence.

Tests were classified as positive or negative by the operator at the time of the procedure, based on induced epicardial vasoconstriction together with the clinical and electrocardiographic response, and recorded as such in the registry. No independent re-adjudication or quantitative coronary analysis was performed, luminal reduction being assessed visually.

Procedure reports of all positive tests were reviewed, unblinded to the result, and classified against the COVADIS criteria [1]. A test was COVADIS-definite when transient subocclusive epicardial narrowing (visually estimated at ⩾90% of luminal diameter), reproduction of the usual chest pain, and ischaemic ST-segment deviation were all documented; positive tests not meeting all three criteria are reported as such, with the missing criterion specified. Isolated T-wave changes were not accepted as fulfilling the electrocardiographic criterion. Multivessel spasm was defined as involvement of more than one epicardial vessel.

Coronary anatomy was classified as angiographically normal (no visible plaque), non-obstructive atherosclerosis (visible plaque with all stenoses below 50% of luminal diameter), or obstructive disease (at least one stenosis of 50% or more). Baseline treatment was that of the admission prescription, and post-test treatment was that of the discharge prescription. Initiation or intensification of vasodilator therapy, the main management endpoint, was defined as the introduction of a CCB, addition of a second CCB, an increase in an unchanged CCB's daily dose, or introduction of a long-acting nitrate, molsidomine, or nicorandil. Beta-blocker withdrawal was analysed separately, since records did not consistently state whether it was attributed to suspected spasm. Antiplatelet and statin changes were likewise recorded separately and reported descriptively, as they may follow the angiographic findings rather than the provocation result. Diagnostic redirection was an alternative diagnosis explicitly retained in the discharge letter after a negative test.

Endpoints

The primary endpoint was the proportion of operator-defined positive first tests. Secondary endpoints were the proportion of tests followed by the initiation or intensification of vasodilator therapy, the occurrence of a procedural event, and the proportion of negative tests followed by diagnostic redirection. Analyses of characteristics associated with a positive test and of the reassessment cohort were exploratory.

Data collection

Registry variables were available for all 152 tests. Smoking status was not documented in the registry for 62 of the 152 tests (41%) and was retrieved from the medical record in every such case, so that it was ascertained for the entire cohort without missing data.

Medical records were reviewed for all 139 first tests (28 positive, 111 negative), providing complete treatment and diagnostic data for the primary cohort. Detailed procedure reports allowing assessment of intra-procedural events were available for all 28 positive tests and for 40 of the 111 negative tests; comparisons of procedural events between groups are therefore exploratory. Follow-up was obtained for all patients with a positive test by review of subsequent consultations, hospitalisations and correspondence recorded in the hospital information system, and was censored at the last documented contact. Recurrent angina was defined as chest pain of the same character documented after the index test, rehospitalisation as any cardiovascular admission, and major adverse cardiac events as the composite of cardiovascular death, myocardial infarction or resuscitated cardiac arrest. Patients with a negative test were generally referred back to their community cardiologist, so follow-up was not available for this group and is not reported.

Statistical analysis

No a priori sample size calculation was performed, as all consecutive tests over the study period were included. Continuous variables are expressed as median (interquartile range) and compared using the Mann-Whitney U test; categorical variables are expressed as counts and percentages, compared using Fisher's exact test with odds ratios (ORs) and 95% confidence intervals (CI), the latter also used for proportions via the exact Clopper-Pearson method. Paired comparisons of binary variables used the exact McNemar test, with discordant counts reported; paired comparisons of the number of antianginal drugs used the Wilcoxon signed-rank test.

The primary cohort contained one observation per patient, so no clustering adjustment was required. Eleven baseline characteristics were compared, for which a Bonferroni-corrected threshold of 0.0045 was indicated; no multivariable model was fitted, given the number of positive tests. A test statistic was reported alongside every P value: the U statistic for the Mann-Whitney test, the OR with its 95% CI for Fisher's exact test, the McNemar chi-square with one degree of freedom for paired binary comparisons, and the W statistic with the matched-pairs rank-biserial correlation for the Wilcoxon signed-rank test. A two-sided $P < 0.05$ was considered significant. Analyses were conducted using Python 3.12 (Python Software Foundation,

Wilmington, DE, United States) with SciPy.

Results

Study population and positivity rate

Of 2636 coronary procedures screened, 468 elective interventions were excluded, leaving 2168 coronary angiograms. Provocation testing was performed in 152 procedures (7.0%) in 139 patients, almost exclusively during diagnostic angiography alone (149/152, 98.0%); three tests included ad hoc angioplasty (Figure *1*).

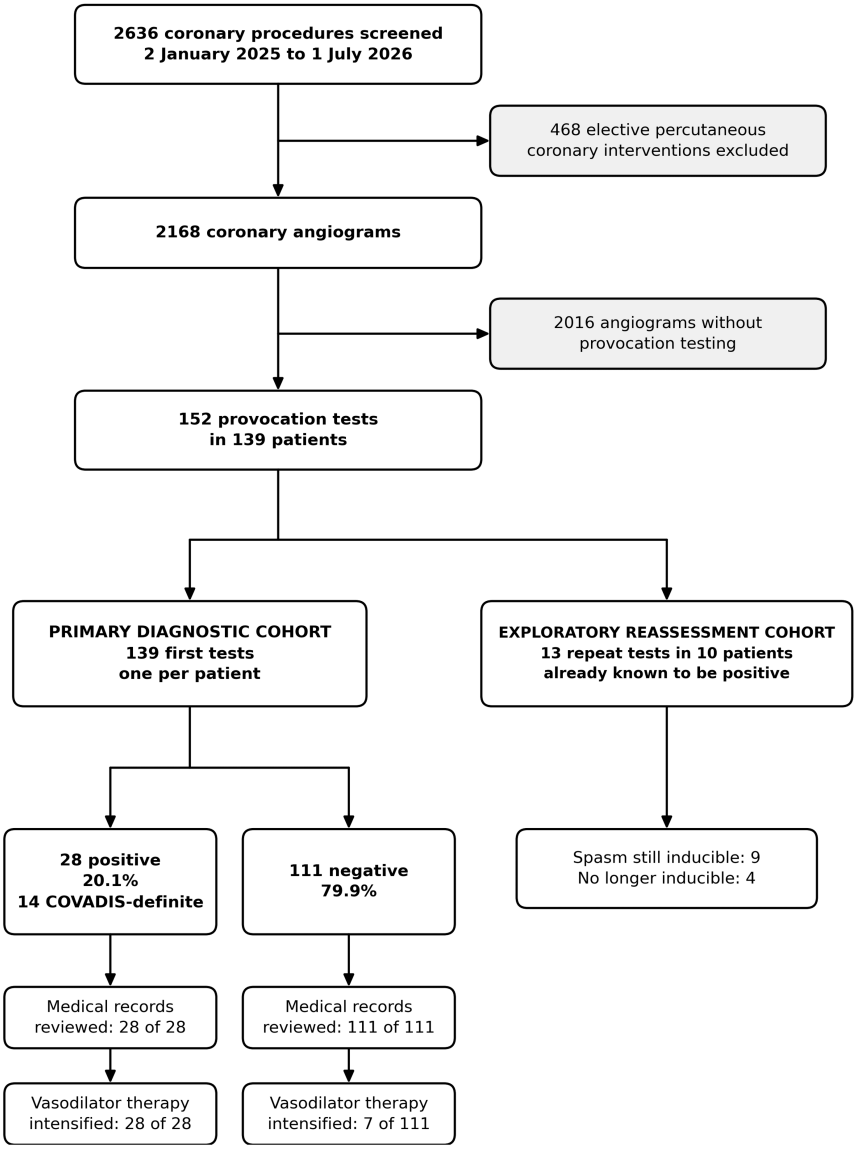


FIGURE 1: Study flow chart.

Of 2636 coronary procedures screened between January 2025 and July 2026, 468 elective percutaneous coronary interventions were excluded. Among 2168 coronary angiograms, 152 provocation tests were performed in 139 patients, comprising a primary diagnostic cohort of 139 first tests (28 positive, 111 negative) and an exploratory reassessment cohort of 13 repeat tests in 10 patients.

The primary diagnostic cohort comprised the 139 first tests, of which 28 were positive as judged by the operator (20.1%, 95% CI 13.8 to 27.8) and 111 were negative. Thirteen further tests were performed in 10 patients already known to be positive and constitute the exploratory reassessment cohort.

The indication was angina without enzyme elevation in 97 patients (69.8%), myocardial infarction with non-obstructive coronary arteries in 28 (20.1%), resuscitated cardiac arrest in 1, and another indication (mainly

persistent or atypical chest pain) in 13 (9.4%). Testing was elective in 132 patients (95.0%). Coronary anatomy was angiographically normal in 95 patients (68.3%), showed non-obstructive atherosclerosis in 29 (20.9%), and obstructive disease in 15 (10.8%). In the latter, the stenosis did not account for symptoms, and no physiological assessment was performed. Thirteen were managed medically and two were scheduled for revascularisation. One of these two also underwent ad hoc angioplasty of a separate lesion during the same (negative) procedure, with provocation testing having been performed first per protocol. The other two ad hoc procedures belonged to the reassessment cohort.

In a sensitivity analysis restricted to the 124 patients with angiographically normal or non-obstructive coronary arteries (excluding the 15 with obstructive disease), the positivity rate was materially unchanged: 24 tests were positive (19.4%, 95% CI 12.8 to 27.4, versus 20.1% in the full cohort), and 12 of these 24 (50.0%) fulfilled all three COVADIS criteria, identical to the proportion in the full positive cohort. Exclusion of patients with concomitant obstructive coronary disease therefore did not materially alter the observed positivity rate.

Patients undergoing provocation were younger than those who did not (median 59 (48-68) versus 69 (60-77) years; Mann-Whitney U = 72844, P < 0.001). Non-invasive ischaemia testing before angiography was uncommon: an exercise test had been performed in three patients and cardiac magnetic resonance in eight, with no myocardial perfusion imaging or stress echocardiography.

Baseline characteristics are shown in Table *1*. Current smoking was the only variable associated with positivity (18/28, 64.3% vs. 41/111, 36.9%; Fisher's exact test, OR 3.07, 95% CI 1.30 to 7.29; P = 0.011), not persisting after Bonferroni correction for the 11 comparisons and regarded as exploratory. Age, sex, body mass index, hypertension, dyslipidaemia, family history, indication, coronary anatomy, electrocardiographic changes, and enzyme elevation did not differ.

Characteristics	Positive, n = 28	Negative, n = 111	Test statistic	P
Age, years	57 (47-66)	60 (49-68)	U = 1392	0.40
Female sex	14 (50.0)	57 (51.4)	OR 0.95, 95% CI 0.41 to 2.17	1.00
Body mass index, kg/m^2	26.0 (24.0-30.4)	25.5 (22.9-28.0)	U = 1792	0.21
Current smoking	18 (64.3)	41 (36.9)	OR 3.07, 95% CI 1.30 to 7.29	0.011
Hypertension	9 (32.1)	36 (32.4)	OR 0.99, 95% CI 0.41 to 2.40	1.00
Dyslipidaemia	12 (42.9)	43 (38.7)	OR 1.19, 95% CI 0.51 to 2.75	0.83
Family history of coronary disease	7 (25.0)	22 (19.8)	OR 1.35, 95% CI 0.51 to 3.57	0.60
Angina without enzyme elevation	21 (75.0)	76 (68.5)	OR 1.38, 95% CI 0.54 to 3.55	0.65
Myocardial infarction with non-obstructive arteries	5 (17.9)	23 (20.7)	OR 0.83, 95% CI 0.29 to 2.43	1.00
Electrocardiographic changes	5 (17.9)	20 (18.0)	OR 0.99, 95% CI 0.34 to 2.92	1.00
Non-obstructive coronary arteries	24 (85.7)	100 (90.1)	OR 0.66, 95% CI 0.19 to 2.25	0.50

TABLE 1: Baseline characteristics according to the result of the first provocation test, n = 139.

Values are n (%) or median (interquartile range). Continuous variables were compared with the Mann-Whitney U test, for which U statistic is given; categorical variables with Fisher's exact test, for which the OR with its 95% CI is given as the effect size. Bonferroni-corrected threshold for the 11 comparisons: P < 0.0045.

OR: odds ratio; CI: confidence interval.

Characteristics of induced spasm and diagnostic certainty

Spasm was focal in 16 tests (57.1%) and diffuse in 12 (42.9%), involving a single vessel in 23 (right coronary artery in 11, left anterior descending in 9, and circumflex in 3) and more than one vessel in 5 (17.9%). The usual chest pain was reproduced in all 28 tests; electrocardiographic changes occurred in 17 (60.7%): ST-segment elevation in 14 and isolated T-wave changes in 3.

A representative sequence of induced subocclusive spasm and its reversal after intracoronary isosorbide dinitrate is shown in Figure *2*, and three further examples illustrating the range of vessels and spasm patterns observed are shown in Figure *3*. Subocclusive narrowing was documented in every positive test's

report. Fourteen of the 28 operator-defined positive tests fulfilled all three COVADIS criteria (50.0%; 10.1% of the 139 first tests), whereas the remaining 14 did not fulfil the electrocardiographic criterion (no change in 11 and isolated T-wave changes in 3).

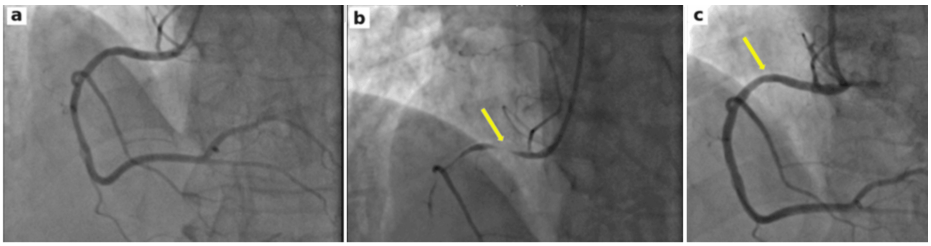


FIGURE 2: Angiographic sequence of a positive provocation test involving the right coronary artery.

Right anterior oblique projection. (a) Baseline. (b) Diffuse subocclusive spasm induced after a 0.20 mg intravenous bolus of methylergometrine. (c) Complete angiographic resolution after intracoronary isosorbide dinitrate. The yellow arrows are digital markings added to the images and indicate the right coronary artery at the site of the induced spasm in (b) and again in (c) after intracoronary isosorbide dinitrate.

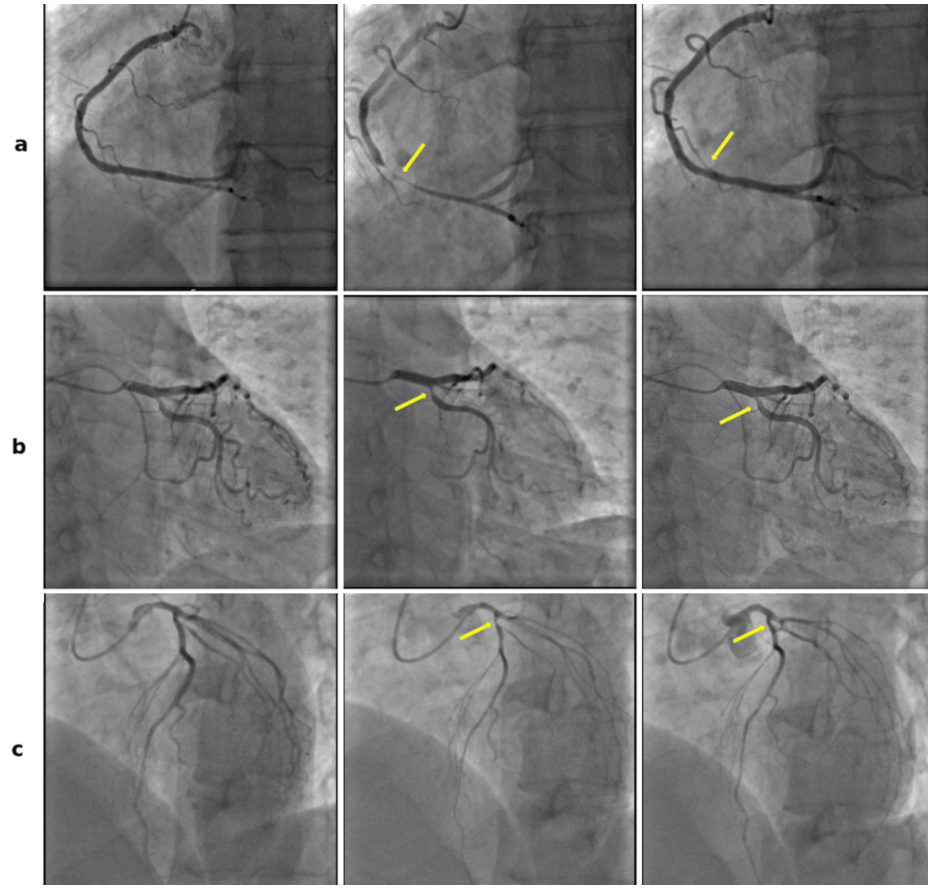


FIGURE 3: Angiographic sequences of three further positive provocation tests, illustrating the range of vessels and spasm patterns observed.

Row (a) right coronary artery, diffuse pattern; row (b) circumflex artery, focal pattern; row (c) left anterior descending artery, diffuse pattern. Columns as in Figure 2: baseline, after intravenous methylergometrine, and after intracoronary isosorbide dinitrate. The yellow arrows are digital markings added to the images: in the middle column, they indicate the segment in which spasm was induced, and in the right column, the same segment after intracoronary isosorbide dinitrate. No arrow is placed on the baseline images.

Procedural events

Transient events occurred during 7 of 28 positive first tests (25.0%, 95% CI 10.7 to 44.9): non-sustained ventricular tachycardia in 3, atrioventricular block or bradycardia in 1, and symptomatic hypotension in 3. All three arrhythmias were self-terminating, with no sustained ventricular tachycardia, ventricular fibrillation, cardioversion, atropine, or vasopressor use; intracoronary isosorbide dinitrate was administered in every case, with angiographic resolution. Among 40 negative tests with retrievable reports, two transient events occurred; the remaining reports were not reviewed, so no cohort-wide event rate can be given. No major complication was recorded in the regional registry for any of the 152 procedures, and none of the transient events identified on review had been declared there.

Changes in medical management

Treatment changes after a positive first test are shown in Table *2*. Vasodilator therapy was initiated or intensified after all 28 positive tests (100%) versus 7 of 111 negative tests (6.3%; risk difference 93.7 percentage points, 95% CI 89.2 to 98.2; Fisher's exact test P < 0.001). This comprised CCB introduction or intensification in 27 and introduction of a long-acting nitrate, molsidomine, or nicorandil in 18. All 28 patients were discharged on a CCB, versus 4 (14.3%) before (McNemar chi-square 22.04, df = 1; P < 0.001); dual CCB therapy rose from none to 6 and long-acting nitrates or molsidomine from 4 to 21 (McNemar chi-square 15.06, df = 1; P < 0.001). The median number of antianginal drugs rose from 0 (0-1) to 2 (2-2) (n = 27 with paired data; Wilcoxon W = 0, rank-biserial correlation 1.00, P < 0.001).

Drug class	Before	After	Discordant pairs[a]	Discordant pairs[b]	Chi-square, df = 1	P
CCB	4 (14.3)	28 (100)	24	0	22.04	<0.001
Long-acting nitrate or molsidomine	4 (14.3)	21 (75.0)	17	0	15.06	<0.001
Beta-blocker	8 (29.6)	0 (0)	0	8	6.12	0.008
Antiplatelet agent	13 (46.4)	21 (75.0)	8	0	–	–
Statin	16 (57.1)	23 (82.1)	8	1	–	–

TABLE 2: Medical treatment before and after a positive first provocation test, n = 28.

Values are n (%). P values are from the exact McNemar test for paired binary data; the McNemar chi-square with one degree of freedom is given as the test statistic. a is the number of patients gaining the drug and b the number losing it; only these discordant pairs contribute to the test. Antiplatelet and statin prescription were not prespecified endpoints and are reported descriptively, without significance testing. Beta-blocker data are for the 27 patients with documented discharge status; discharge beta-blocker status was missing in one patient who was not on a beta-blocker at baseline, and all eight patients receiving a beta-blocker before the test had it withdrawn.

CCB: calcium channel blockers.

Beta-blocker prescription behaved differently in the two groups. After a positive test, all eight patients receiving a beta-blocker before testing had it withdrawn, and none of the 27 patients with documented discharge beta-blocker status was receiving one (McNemar chi-square 6.12, df = 1; P = 0.008). After a negative test, beta-blocker prescription was unchanged overall (37 before, 37 after), 10 patients having the drug withdrawn and 10 others having it introduced (McNemar chi-square 0.05, df = 1; P = 1.00), indicating no directional change attributable to the test result.

Antiplatelet and statin prescriptions, reported separately, increased after positive tests (from 13 to 21 and from 16 to 23, respectively) but changed little after negative tests (from 51 to 50 and from 54 to 57), consistent with these changes following the angiographic findings rather than the provocation result.

De-escalation after a negative test occurred in a substantial minority of cases: the median number of antianginal drugs decreased from 1 (0-1) to 0 (0-1) (Wilcoxon W = 280, rank-biserial correlation 0.48, P = 0.003), with a reduction in 32 of 111 tests (28.8%) and a CCB withdrawn after 25. By contrast, an alternative diagnosis was retained after 75 of 111 negative tests (67.6%); the diagnoses retained, and the reasons for the absence of redirection in the remaining 36, are detailed in Table *3*.

Category	n (%)
Diagnostic redirection	75 (67.6)
Stable coronary artery disease	17 (15.3)
Other cardiac diagnosis	33 (29.7)
Non-cardiac cause	22 (19.8)
Microvascular angina	3 (2.7)
No redirection	36 (32.4)
Cause undetermined	24 (21.6)
Previously suspected non-cardiac cause confirmed	12 (10.8)

TABLE 3: Diagnoses retained after a negative provocation test, n = 111.

Values are n (%) of the 111 negative first tests. Subcategories are mutually exclusive within each heading. No statistical testing was performed on this descriptive breakdown.

Exploratory reassessment cohort

Ten patients underwent 13 further tests, all having been positive at their first test. Spasm remained inducible in 9 (69.2%) and was no longer inducible in four patients (30.8%). Among tests that remained positive, the usual chest pain was reproduced in five of nine compared with 28 of 28 first positive tests, and electrocardiographic changes were present in two of nine compared with 17 of 28. These descriptive comparisons involve partly the same patients, are not independent, and no formal statistical testing was performed; they are hypothesis-generating.

Follow-up

Follow-up was available for all 28 patients with a positive first test (median 6.0 (3.0-11.2) months). Recurrent angina occurred in eight (28.6%) and rehospitalisation in nine patients (32.1%), with no major adverse cardiac event.

Discussion

In this consecutive series, intravenous methylergometrine provocation identified operator-defined positivity in one fifth of patients at a first test, half of these tests being COVADIS-definite. Current smoking was the only baseline characteristic associated with positivity, though this did not survive correction for multiple testing. Transient events occurred during a quarter of positive tests but all resolved with intracoronary nitrate alone. Vasodilator therapy was initiated or intensified in every positive-test patient, whereas a negative test more often redirected the diagnosis than led to de-escalation.

Our operator-defined positivity rate of 20.1% lies below published figures, series using intracoronary acetylcholine generally reporting rates of 30% to 50% in comparable populations [4,13]. Two features of our protocol probably contribute: First, the intravenous route is considered less sensitive than the intracoronary route, and intracoronary acetylcholine is the reference agent in recent consensus documents [1,4,5]. Localised or low-intensity spasm may have gone undetected. This difference has been quantified in a French series of 427 patients comparing the two routes of ergonovine injection, in which the positivity rate was 24% by the intracoronary route versus 9% by the intravenous route after propensity score matching, a threefold difference [7]. Our strict COVADIS-defined estimate of 10.1% is remarkably close to their intravenous figure, suggesting reproducibility of this route's performance across independent French centres. Our figure should be read as the performance of a given protocol in a referred population rather than as the prevalence of vasospasm among patients investigated for chest pain.

Second, and conversely, only half of the operator-defined positive tests fulfilled all three COVADIS criteria, the electrocardiographic component being the one most often absent despite systematic pre- and post-provocation 12-lead electrocardiogram recording. Because the electrocardiogram was not recorded continuously, transient electrical changes occurring between the two recordings cannot be excluded, and this absence may reflect either genuine electrical silence or a change missed between recordings. The study therefore provides two complementary estimates, 20.1% operator-defined and 10.1% strictly COVADIS-defined, neither of which should be read as the true prevalence of vasospastic angina in this referred population: the intravenous route may miss genuine spasm, while some operator-defined responses, resting on a visual rather than quantitative angiographic estimate, may not correspond to true vasospastic angina.

Prospective application of the full COVADIS definition with quantitative coronary analysis would be required to resolve the question.

Smoking was the only characteristic associated with a positive test, with a threefold increase in odds, consistent with its recognised role as the principal modifiable risk factor for vasospastic angina [14], though the association did not persist after correction for multiple comparisons and is presented as exploratory. The ascertainment method is worth emphasising: smoking status was missing from the registry for 41% of tests and was retrieved individually from the records; had these missing values been treated as the absence of smoking, the estimate would have differed materially, illustrating a general hazard of registry-based work. The absence of an association with age, sex, indication or conventional risk factors underlines that clinical profile does not obviate testing, though with only 28 positive tests, only large differences could have been detected.

Few studies have quantified, in paired analysis, the treatment change that follows provocation testing. Vasodilator therapy was initiated or intensified in every patient with a positive test and in fewer than one in 10 of those with a negative test, and the median number of antianginal drugs rose from none to two.

Part of this change is expected, since calcium channel blockade is first-line treatment for vasospastic angina; what the paired analysis adds is its magnitude and completeness, and the contrasting behaviour of beta-blockers, a class that may aggravate spasm through unopposed alpha-adrenergic vasoconstriction: withdrawal was systematic after a positive test, whereas after a negative test withdrawals and introductions were exactly balanced, suggesting decisions unrelated to the test result. Restricting the endpoint to vasodilators was deliberate: antiplatelet and statin prescription changed appreciably only after positive tests, in a population where a third had visible atherosclerosis, plausibly following the angiogram rather than the provocation result.

It must be emphasised that these data document what clinicians did with the result, not whether patients benefited. There was no control group, no structured symptom assessment before and after the test, and no comparable follow-up in patients with a negative test. Whether provocation-guided management improves symptoms or outcome, as stratified functional testing has been shown to do in microvascular and vasospastic angina [8], cannot be addressed by this study.

Against our initial expectation, a negative test more often led to diagnostic redirection than to de-escalation: an alternative diagnosis was retained in two thirds of cases, whereas antianginal drugs were reduced in 32 of 111 tests (28.8%) and a CCB was withdrawn in 25. Its clinical value thus appears to lie primarily in closing a hypothesis and reorienting management, although de-escalation, while a minority outcome, was not negligible. That the cause of symptoms remained undetermined after one fifth of negative tests is a reminder of the limits of an assessment that did not include evaluation of the coronary microcirculation: only three patients received a diagnosis of microvascular angina, a figure likely underestimated in the absence of systematic measurement of microvascular function [5].

Transient events occurred during a quarter of positive tests. All three ventricular arrhythmias were non-sustained and self-terminating, with no sustained ventricular tachycardia, ventricular fibrillation, cardioversion, atropine, or vasopressor use. These are expected manifestations of provoked spasm in a monitored environment and should be read as such rather than as a rate of major complications; a large pooled analysis of intracoronary acetylcholine testing, using a different provocation agent, similarly reported major complications in only 0.5% of procedures, with no deaths [6,15]. Our events remain clinically significant, however, and our design permits no safety estimate for the cohort as a whole, since procedure reports were retrievable for only a subset of negative tests.

One observation is relevant to registry users. None of the events identified had been declared in the regional registry, which reported no complication for any of the 152 procedures: administrative registries capture established complications, not transient intra-procedural events, and safety data from such sources warrant caution.

Repeat testing under antispastic treatment is seldom reported. In this selected reassessment cohort, spasm remained inducible during 9 of 13 repeat tests performed under antispastic therapy. This observation is hypothesis-generating only: the cohort is small, the patients also contribute to the primary analysis, and no independent comparison group was available. Prospective evaluation would be required before it could inform clinical decisions. Whether repeat testing should influence non-pharmacological decisions cannot be addressed by a series of this size and would require dedicated, adequately powered studies.

This retrospective single-centre study included 28 positive first tests, precluding multivariable analysis and permitting detection of only large differences. Test positivity was operator-determined without independent adjudication, resting on a visual estimate of subocclusive narrowing rather than quantitative analysis; only half of the positive tests fulfilled all three COVADIS criteria. Selection for testing followed operator discretion without formal written criteria, limiting extrapolation of the positivity rate elsewhere. The intravenous route is less sensitive than intracoronary acetylcholine, so our positivity rate is not comparable

with contemporary reference series, and procedural events were ascertained for all positive but only 40 negative tests, precluding a complete safety estimate.

Treatment and diagnostic data were available for the entire primary cohort, but procedural events could be ascertained from procedure reports for only 40 of 111 negative tests, so the comparison of procedural safety between groups remains exploratory. Follow-up was available only for patients with a positive test, as our centre acts as a referral centre and patients with a negative test return to their referring cardiologist; this missingness depends on the test result itself, so no prognostic comparison between groups was performed, and a median follow-up of six months is too short to assess events occurring over years. Finally, characteristics other than smoking are derived from the registry, where an explicit absence cannot be distinguished from an uncompleted item.

Conclusions

Intravenous methylergometrine provocation identified operator-defined positivity in one fifth of patients undergoing a first diagnostic test, half of these tests being COVADIS-definite. Vasodilator therapy was initiated or intensified in every patient with a positive test, all of whom were discharged on a CCB, and no beta-blocker was prescribed among those with documented discharge status. A negative test more often redirected the diagnosis than led to treatment de-escalation. Transient clinically significant events occurred during a quarter of positive tests and resolved without electrical cardioversion, atropine, or vasopressor support. These findings describe what clinicians did with the result rather than whether patients benefited, and the exploratory observation that spasm remained inducible during some repeat tests under treatment requires prospective confirmation.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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