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Coronary spasm and vasomotor dysfunction as a cause of MINOCA

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ABSTRACT

Increasing evidence has shown that coronary spasm and vasomotor dysfunction may be the underlying cause in more than half of myocardial infarctions with non-obstructive coronary arteries (MINOCA) as well as an important cause of chronic chest pain in the outpatient setting. We review the contemporary understanding of coronary spasm and related vasomotor dysfunction of the coronary arteries, the pathophysiology and prognosis, and current and emerging approaches to diagnosis and evidence-based treatment.

Coronary spasm (CS) is defined as diffuse or focal severe vasoconstriction of the coronary arteries resulting in impaired myocardial perfusion[1]. It was first described in 1959 by Prinzmetal as anginal pain associated with transient ST-segment elevations or depressions on an electrocardiogram (ECG)[2,3]. CS was historically thought to be a condition predominantly affecting middle-aged males in East Asia and was rare in European and North American populations; more recent data suggest that it may be a common cause of myocardial infarction with non-obstructive coronary arteries (MINOCA) in European and North American patients[4], with a more equal sex distribution[5]. Microvascular spasm has been recognised in the last 20 years and is more poorly characterised. CS, both epicardial and microvascular, remains an important and likely underdiagnosed cause of chronic chest pain in the outpatient setting. We describe advances in our understanding and the definition of CS, techniques for diagnosis, epidemiology and the natural history of the condition, and therapeutic modalities.

Coronary spasm and vasomotor dysfunction

Initially, CS was considered a disease of the epicardial coronary arteries, but, as understanding increased, spasm of the arterioles within the microcirculation was also identified. CS is best considered as part of a spectrum of vasomotor disorders affecting the coronary arteries and may coexist with coronary microvascular dysfunction (CMD). Patients with vasomotor disorders have dysregulation of vasoconstriction and vasodilatation of the coronary vasculature, leading to episodic ischaemia and chest pain. Patients may present with MINOCA or sudden cardiac death[1] or, more commonly, with chronic chest pain – either angina with non-obstructive coronary arteries (ANOCA) or ischaemia with non-obstructive coronary arteries (INOCA).

KEYWORDS: adjunctive pharmacotherapy, miscellaneous, optical coherence tomography, out-of-hospital cardiac arrest

Pathophysiology

The coronary arteries are dynamic regulators of coronary flow; they constrict and dilate to regulate myocardial perfusion and match supply to demand. Vasodilation occurs due to an increase in endothelium-derived relaxing factors including nitric oxide (NO) and relaxation of the vascular smooth muscle cells (VSMCs). The principal abnormality in CS is hyperreactivity of the VSMCs within the media, with increased sensitivity to intracellular calcium concentrations that results in an increased propensity towards hypercontraction[6]. The endothelium and the perivascular adipose tissue (PVAT) within the adventitia[6] both secrete signalling factors that modulate vasoconstriction and vasodilation **(Figure 1)**. In epicardial coronary arteries, *in vitro* studies have shown induction of spasm regardless of whether the endothelium was intact or removed, suggesting that hypercontraction of the VSMCs is the major abnormality[7].

The final pathway for CS is Rho-kinase (RoK) inhibition of myosin light chain phosphatase, resulting in inhibited myosin dephosphorylation and prolonged actin-myosin coupling[6]. RoK activity is increased in patients with CS, especially in those with active anginal symptoms[8]. Inflammation of the PVAT may lead to upregulation of RoK activity and VSMC hyperreactivity[6]. The association between PVAT inflammation and CS may explain why CS is more prevalent in smokers since nicotine is associated with chronic low-grade inflammation.

Microvascular spasm was described in 2002 in a cohort of patients with known epicardial CS. Patients with ischaemic ECG changes, chest pain and increased coronary sinus lactate in response to lower doses of acetylcholine (ACh) in the absence of severe epicardial spasm were considered to have microvascular spasm, and this occurred in 25% of patients in this cohort with known epicardial CS[9]. Uncertainty exists regarding the overlap of microvascular CS and endothelium-dependent CMD. Both are diagnosed via chest pain, ECG changes and ischaemia in response to ACh[10]. However, microvascular spasm is considered an abnormality of the microvascular VSMC, while endothelium-dependent CMD results from an imbalance in endothelium-derived vasoconstricting and vasodilating agents. In a normal heart, low-dose ACh causes microvascular vasodilation and a >50% increase in coronary blood flow (CBF) due to an increase in endothelium-derived vasodilating factors. At higher doses, patients susceptible to CS will manifest VSMC-mediated coronary vasoconstriction. However, VSMC-mediated vasoconstriction may also occur at lower doses of ACh in some patients with epicardial CS.

Therefore, it is not possible to reliably distinguish isolated microvascular spasm from endothelium-dependent CMD *in vivo* **(Figure 2)**.

The guidelines also reflect this uncertainty. The European Association of Percutaneous Cardiovascular Interventions guidelines label patients with chest pain/ECG changes but no significant epicardial vasospasm in response to ACh as experiencing microvascular spasm, whereas the American College of Cardiology guidelines label this event endothelium-dependent CMD[11]. Ischaemia due to endothelium-dependent CMD is associated with increased circulating endothelium-derived vasoconstricting agents and decreased cyclic guanosine monophosphate[12], and CBF improves with L-arginine, a signalling pathway mediated by the endothelium[10] **(Figure 1)**. Therefore, endothelium-dependent CMD and microvascular CS are not different names for the same condition. Doppler CBF measurements demonstrate that approximately 30% of patients have a decrease in CBF with ACh, while the remainder have an increase[13]. We consider patients with a decrease in CBF to have microvascular spasm, since CBF will decrease if the microcirculatory resistance arterioles vasoconstrict, while a CBF increase of 0-49% is diagnosed as endothelium-dependent CMD.

Patients may have both epicardial and microvascular CS. Diagnosis is via ACh rechallenge. If epicardial spasm is provoked with ACh, nitroglycerine (e.g., 200 µg) is given to reverse epicardial vasoconstriction. ACh is then redosed at 100-200 µg, and if symptoms/ECG changes reoccur, the patient has coexisting microvascular spasm. Microvascular spasm is less responsive to nitroglycerine, as there is diminished biotransformation of nitroglycerine in vessels <100 µg in diameter[14].

Epidemiology and prevalence of CS

The estimated prevalence of CS varies widely, between 4-49% in large case series[4,15-17] **(Table 1)**, likely reflecting differences in patient selection (particularly ethnicity and presence/absence of CAD), inconsistent inclusion of microvascular CS, and differing provocation agents and diagnostic criteria for CS. The true incidence in INOCA and MINOCA patients remains unknown, since provocation testing is not routinely performed and prior studies have been in highly selected patient populations. Additionally, most studies of MINOCA did not involve routine provocation testing, which likely contributed to the underestimation of the true prevalence of CS. Women are less likely to

Abbreviations

|					
ACh	acetylcholine	**COVADIS**	Coronary Vasomotor Disorders International Study Group	**MB**	myocardial bridging
ANOCA	angina with non-obstructive coronary arteries			**MINOCA**	myocardial infarction with non-obstructive coronary arteries
		CS	coronary spasm		
CAD	coronary artery disease	**DHP**	dihydropyridine	**NO**	nitric oxide
CBF	coronary blood flow	**ECG**	electrocardiogram	**PVAT**	perivascular adipose tissue
CCBs	calcium channel blockers	**ER**	ergonovine	**RAS**	renin-angiotensin system
CFR	coronary flow reserve	**ICD**	implantable cardioverter defibrillator	**RoK**	Rho-kinase
CMD	coronary microvascular dysfunction	**INOCA**	ischaemia with non-obstructive coronary arteries	**SCD**	sudden cardiac death
				VSMC	vascular smooth muscle cell
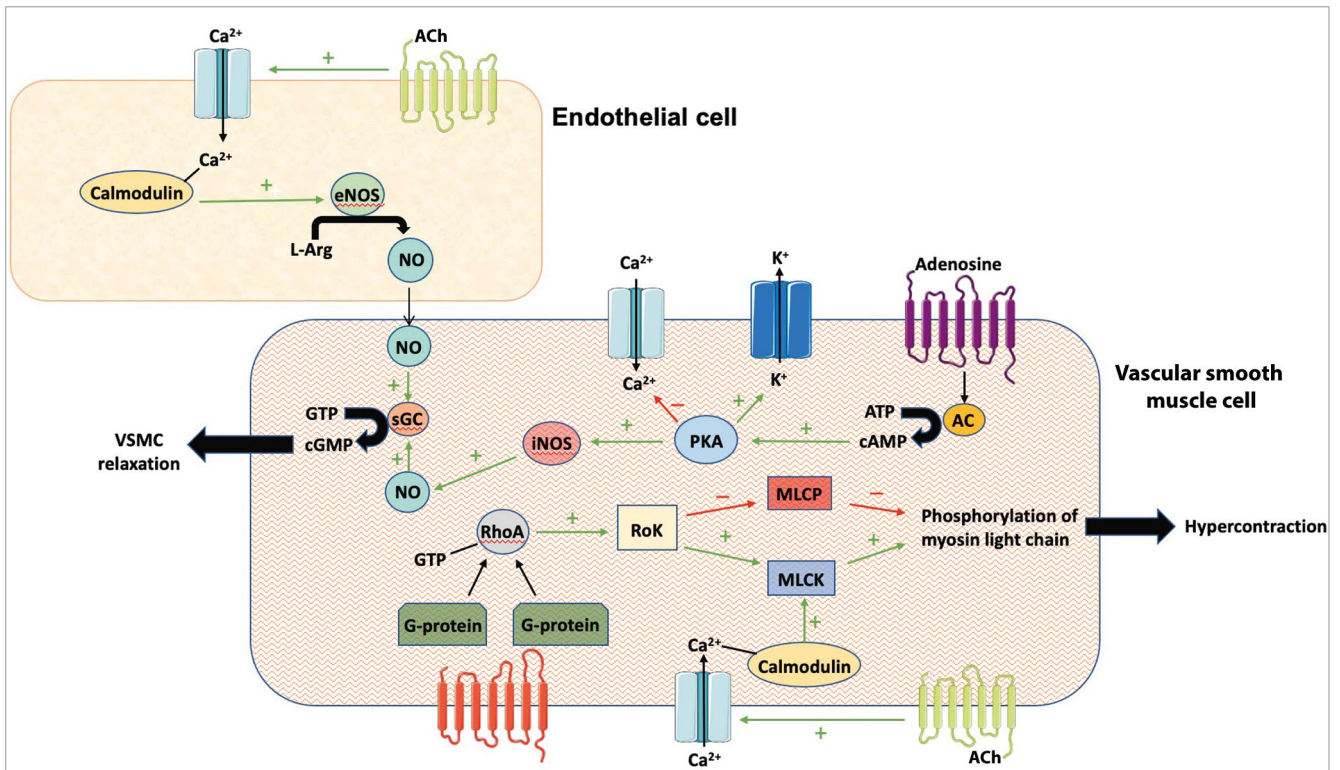
Figure 1. *Cellular interplay between endothelial- and VSMC-mediated signalling pathways that promote relaxation and contraction. AC: adenylyl cyclase; ACh: acetylcholine; ATP: adenosine triphosphate; CA²⁺: calcium; cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; eNOS: endothelial nitric oxide synthase; GTP: guanosine triphosphate; iNOS: inducible nitric oxide synthase; L-Arg: L-arginine; K⁺: potassium; MLCK: myosin light chain kinase; MLCP: myosin light chain phosphate; NO: nitric oxide; PKA: protein kinase A; RhoA: Ras homolog family member A; RoK: Rho-kinase; sGC: soluble guanylate cyclase; VSMC: vascular smooth muscle cell*

have typical angina or undergo angiography, and underdiagnosis may be more common in women[18]. CS frequently coexists with CAD, and early studies of "variant angina" were in patients with severe epicardial fixed stenoses with superimposed CS causing ST-elevation[19-23]. As understanding

improved, patients with the same clinical presentation but mild/no underlying epicardial CAD were identified[24-28].

Several small series in patients with MINOCA estimate CS prevalence to be between 16% and 71%[4,16,17,29,30] **(Table 1)**. In series which included both microvascular and epicardial CS,
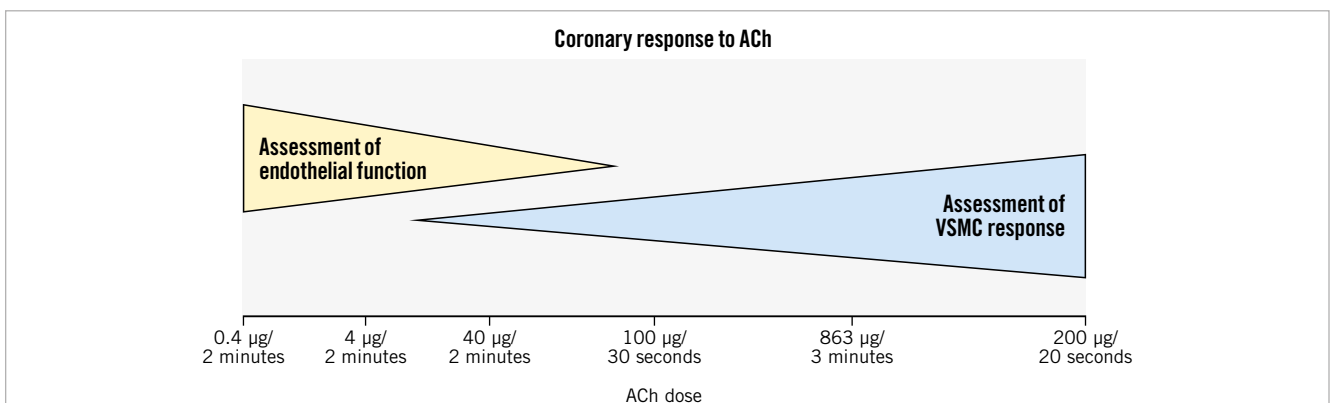

Figure 2. *Acetylcholine (ACh) allows diagnosis of endothelium-dependent CMD and CS. Endothelial function is assessed at lower doses of ACh, while patients with CS have VSMC-mediated vasoconstriction at higher doses of ACh. The overlap between the two doses makes it difficult to reliably differentiate endothelium-dependent CMD from isolated microvascular spasm. The x-axis includes common dosing patterns used in different protocols worldwide. CMD: coronary microvascular dysfunction; CS: coronary spasm; VSMC: vascular smooth muscle cell*

EuroIntervention 2024;20:e123-e134 • Zachary S. Yaker et al.

e125

Table 1. Provocative studies of CS, divided by severity of coronary artery disease.

Study	Population	ACh dose	ER dose	Diagnostic criteria	Results: % positive spasm test	Complications
MINOCA						
Kanazawa et al, 1997[29] Japan	20 patients (age 57±10 years, 70% male) with rest angina; 50% had ST-elevation with chest pain; 60% had no CAD, and the remainder had <75% CAD	50 µg then 100 µg	40 µg	Not defined	100%	None
Da Costa et al, 2001[17] France	91 patients (age 50±13 years, 63% male) with MINOCA		40 µg	Narrowing >70%	16%	None
Ong et al, 2008[16] Germany	488 patients (age 66±12 years, 65% male) with ACS. 86/116 with no culprit lesion/ alternative diagnosis given ACh	20-100 µg LCA 80 µg RCA if no spasm in LCA		Narrowing >75% with reproduction of symptoms. If symptoms and ECG changes but no epicardial spasm, diagnosis of microvascular CS.	49% of patients given ACh	None
Montone et al, 2018[4] Italy	80 consecutive patients (age 63±11 years, 50% male) with MINOCA, no coronary thrombus/unstable plaque	20-200 µg LCA 20-50 µg RCA	8-64 µg LCA 8-40 µg RCA	Narrowing >90% with symptoms and ischaemic ECG changes. If symptoms and ECG changes but no epicardial spasm, diagnosis of microvascular CS.	46%: of these, 65% epicardial spasm, 35% microvascular spasm	2 transient bradyarrhythmias
INOCA						
Suzuki et al, 1992[30] Japan	26 patients (age 54±10, 91% male), 11 with typical vasospastic angina (1 had >50% atheroma) and 15 with chest pain (8 had >50% atheroma)	25-100 µg	1-30 µg	Narrowing >99% with angina and ischaemic ECG changes	ACh: 82%, ER: 100% in vasospastic angina group None in CP group	None
Harding et al, 1993[15] North America	3,447 patients (median age 51, IQR 43-56, 55% male) with <50% CAD and with stable (32%), progressive (55%) and unstable (12%) angina		50-150 µg IV	Narrowing >75%	4%	11 patients (0.03%): MI in 4, VT/VF in 7
Wang et al, 2002[32] Taiwan	93 patients (age 57±14, 59% male) with suspected ischaemia and CAD <50%		1-30 µg	Narrowing >90% with chest pain and ischaemic ST-elevation changes	71% in MINOCA (23 patients) 30% in INOCA (70 patients)	None
Sueda et al, 2003[31] Japan	193 patients (age 62±10 years, 62% male) with <50% CAD	20-100 µg LCA 20-80 µg RCA	16-64 µg LCA 10-40 µg RCA	Narrowing >99%	ACh: 33% ER: 32%	None
Predominantly obstructive CAD						
Bertrand et al, 1982[19] France	1,089 patients undergoing coronary angiography Group A: 248 with atypical chest pain Group B1: 117 with exertional angina Group B2: 138 with exertional and rest angina Group C: 203 with rest angina; 78/203 had ST- elevation during angina Group D1: 116 with transmural MI <6 weeks before Group D2: 65 with transmural MI >6 weeks before Group E: 154 with valvular heart disease Group F: 49 with cardiomyopathy Excluded severe left main/3-vessel disease		400 µg IV	Narrowing >75%	Group A: 1.2% spasm; 89% had normal/ near-normal angiograms Group B1: 4% spasm; 20% mild CAD Group B2: 14% spasm; 42% mild CAD Group C: 38% spasm; 46% mild CAD Group D1: 20% spasm; 7% minimal CAD Group D2: 6% spasm; 5% mild CAD Group E: 2% spasm; 86% mild CAD Group F: 0% spasm; 100% normal angiograms	0.6% (4 VF, 1 VT, 1 transient CHB)
Mark et al, 1984[20] North America	109 patients with variant angina with transient ST-segment elevation (spontaneous or after ER)		300 µg IV	Narrowing >75%	9/12 (75%)	None
Yasue et al, 1986[21] Japan	28 patients (83% male) with chest pain plus ST-elevation; 72% had >50% CAD	10-80 µg LCA 10-50 µg RCA		Narrowing >25%	93%	Transient bradyarrhythmias with injection of ACh into RCA

Table 1. Provocative studies of CS, divided by severity of coronary artery disease (cont'd).

Study	Population	ACh dose	ER dose	Diagnostic criteria	Results: % positive spasm test	Complications
Nosaka et al, 1987[23] Japan	3,000 consecutive patients Group I: 1,145 with angina (653 at rest) Group II: 398 with MI Group III: 648 with atypical chest pain Group IV: 809 with non-ischaemic heart disease			Total or subtotal occlusion	Group I: 22% Group II: 23% Group III: 1.2% Group IV: 3.7% Majority of group I/II had obstructive CAD	None
Sueda et al, 1999[22] Japan	685 patients (age 63±8 years, 70% male)	20-100 µg LCA 20-80 µg RCA		Narrowing >99% with chest pain and/or ECG changes	32%	0.3% haemodynamic instability with ACh
Mixed CAD/INOCA						
Cipriano et al, 1979[29]	90 patients (mean age 48 years, 52% male): 18 with typical angina, 56 atypical chest pain, 9 variant angina, 7 heart transplant		0.05-0.25 mg	Narrowing >85%	12%	None
Okumura et al, 1988[24]	Group 1: 70 patients (mean age 57 years, 85% male) with chest pain plus ST-elevation Group 2: 93 patients (mean age 54 years, 69% male) with atypical chest pain	20-100 µg LCA 20-50 µg RCA	200 µg IV	100% occlusion or severe vasoconstriction plus chest pain and/or ECG changes	Group 1: 90%, 36% with significant CAD Group 2: 1%, 12% with significant CAD	Transient bradycardia with ACh into RCA
Sueda et al, 2000[25] Japan	40 patients with rest angina and ischaemia on ECG 24 patients with atypical chest pain Trial of triple provocation testing: ACh, ER, then ACh + ER	20-100 µg LCA 20-80 µg RCA	16-64 µg LCA 10-40 µg RCA	Narrowing >99% plus chest pain and/or ECG changes	Rest angina: ACh, 55%; ER, 33%; ACh+ER, 92% Atypical chest pain: ACh, 0%; ER, 0%; ACh+ER, 8%	None
Sueda et al, 2004[26] Japan	1,508 patients undergoing first coronary angiography	20-100 µg LCA 20-80 µg RCA	16-64 µg LCA 10-40 µg RCA	Narrowing >99%	ACh: 36% ER: 30%	1% VT, 0.3% severe hypotension, 0.1% cardiac tamponade 1 prolonged spasm >15 min with ER testing 138 (16%) transient AF with ACh
Komatsu et al, 2016[27]	47 patients (age 43±13 years, 94% male) who survived OOHA with no organic heart disease. Normal LV function	20-100 µg LCA 20-50 µg RCA		Narrowing >90% plus chest pain or ECG changes	CS alone: 15% CS+OOHA: 51%	PAF 10% Transient bradyarrhythmia 16% VA 3%

ACh: acetylcholine; ACS: acute coronary syndrome; AF: atrial fibrillation; CAD: coronary artery disease; CHB: complete heart block; CS: coronary spasm; ECG: electrocardiogram; ER: ergonovine; INOCA: ischaemia with non-obstructive coronary arteries; IQR: interquartile range; IV: intravenous; LCA: left coronary artery; LV: left ventricular; MI: myocardial infarction; MINOCA: myocardial infarction with non-obstructive coronary arteries; OOHA: out-of-hospital cardiac arrest; PAF: paroxysmal atrial fibrillation; RCA: right coronary artery; VA: ventricular arrhythmia; VF: ventricular fibrillation; VT: ventricular tachycardia

50-70% of spasm was epicardial, and the remaining spasm was microvascular, defined as ECG changes/chest pain in response to ACh in the absence of epicardial vasospasm – a definition which likely also captured patients with endothelium-dependent CMD. Estimates for CS prevalence in patients with ANOCA **(Table 1)** appear markedly higher in Asian populations, particularly in Japan[15,31,32]. A small comparative study demonstrated higher rates of impaired vasoreactivity in Japanese compared to European patients with CAD (80% vs 37%) 7-10 days after MI[33]; however, no studies have elucidated whether this relates to genetic or environmental factors. Epicardial CS appears to be more common in men and microvascular CS in women[34], with the overall prevalence of CS in patients with MINOCA being similar between sexes[4].

CS commonly coexists with myocardial bridging (MB). In one study, 60% of patients with MB, defined as >30% phasic compression on angiography, had significant CS (>70% vasoconstriction) within the bridged segment during ACh infusion **(Figure 3)**[35]. Patients with MB and CS were more likely to
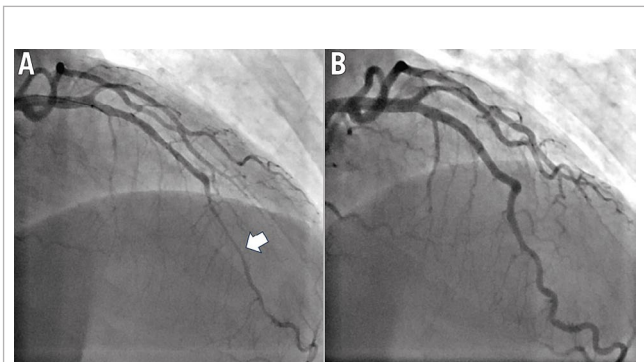

Figure 3. *Coronary angiography of the bridged segment of the LAD. A) Coronary spasm is observed during ACh infusion. B) Resolution of spasm following nitroglycerine administration. ACh: acetylcholine; LAD: left anterior descending artery*

EuroIntervention 2024;20:e123-e134 • Zachary S. Yaker et al.

e127

have recurrent angina and hospitalisation for chest pain compared to patients with MB without CS[35]. Atherosclerosis is more likely to form proximal to a myocardial bridge due to non-laminar flow in this area, while the increased mechanical and shear stress secondary to compression within the bridge are thought to lead to endothelial dysfunction and increased susceptibility to CS[36].

Invasive provocation testing

The gold standard for diagnosis is invasive provocative testing using ACh or, less commonly, ergonovine (ER) during cardiac catheterisation with continuous monitoring of symptoms and ECG **(Figure 4, Figure 5)**. ACh is short-acting and, therefore, needs to be administered as an intracoronary bolus or infusion. The administration of ER can be intracoronary or intravenous. Calcium channel blockers (CCBs) and long-acting nitrates are usually held for 48 hours and short-acting nitrates for 6 hours prior to testing.

Diagnostic criteria and provocation testing protocols vary between institutions. The Coronary Vasomotor Disorders International Study Group (COVADIS) group proposed a standardised definition to address these limitations: 1) a spontaneous episode of angina that is nitrate responsive and has at least one of the following characteristics: occurs at rest (especially between late night and early morning), marked reduction in exercise tolerance in the morning, precipitated by hyperventilation, or suppressed by CCBs; 2) transient ischaemic ECG changes in at least two contiguous leads; and 3) transient coronary stenosis of >90% with associated angina or ischaemic ECG changes, either spontaneously or in response to a provocative stimulus[2]. The definition of microvascular spasm often follows the COVADIS criteria of chest pain and ECG changes during provocation testing but, in the absence of severe epicardial vasoconstriction[37], with the caveats of overlap with endothelial-dependent CMD as detailed above.

The COVADIS definition has high specificity. However, a major limitation in the diagnosis of CS has been the large variation in practice for provocation testing, particularly with respect to the dose and rate of administration of the provocation agent[38]. Using only lower-dose ACh (e.g., 50 μg over 3 minutes), the >90% threshold for vasospasm will underdiagnose epicardial CS, while only using higher doses may underdiagnose endothelium-dependent CMD **(Figure 2)**. This emphasises the importance of a standardised diagnostic protocol that includes doses and rate of administration. With regard to the percentage of vasospasm considered diagnostic, studies in MINOCA patients used >70-75% vasoconstriction[5,16] to define coronary spasm, and it is our experience that chest pain and ischaemic ECG changes can be seen at this threshold.

ACh acts on the muscarinic receptors of endothelial cells and VSMCs. In a healthy artery, ACh will stimulate endothelial-derived NO release, resulting in mild vasodilation of the epicardial artery[39]. In patients with endothelial dysfunction, there is inadequate endothelial release of NO, and ACh injection results in VSMC contraction and epicardial vasoconstriction[39] **(Figure 1)**. ACh may be administered via an intracoronary infusion catheter or bolus injections. A common protocol is at 10-20 μg, 50 μg then 100 μg in the left coronary artery over 30 seconds[4,15-17,19-32]. ER is an alternative, less commonly used provocation agent. ER binds to serotonergic 5HT2 receptors to induce vasoconstriction. Intracoronary ER is administered in 5 to 10 μg increments up to a maximum of 50 μg[4,15-17,19-32]. Some series found ACh to be more sensitive than ER, particularly in men, with spasm provoked in 81% of males versus 54% with ER[40], and it is therefore our preferred agent.
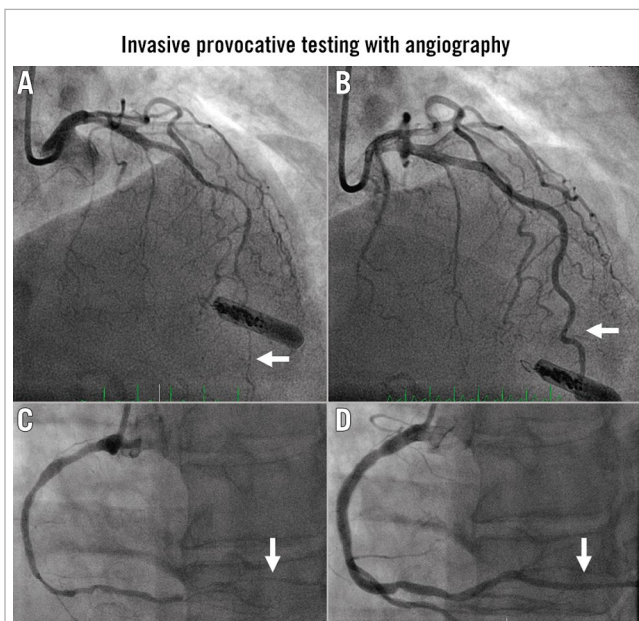

Figure 4. *Angiography of the mid- to distal LAD (white arrows). A) After ACh administration and B) after intracoronary nitroglycerine. C) The RCA with obliteration of the PDA associated with inferior ST-elevation and chest pain. D) The same artery after nitroglycerine.*
ACh: acetylcholine; LAD: left anterior descending artery; PDA: posterior descending artery; RCA: right coronary artery
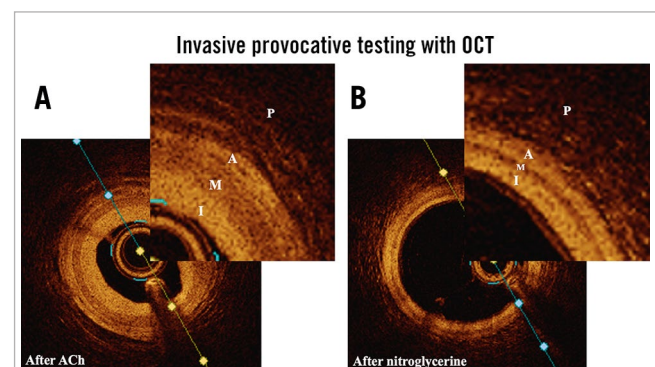

Figure 5. *OCT of the same LAD artery. A) After administration of 50 μg ACh and B) after nitroglycerine. Ninety percent spasm was induced with higher doses of ACh but would not have allowed high-quality OCT acquisition. During CS, the VSMC in the media (M) contract and the media is therefore thicker. A: adventitia; ACh: acetylcholine; CS: coronary spasm; I: intima; LAD: left anterior descending; OCT: optical coherence tomography; P: perivascular adventitial tissue; VSMC: vascular smooth muscle cell*

Invasive assessment of CMD

Invasive testing for CS is usually performed in conjunction with assessment for CMD. ACh is used to diagnose both CS and endothelium-dependent CMD, while the administration of adenosine allows diagnosis of endothelium-independent CMD. The ratio of CBF at rest and CBF with adenosine is the coronary flow reserve (CFR). CFR >2.5 is normal, while CFR <2.0-2.5 is diagnostic of endothelium-independent CMD. CFR and microvascular resistance may be measured invasively using a Doppler or thermodilution wire[41]. Endothelium-independent CMD may also be diagnosed non-invasively using positron emission tomography or magnetic resonance imaging, with measurement of myocardial perfusion at rest and during adenosine administration; the CFR can then be calculated from the ratio of these measurements[42].

Invasive testing is generally safe, with mild adverse reactions in 9% of cases (mostly transient atrial fibrillation)[41] and <0.5% with serious complications **(Table 1)**[39].

Management

In patients with classic symptoms of CS and absence of obstructive CAD, an empirical trial of CCBs can be both diagnostic and therapeutic[43]. Further testing may be indicated if symptoms persist despite medical therapy or if there is diagnostic uncertainty **(Table 2)**.

A management algorithm is shown in **Figure 6**. Smoking cessation is key[44]. The first-line pharmacological treatment is a CCB, which prevents vasoconstriction by inhibiting the flow of calcium into the VSMCs. Overall, 40% of patients will be rendered angina-free with CCBs[45]. Non-dihydropyridine (DHP) CCBs are the preferred first-line agent[43], while a combination of non-DHP and DHP CCBs is recommended for ongoing symptoms. Moderate to high doses are often needed, e.g., verapamil 240-480 mg daily, diltiazem 180-540 mg daily, nifedipine 60-120 mg daily[46]. CCBs may be more effective if taken at night[14].

Short-acting nitrates are first-line agents for acute attacks[47]. Nitrates increase local concentrations of NO, leading to vasodilation[47]. Long-acting nitrates should be avoided if possible, since tolerance may occur; however, they remain a third-line agent[48]. The NO donor and arterial potassium adenosine triphosphate channel agonist nicorandil[47], the RoK inhibitor fasudil[49], and renin-angiotensin system (RAS) inhibitors[50] are all second-line alternatives.

Statins decrease symptoms when used in combination with CCBs, likely by improving endothelial function[51], and are recommended in patients with CS and hyperlipidaemia (low-density lipoprotein >100 mg/dl). L-arginine, a precursor to NO, is effective in patients with reduced endothelial NO-synthase activity[45].

Treatment of MB with coexisting CS may be challenging. CCBs reduce myocardial contractility and decrease hypercontractility. In patients with a haemodynamically significant bridge and symptoms refractory to medical treatment, unroofing surgery is effective at relieving systolic compression and may also improve endothelial function within the bridged segment[52].

The optimal treatment of microvascular spasm remains unclear. CCBs are less effective in CMD than epicardial CS[53].

In patients with ECG changes/chest pain with ACh, in the absence of epicardial spasm (likely a combination of microvascular spasm and endothelium-dependent CMD), 30% had persistent chest pain despite treatment with CCBs and

Table 2. COVADIS indications for invasive provocation testing[2].

Class I – strong indications	
	History suspicious for CS, including: rest angina relieved by nitrates, diurnal variation in symptoms, angina at rest without obstructive CAD, symptoms unresponsive to empirical CS therapy
	ACS presentation with no culprit lesion
	Unexplained cardiac arrest
	Unexplained syncope with antecedent chest pain
	Recurrent angina at rest following successful PCI
Class IIa – good indications	
	Patients diagnosed with CS non-invasively and unresponsive to therapy
	Determine the site and mode of spasm in patients with documented spontaneous CS
Class IIb – controversial indications	
	Patients diagnosed with CS non-invasively and responsive to therapy
Class III – contraindications	
	Emergent ACS
	Severe fixed multivessel CAD
	Severe myocardial dysfunction
	No symptoms suggestive of CS

ACS: acute coronary syndrome; CAD: coronary artery disease; COVADIS: Coronary Vasomotor Disorders International Study Group; CS: coronary spasm; PCI: percutaneous coronary intervention
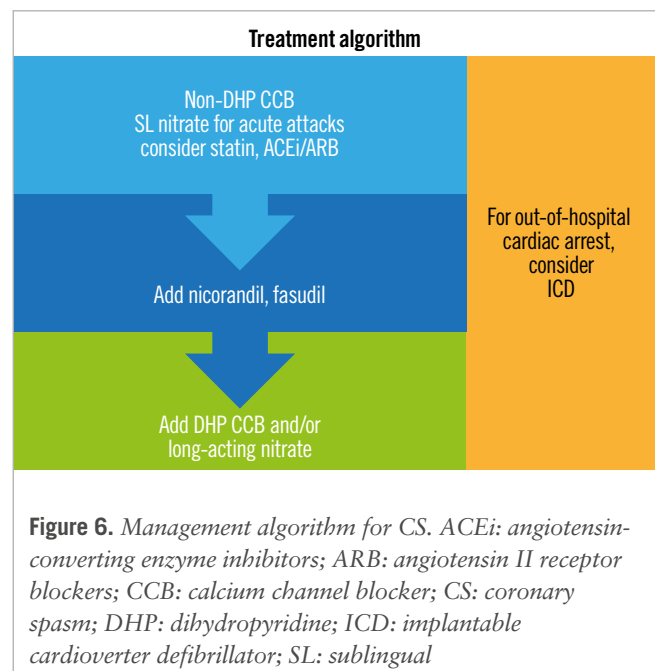

Figure 6. *Management algorithm for CS. ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; CCB: calcium channel blocker; CS: coronary spasm; DHP: dihydropyridine; ICD: implantable cardioverter defibrillator; SL: sublingual*

angiotensin-converting enzyme inhibitors (ACEi)[54]. Nitrates are less effective in relieving microvascular spasm[55], while RAS inhibition may be more effective in microvascular compared to epicardial CS[50]. In general, we follow the same treatment algorithm as for epicardial CS but with earlier consideration of ACEi.

In patients who have had ventricular arrhythmias or cardiac arrest secondary to CS, recurrent arrhythmias may occur, even with maximally tolerated medical therapy[24]. Patients who presented with ventricular arrhythmia/aborted sudden cardiac death (SCD) had a poorer prognosis in one study (12% vs 1% with 4-year cardiac mortality)[56], but similar in

Table 3. Studies reporting prognosis of CS.

Study	n	Population	CAD/LV function	Prognosis
Waters et al, 1983[64] Canada	169	Hospitalised with variant angina	63% with >70% CAD; 24% abnormal LV function	5-year survival: 87% 5-year MI-free survival: 75% 5-year survival with <70% CAD: 98%
Mark et al, 1984[20] USA	109	Variant angina	92% with >75% CAD; 17% EF <40%	5-year survival: 76% 5-year infarct-free survival: 59%
Nakamura et al, 1987[61] Japan	349	Vasospastic angina	20% with no CAD; 47% fixed stenosis <75%, 33% fixed stenosis >75%; no data on LV function	2% SCD 5% MI at 3.4-year follow-up 48 patients with no CAD: 0 SCD, 2 MI, 4 VT/VF
Walling et al, 1987[65] Canada	217	Variant angina	60% with >70% CAD; 23% abnormal LV function	5-year survival: 89% 5-year MI-free survival (total population): 69% 5-year MI-free survival with <70% CAD: 68%
Yasue et al, 1988[62] Japan	245	Hospitalised with variant angina	60% with >75% CAD; 6% abnormal LV function	5-year survival: 97% 5-year MI-free survival: 83% 5-year survival with <75% stenosis: 82%
Da Costa et al, 2001[17] France	91	91 with MINOCA compared to 91 controls with acute MI plus CAD >50%	0% with >50% CAD; mean LVEF 60% (47-73%)	35-month survival: 95% in MINOCA, 92% in MI+CAD.
Wang et al, 2002[32] Taiwan	93	Patients presenting to emergency department with suspected cardiac ischaemia and insignificant CAD	No significant CAD; mean LVEF 69% (60-78%)	Median 25-month follow-up. ER positive group: 97% survival, 95% MACE-free. Troponin I-positive group: 96% survival, 91% MACE-free.
Ong et al, 2011[66] Germany	44	Suspected ACS with no culprit lesion on angiogram	No significant CAD; median LVEF 70% (62-78%)	3-year survival: 99% 3-year coronary event-free survival: 100%
Takagi et al, 2011[57] Japan	1,429	Vasospastic angina	14% with >50% CAD, 2% OOHA	5-year survival: 98% 5-year MACE free survival: 91% (MI, unstable angina, HF, appropriate ICD shock) 5-year MI: 0.6%
Matsue et al, 2012[58] Japan	23	VA plus vasospastic angina	No documented CAD, normal LV function	Median follow-up 2.9 years: 100% survival, 83% free of VF
Cho et al, 2016[67] South Korea	986	Vasospastic angina presenting with (n=149) or without ACS (n=837)	7% with >50% CAD	5-year MI: 4% in the non-ACS group, 10% in the ACS group 5-year all-cause mortality: 2% in non-ACS, 6% in ACS
Ahn et al, 2016[56] South Korea	188	Variant angina with aborted SCD, compared to 1,844 patients with variant angina without aborted SCD	Angiographically normal coronary arteries; no structural heart disease	5-year cardiac death: 11.5% vs 1.3% 5-year rates of VT: 14%
Montone et al, 2018[4] Italy	37	Patients with MINOCA: 24/80 epicardial spasm; 13/80 microvascular spasm	1% obstructive CAD; median LVEF 58% (54-62)	5-year survival: 62% 5-year MI-free survival: 72% 5-year cardiac death-free survival: 78%

Epicardial CAD is expressed as "x% with >y% CAD" e.g., 63% with >70% CAD means 63% of patients had an epicardial stenosis of >70%. ACS: acute coronary syndrome; CAD: coronary artery disease; CS: coronary spasm; EF: ejection fraction; ER: ergonovine; HF: heart failure; ICD: implantable cardioverter defibrillator; LV: left ventricular; LVEF: left ventricular ejection fraction; MACE: major adverse cardiac events; MI: myocardial infarction; MINOCA: myocardial infarction with non-obstructive coronary arteries; OOHA: out-of-hospital cardiac arrest; SCD: sudden cardiac death; VA: ventricular arrhythmia; VF: ventricular fibrillation; VT: ventricular tachycardia

another (3% vs 2%)[57], compared to CS alone. The role of implantable cardioverter defibrillators (ICDs), in addition to medical therapy in CS plus aborted SCD, is still debated but often recommended based on these data[56,58]. ICDs are not recommended in CS without documented ventricular arrhythmias/cardiac arrest.

Percutaneous coronary intervention (PCI) is not generally recommended for CS, as spasm is likely to recur outside of the stented segment[59]. However, in selected patients with focal CS refractory to medical therapy, PCI may be reasonable[59]. Sympathectomy, involving ablation of the T2-T4 sympathetic ganglia, decreased angina in one small study[60]; however, there was no angiographic re-evaluation to assess if vasoconstriction was resolved. Less invasive methods such as spinal cord stimulators may be more appropriate.

Patients should avoid ergot-containing and anticholinesterase agents, cocaine and amphetamines. Serotonin-containing medications should only be used with caution.

Prognosis

Studies reporting prognosis are heavily dependent on the population, particularly in the presence of concomitant CAD **(Table 3, Figure 7)**[4,17,20,32,56-58,61-67]. Prognosis is generally favourable in CS without CAD, acute coronary syndrome or arrhythmia, although recurrent hospitalisation for angina is common. Prognosis was worse with concomitant CAD[4,20,61-67]. Patients with MINOCA tend to have worse prognoses than those with INOCA[4,17,20,32,56-58,61-67], particularly if CS is present (major adverse cardiac events rates 13% vs 5%)[55].

Spontaneous remission may be seen without medical therapy in 30% of cases[68], but long-term CCB maintenance is generally recommended to reduce future risk of arrhythmia or MI **(Central illustration)**.

Clinical challenges and future research directions

Patients who remain chest pain-free with medical therapy generally have excellent long-term outcomes. However, patients
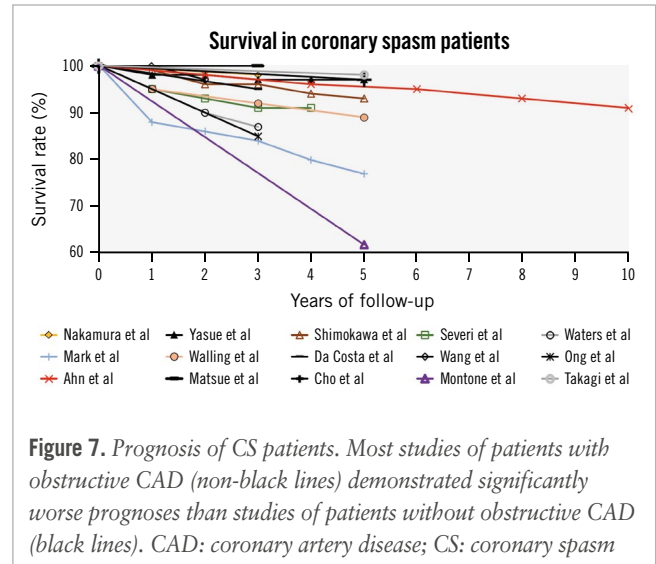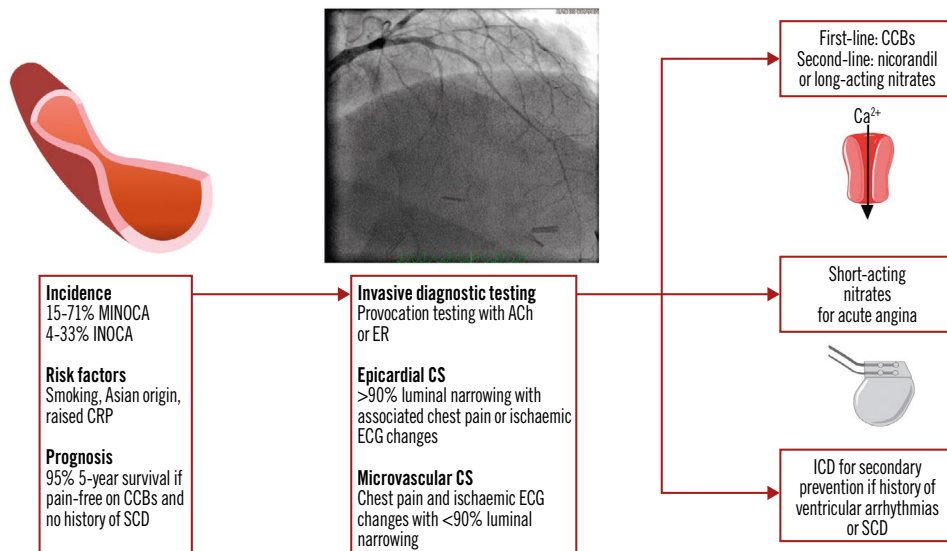
Figure 7. *Prognosis of CS patients. Most studies of patients with obstructive CAD (non-black lines) demonstrated significantly worse prognoses than studies of patients without obstructive CAD (black lines). CAD: coronary artery disease; CS: coronary spasm*

EuroIntervention — Central **Illustration**

Coronary artery spasm.

First-line: CCBs
Second-line: nicorandil or long-acting nitrates

Ca²⁺

Incidence
15-71% MINOCA
4-33% INOCA

Risk factors
Smoking, Asian origin, raised CRP

Prognosis
95% 5-year survival if pain-free on CCBs and no history of SCD

Invasive diagnostic testing
Provocation testing with ACh or ER

Epicardial CS
>90% luminal narrowing with associated chest pain or ischaemic ECG changes

Microvascular CS
Chest pain and ischaemic ECG changes with <90% luminal narrowing

Short-acting nitrates for acute angina

ICD for secondary prevention if history of ventricular arrhythmias or SCD

Zachary S. Yaker *et al.* • *EuroIntervention* 2024;20:e123-e134 • DOI: 10.4244/EIJ-D-23-00448

ACh: acetylcholine; Ca²⁺: calcium; CCB: calcium channel blocker; CRP: C-reactive protein; CS: coronary spasm; ECG: electrocardiogram; ER: ergovine; ICD: implantable cardioverter defibrillator; INOCA: ischaemia with non-obstructive coronary arteries; MINOCA: myocardial infarction with non-obstructive coronary arteries; SCD: sudden cardiac death

with ongoing symptoms remain a therapeutic challenge. Differentiation of microvascular spasm from endothelium-dependent CMD may be helpful. Case studies have reported success with phosphodiesterase-5 inhibitors and guanylate cyclase stimulators[69]. Further work is needed. The pain clinic can help with quality of life, including the consideration of spinal cord stimulators.

Conclusions

CS is an important cause of chest pain and continues to be underdiagnosed. CS is easier to recognise on provocation testing, while microvascular CS is less defined. Recent studies suggest CS and vasomotor abnormalities are a common cause of MINOCA. Patients with CS treated with CCBs who are rendered pain-free typically have an excellent prognosis; however, the management of patients who are still symptomatic despite maximal available medical therapy remains challenging. Improved recognition is key to appropriate referral for provocation testing and timely diagnosis.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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