

# INOCA and MINOCA

## Coronary vasomotor disorders in clinical practice

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Many patients with angina and/or myocardial infarction do not have obstructive coronary artery disease. Clinicians' awareness of ischaemia with no obstructive coronary artery disease (INOCA) and myocardial infarction with no obstructive coronary artery disease (MINOCA) may help such patients who have ongoing chest symptoms after a 'normal' angiogram.

### KEY POINTS

- Angina or myocardial infarction may occur in patients with no obstructive coronary stenosis.
- Ischaemia with non-obstructed coronary arteries (INOCA) can be caused by coronary microvascular dysfunction and/or coronary vasospasm.
- The differential diagnoses for myocardial infarction with non-obstructed coronary arteries (MINOCA) include coronary plaque disruption, vasospasm, spontaneous coronary thrombosis or embolism, and myocarditis, among others.
- Coronary angiography and CT coronary angiography are not able to detect vasomotor disorders; hence, these conditions are often under-recognised.
- INOCA and MINOCA should be suspected in patients with persistent ischaemic chest pain without a clear cause; subspecialist referral to physicians with expertise in invasive testing for angina may be helpful.
- Patients with INOCA and MINOCA may be at risk of major adverse cardiac events, making GP awareness of vasomotor disorders crucial for delivering optimal preventive therapy and risk factor management.

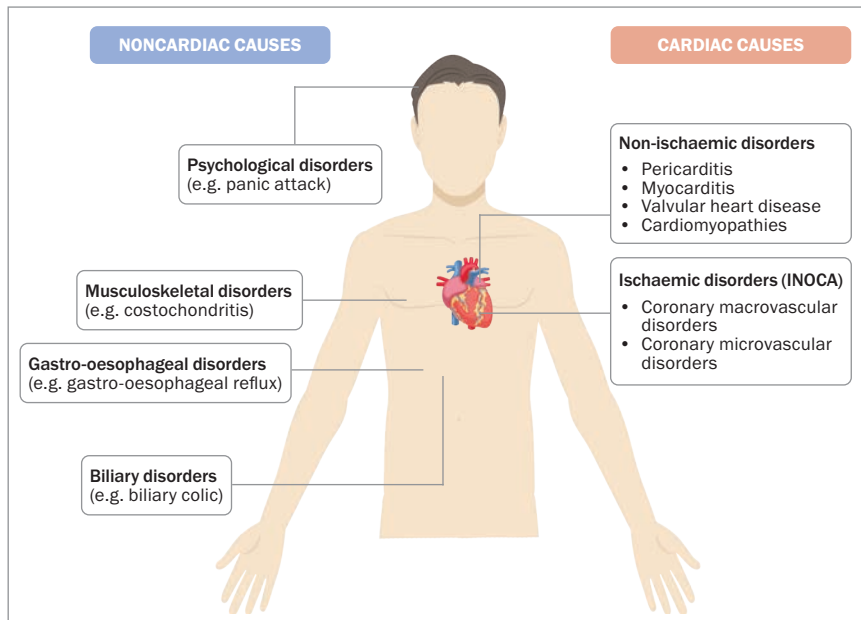


Up to half of patients with angina who are referred for invasive coronary angiography have non-obstructive coronary artery disease (CAD).<sup>1</sup> These patients may return to their GP with a diagnosis of 'noncardiac chest pain', representing an ongoing diagnostic and therapeutic challenge. However, many of these patients have an underlying ischaemic aetiology for their pain and disorders of coronary vasomotion may be relevant. Ischaemia with non-obstructed coronary arteries (INOCA) and myocardial infarction with non-obstructed coronary arteries (MINOCA) are not typically diagnosed during routine coronary angiography. As a result, they represent an important cause of chest symptoms that are typically under-recognised or misdiagnosed, despite their association with morbidity, impaired quality of life and future healthcare resource use.

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**Figure 1.** Common causes of chest pain in patients with non-obstructed coronary arteries.

Abbreviation: INOCA=ischaemia with non-obstructive coronary arteries.

Adapted from Beltrame JF, Tavella R, Jones D, Zeitz C. Management of ischaemia with non-obstructive coronary arteries (INOCA). *BMJ* 2021; 375: e060602.

INOCA is an umbrella term encompassing two major coronary vasomotor disorders that may cause ischaemia without obstructive CAD: coronary microvascular dysfunction, coronary vasospasm or both. This article aims to improve awareness of INOCA and MINOCA by providing an overview of their pathophysiology and outlines how specialist input can help with diagnosis and management.

### How can ischaemia or myocardial infarction develop without blocked arteries?

The diagnosis of chest pain in patients with non-obstructive coronary arteries requires a consideration of cardiac and noncardiac causes (Figure 1). Ischaemic disorders typically occur because of a mismatch between myocardial oxygen supply and demand. This can occur in patients with or without obstructive CAD. Coronary microvascular dysfunction or a propensity to epicardial artery spasm may drive ischaemic coronary syndromes. These syndromes can be divided by

anatomy into pathophysiological mechanisms (Figure 1).

#### Vasospasm

Vasospastic angina (VSA), formally known as ‘Prinzmetal’s angina’, is typically described as recurrent glyceryl trinitrate (GTN)-responsive ischaemic chest pain. It often presents with diurnal variation and early morning preponderance of symptoms. Prinzmetal variant angina is the rarer subtype, typically with the worst prognosis, driven by transient focal (or multivessel) occlusive proximal large coronary artery spasm. It is often seen in young smokers with characteristic episodic ST segment elevation during attacks that occur predominantly at rest.<sup>2</sup> Spontaneous myocardial infarction, ventricular arrhythmia and sudden cardiac death may result. Notably, the more common form of VSA is distinct: distal, diffuse subtotal epicardial vasospasm and characterised by ST segment depression, which may occur during physical exertion. Diurnal variation is seen in both types, with early morning episodes being common.

#### Coronary microvascular dysfunction

The pathophysiology of coronary microvascular dysfunction is complex. It involves factors including structural abnormalities, variations in resting microvascular tone, propensity to microvascular spasm or inadequate microvascular dilation in response to increased myocardial oxygen demand (functional coronary microvascular dysfunction; Figure 2).<sup>3</sup>

**MINOCA accounts for up to 10% of myocardial infarction presentations, presenting clinically as an ST segment elevation myocardial infarction (STEMI) or a non-ST elevation myocardial infarction (NSTEMI)**

#### Mixed

Coronary microvascular dysfunction may also be found in patients with coronary spasm and these patients may have a worse prognosis.<sup>4</sup> Myocardial ischaemia caused by epicardial artery spasm or coronary microvascular dysfunction is only one of many potential factors that may contribute to a patient’s symptoms of angina. Other important considerations include the presence of coexisting pathologies or psychological factors, which are common and may be compounded by prolonged diagnostic uncertainty. Patients may also present with angina despite having normal microvascular function, likely because of altered pain perception and nociceptive changes. Importantly, patients with non-anginal chest pain may undergo evaluation for other potential causes, but testing for vasomotor disorders is not indicated for noncardiac pain.

#### Myocardial infarction without obstructive coronary artery disease (MINOCA)

MINOCA accounts for up to 10% of myocardial infarction presentations, presenting clinically as an ST segment elevation myocardial infarction (STEMI) or a non-ST elevation myocardial infarction (NSTEMI).

MINOCA should be thought of as an umbrella term with diverse underlying pathophysiology including coronary and noncoronary causes (Figure 2).

MINOCA refers specifically to myocardial infarction caused by coronary-related issues (e.g. coronary spasm, thrombosis, plaque disruption) without significant coronary artery obstruction. MINOCA mimics (e.g. myocarditis, Takotsubo cardiomyopathy) present similarly but have non-coronary causes and are thus excluded from the diagnosis of MINOCA in the latest guidelines.

MINOCA has a more favourable 12-month all-cause mortality compared with ischaemia from obstructive CAD. However, it is associated with considerable morbidity, including the risk of recurrence and hospitalisation. The causes of MINOCA are well defined; therefore, recent international guidelines suggest identification of the underlying cause to provide tailored therapy.<sup>5</sup>

### Clinical presentation and risk factors

Patients with INOCA typically present similarly to patients with obstructive CAD: with angina (typical or atypical) or angina-equivalent symptoms. Although INOCA shares common cardiovascular risk factors with obstructive CAD (e.g. smoking, hypertension and dyslipidaemia), unlike obstructive CAD, it is more prevalent in women and in younger patients.<sup>6,7</sup> INOCA has also been linked to systemic inflammatory disorders such as systemic lupus erythematosus and rheumatoid arthritis, even in the absence of traditional cardiovascular risk factors.<sup>8,9</sup> Additionally, INOCA is linked to psychosocial stress, adding complexity to its diagnosis and management.<sup>10</sup>

### Diagnosis

The diagnosis of INOCA first relies on the treating medical practitioner having a high index of clinical suspicion and excluding alternative causes for chest pain (Figure 1), followed by a referral, ideally

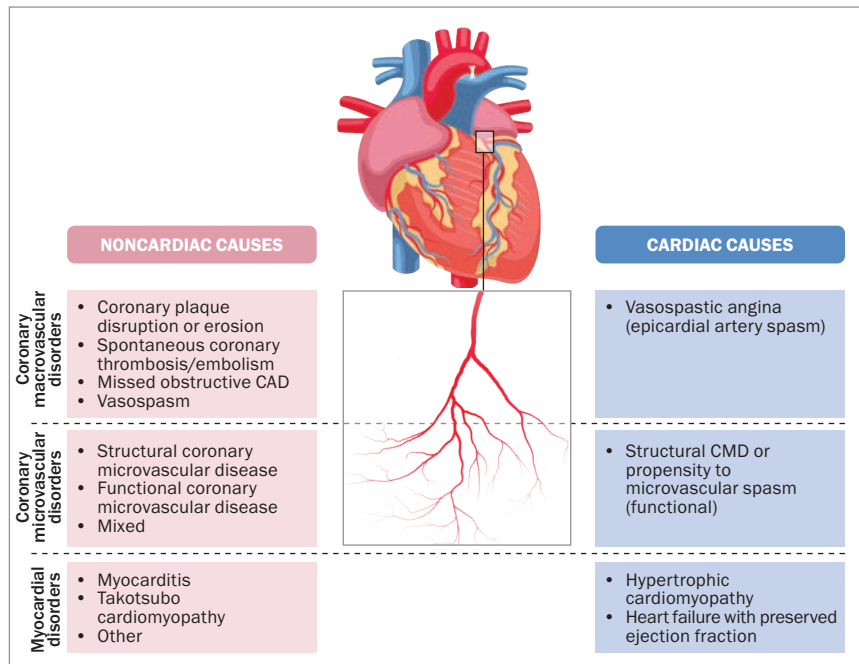


Figure 2. Noncardiac and cardiac causes of MINOCA and INOCA.

Abbreviations: CMD = coronary microvascular dysfunction; INOCA = ischaemia with non-obstructive coronary arteries; MINOCA = myocardial infarction with non-obstructive coronary arteries. Adapted from: Ford TJ, Berry C. Angina: contemporary diagnosis and management. *Heart* 2020; 106: 387-398.

to a physician or centre with expertise in the diagnosis of vasomotor disorders. Noninvasive stress testing lacks sensitivity for the diagnosis of coronary microvascular dysfunction – a ‘negative’ stress test cannot be used to rule out INOCA from microvascular dysfunction.<sup>11</sup>

Coronary angiography is performed to exclude obstructive CAD (including assessment for functionally obstructive lesions), followed by invasive functional angiographic testing – the gold standard for the diagnosis of coronary vasomotor disorders. Testing is rarely performed during routine clinical practice in Australia, which may be associated with a lack of subspecialist training and funding (there is no standardised Medicare item number). In addition, physicians may be concerned about procedural safety and the time required. Historically, a reluctance to perform invasive functional angiographic testing may also stem from clinicians’ scepticism about the diagnosis of ischaemic syndromes without obstructive CAD, particularly given the perceived lack of treatment options.

During functional testing, coronary microvascular dysfunction is assessed by measuring coronary blood flow in response to adenosine, a potent vasodilator. The presence of inducible coronary artery spasm is assessed by provocative spasm testing with intracoronary acetylcholine (Figure 3). Typically, this takes a skilled interventional cardiologist no more than 20 minutes and allows confirmation of the diagnosis of INOCA according to standardised criteria, as well as the identification of the INOCA subtype.<sup>12</sup>

Testing has been evaluated in a randomised controlled trial, showing evidence of safety as well as improved patient health-related quality of life.<sup>15</sup> The Cardiac Society of Australia and New Zealand Coronary Vasomotor Dysfunction Working Group, chaired by Professor John Beltrame, recently completed a consensus statement and protocol to help improve standardised assessment for INOCA and MINOCA using functional coronary angiography.

**CASE STUDY: A PATIENT WITH MINOCA RESULTING FROM CORONARY SPASM****Presentation**

Dave, a 65-year-old man, presented with two episodes of ischaemic chest pain at rest without troponin elevation. He has a history of hypertension and dyslipidaemia, and a strong family history of CAD. He underwent an expedited outpatient definitive coronary angiogram, which revealed mild non-obstructive CAD. A statin, beta blocker and aspirin were commenced, and he was discharged to outpatient follow up.

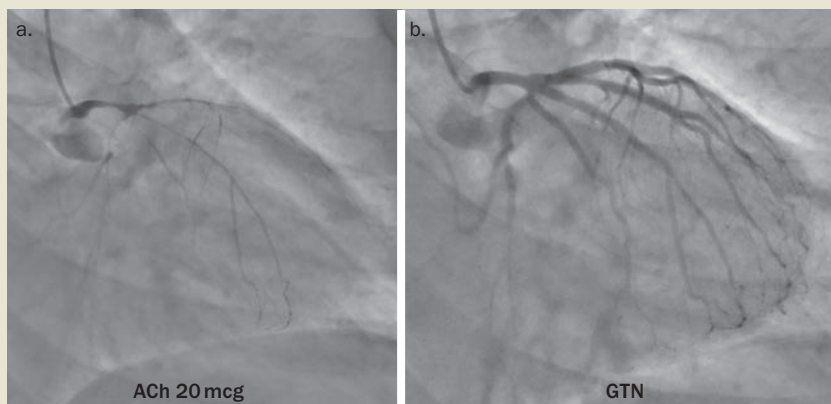
Dave re-presented to the emergency department within weeks of his index angiogram after four bouts of ischaemic chest pain in the early morning hours. He was diagnosed with a limited non-ST elevation myocardial infarction, with the level of high-sensitivity troponin I peaking at 200 ng/L. He admitted that he had been forgetful with his preventive medical therapies. The longest episode lasted 10 minutes.

Dave underwent early outpatient invasive coronary angiography from the radial approach, revealing an unchanged pattern of mild diffuse non-obstructive epicardial CAD. Follow on functional testing for microvascular disease and propensity to spasm was performed. This took about 10 to 15 minutes and was performed during the same procedure as his repeat coronary angiogram. Functional testing showed multivessel proximal subtotal occlusion (more than 90% constriction) of the major left-sided coronary arteries (coronary spasm; Figure 3a).<sup>13</sup> This reproduced Dave's angina and was associated with ischaemic ECG changes. After GTN administration, his symptoms spontaneously resolved, and repeat angiography revealed the dynamic nature of coronary spasm with resolution of his previous severe spasm (Figure 3b). Invasive testing of the coronary microcirculation was normal.

A new diagnosis of vasospastic angina was made, which would not have been made without functional testing. Dave's vasospastic angina had also caused a limited MINOCA. His beta blocker was weaned and stopped, and he was commenced on amlodipine 5 mg daily, building to 10 mg after two weeks. He was re-prescribed a high-dose statin (atorvastatin 80 mg) and invited to participate in cardiac rehabilitation (incorporating lifestyle modifications, education about angina, the risk of longer-term vascular events and the use of medical therapies such as statins for plaque stabilisation and the use of a GTN spray).

**Discussion**

In Dave's case, he experienced MINOCA, where the myocardial infarction was related to a propensity for coronary spasm. Although his angiogram showed minor atherosclerotic plaque, the diagnosis of coronary spasm-induced myocardial infarction was confirmed using provocation testing. During this testing, a low-dose bolus injection of acetylcholine into the left coronary system induced severe diffuse multivessel occlusive spasm, which reproduced his symptoms. This highlights the importance of functional testing in identifying coronary vasospasm when angiography alone does not reveal significant obstructive disease. This explanation underscores how provocation testing is crucial in diagnosing vasospastic angina, particularly in MINOCA cases, where the cause might not be apparent from a standard angiogram.



**Figure 3.** MINOCA, resulting from coronary spasm. (a, left) Left-sided coronary angiography of profound proximal multivessel coronary spasm predominantly involving the left main, left anterior descending and circumflex coronary arteries. This was provoked during functional testing with 20 mcg ACh, administered via the diagnostic catheter at a low dose during coronary angiography. (b, right) Repeat angiography following GTN administration revealed resolution of diffuse multivessel spasm.

Abbreviations: ACh = acetylcholine; CAD = coronary artery disease; GTN = glyceryl trinitrate; MINOCA = myocardial infarction with non-obstructive coronary arteries.

A case example of a patient with INOCA and MINOCA is presented in the Box.

**Prognosis**

Patients with stable coronary syndromes, including INOCA, have elevated risks of major adverse cardiovascular events (including death, nonfatal myocardial infarction or stroke, and hospitalisation for heart failure or angina), compared with the general population. This elevated risk is not reflected in standard cardiovascular risk assessment tools. Beyond physical morbidity, these patients experience significant psychosocial distress, a compromised quality of life and increased healthcare resource use, primarily because of persistent, undiagnosed symptoms.

Most cardiologists would agree that coronary vasomotor disorders are important to identify in patients with ongoing symptoms. Importantly, the biggest driver of cardiac events is the large burden of atherosclerotic plaque, irrespective of the presence of luminal obstruction; hence, patients with INOCA, but with diffuse coronary artery atherosclerosis, require consideration of disease-modifying therapies, including statins and ACE inhibitors.<sup>14</sup>

**Treatment: personalised care**

Once the treatable disorder of coronary vasomotion is determined using invasive functional evaluation, treatment is tailored to the underlying cause with the aim of reducing longer-term cardiovascular risk, in addition to anti-ischaemic therapies aimed at reducing angina burden.

Nonpharmacological measures are fundamental in the management of INOCA. Participation in a cardiovascular rehabilitation program is invaluable for improving cardiovascular fitness and helping patient illness understanding, as well as for education and the alleviation of the psychosocial distress associated with a new diagnosis of heart disease.

Individualised pharmacological treatment has been shown to be more effective

in alleviating angina symptoms compared with standard care.<sup>15</sup> For vasospastic angina, this may involve the use of calcium channel blockers (e.g. amlodipine or diltiazem) and long-acting nitrates. The management of coronary microvascular disorders is complex because of the diverse pathophysiological mechanisms and varies depending on the subtype. Typically, selective beta blockers are the first-line treatment for coronary microvascular dysfunction (e.g. bisoprolol), but calcium channel blockers may also be tried. Importantly, in patients with predominantly coronary microvascular dysfunction (microvascular angina), nitrates may be detrimental and associated with a reduced exercise capacity and worsening of symptoms, which may be related to nitrate tolerance and steal phenomena. There is an ongoing need for the development of targeted therapies for coronary microvascular dysfunction.

### Conclusion

Ischaemic coronary syndromes frequently occur without obstructive epicardial CAD. Microvascular or vasospastic angina may be responsible for ongoing chest pain in patients after a 'negative' angiogram, leading to missed diagnosis and suboptimal patient care. Increased awareness, early detection and appropriate referral by GPs for patients with persistent ischaemic chest pain has the potential to improve the quality of life for these patients. **MT**

### References

A list of references is included in the online version of this article ([www.medicinetoday.com.au](http://www.medicinetoday.com.au)).

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### ONLINE CPD JOURNAL PROGRAM

List at least three risk factors for ischaemia with non-obstructed coronary arteries (INOCA).



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