# Unexplained chest pain

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## When to consider ischemia with non-obstructive coronary arteries (INOCA)

Have you ever had a patient with recurrent chest pain but normal or non-obstructive coronary arteries on a coronary angiogram/CT coronary angiogram? Is their chest pain psychological? Is it musculoskeletal? Is it gastroesophageal? Is it due to other cardiac causes e.g. pericarditis?

### Consider this patient

A 55yo, thin southeast Asian female with no cardiac risk factors, and no significant past medical history; who has chest pain walking uphill. Her stress test was normal, and the subsequent CT coronary angiogram (CTCA) was normal. She had no improvement with long-acting nitrates. She has had symptoms for >1 year.

*Not the patient's real image

What do you do next?

### What is INOCA?

INOCA is ischaemia with non-obstructive coronary arteries. These patients have symptoms/signs of ischaemic but non-obstructive coronary artery disease (<50% stenosis) on CTCA/coronary angiogram.[1]

### Prevalence:

It is highly prevalent: >50% of women and >30% of men with non-obstructive coronary artery disease on a Coronary Angiogram and evidence of angina.[2] Up to 50% of patients with known or suspected angina have INOCA.[3] Of these, 80% are found to have microvascular and vasospastic angina when studied using specific tests.[3,4]

### Prognosis:

INOCA have reported an increased risk of major adverse cardiovascular events (MACE), a threefold to fourfold increased risk of hospital admission.[5,6] A meta-analysis reported an overall estimated incidence of MACE (all-cause mortality and myocardial infarction) of 0.98 per 100 person-years, compared with 0.2 per 100 person-years reported in a similarly aged general population in North America.[3] An international

registry of microvascular angina reported an annual MACE incidence of 7.7% per patient-year.[7]

These conditions are associated with impaired quality of life, as well as greater morbidity and health resource utilisation.[8,9,10] An estimated 50% of patients with stable chest pain and normal angiography will experience recurrent episodes of chest pain, similar to those with obstructive coronary artery disease.[11,12] In addition, about 15-25% of these patients are readmitted with chest pain or undergo repeat angiography (or both).[4] Patients with chest pain and nonobstructive coronary arteries have a reduced quality of life at 12 months, compared with healthy controls.[7]

### Identifying INOCA patients:[13]

1. **Exclude non-cardiac causes:** eg. psychological, musculoskeletal, gastro-oesophageal, and biliary.

2. **Exclude non-ischaemic cardiac causes:** e.g., pericarditis, myocarditis, valvular heart disease.

3. **Look for ischaemia:** typical chest pain with exertion/stress; ischaemic ECG changes; abnormal myocardial perfusion on stress imaging; stress-induced regional wall motion abnormalities.

4. **Do structural coronary angiography:** invasive coronary angiogram or CT coronary angiogram. Coronary artery stenosis <50%.

5. **Do functional coronary angiography/coronary physiology testing:**

These patients may have disorders of vasomotion. When we do coronary angiograms, we look at the epicardial coronary arteries. However, 90% of the coronary circulation is supplied by microvascular circulation. We can do "functional" coronary angiography/coronary physiology tests in the cardiac catheter theatre to identify patients with INOCA and look at the microvascular circulation. In some institutions, such as Macquarie University Hospital we use Abbott's PressureWire™ X Guidewire and Coroventis CoroFlow Cardiovascular System.

We exclude obstructive coronary artery stenosis with a fractional flow reserve wire. Then we can study the microvascular system and diagnose microvascular dysfunction; and perform vasoreactivity testing (using acetylcholine), for epicardial or microvascular vasospasm. Thus, we can diagnose INOCA and identify whether it is a coronary macrovascular or microvascular disorder - see table below.

Functional coronary angiography helps to define the underlying pathophysiologic mechanism and the INOCA endotype:[14]

- **Microvascular angina:**
  symptoms of myocardial ischaemia; absence of obstructive coronary artery disease (<50% stenosis or FFR>0.80); objective evidence of myocardial ischaemia, evidence of impaired coronary microvascular function (on coronary physiology testing).

- **Vasospastic angina:**
  >90% epicardial vasoconstriction (during vasoreactive testing), reproduction of usual anginal symptoms, and ischaemic ECG changes.

- **Mixed (microvascular and vasospastic):**
  overlap condition meeting criteria for both microvascular angina and vasospastic angina.

- **Non-cardiac symptoms:**
  unobstructed coronary arteries with normal coronary function test results.

Diagnosing microvascular dysfunction and/or vasospastic angina can help guide our management, which is associated with less angina and better quality of life.

**Table 1 | Clinical attributes of INOCA coronary vasomotor disorders.[13]**

| | Diagnostic investigation | Putative mechanism | Clinical presentation | Nitrate response |
|---|---|---|---|---|
| **Coronary macrovascular disorders** | | | | |
| Vasospastic angina | Spontaneous or inducible coronary artery spasm | Coronary artery spasm | Rest or unstable angina; smoking is a risk factor | Prompt |
| **Coronary microvascular disorders** | | | | |
| Cardiac syndrome X | Positive stress ECG | Impaired microvascular vasodilation | Stable exertional angina; high prevalence in female patients | Limited |
| Microvascular angina | Impaired coronary flow reserve | Impaired microvascular vasodilation | Often rest angina; often female patients | Limited |
| Coronary slow flow phenomenon | Delayed vessel opacification on angiography | Increased microvascular resistance | Unstable angina; smoking is a risk factor | Variable |
| Microvascular spasm | Inducible pain and ischaemic ECG changes with acetylcholine, but no coronary artery spasm | Microvascular spasm | Unstable angina; often female patients | Variable |

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## Management

Depends on the underlying pathophysiologic mechanism/the clinical "endotype":

**Guideline-recommended treatments based on clinical endotype:[15]**

| Diagnosis | Treatment | |
|---|---|---|
| **Microvascular angina** | Beta-blockers (nebivolol 2.5-10mg od); calcium channel blockers (amlodipine 10mg od) Nicorandil (10-20mg bd) | ACE inhibitors (ramipril 2.5-10mg od) A2RB <br>• Stop nitrates |
| **Vasospastic angina** | Calcium channel blockers (verapamil 20mg od/ diltiazem 120-360mg od) Nitrates (ISMN 20-120mg od) | Nicorandil (10-20mg bd) |
| **Mixed microvascular and vasospastic angina** | Calcium channel blockers (amlodipine, verapamil, diltiazem) Nicorandil | ACE inhibitors |
| **Non-Cardiac symptoms** | Discontinue antianginal medication, and consider continuing cardiovascular risk reduction medication (eg. Statin) if coronary artery disease present | |
| **Cardiovascular risk reduction** | Statins Antihypertensives | Lifestyle: smoking cessation, exercise, cardiac rehabilitation, mediterranean diet, cognitive behaviour therapy, weight reduction if overweight. |

Getting back to the initial case – we performed a coronary physiology study, and the diagnosis of coronary microvascular dysfunction/microvascular angina was made. We changed her over to a beta-blocker (as long-acting nitrates are not of benefit) to help with her symptoms and added a statin (event prevention).

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