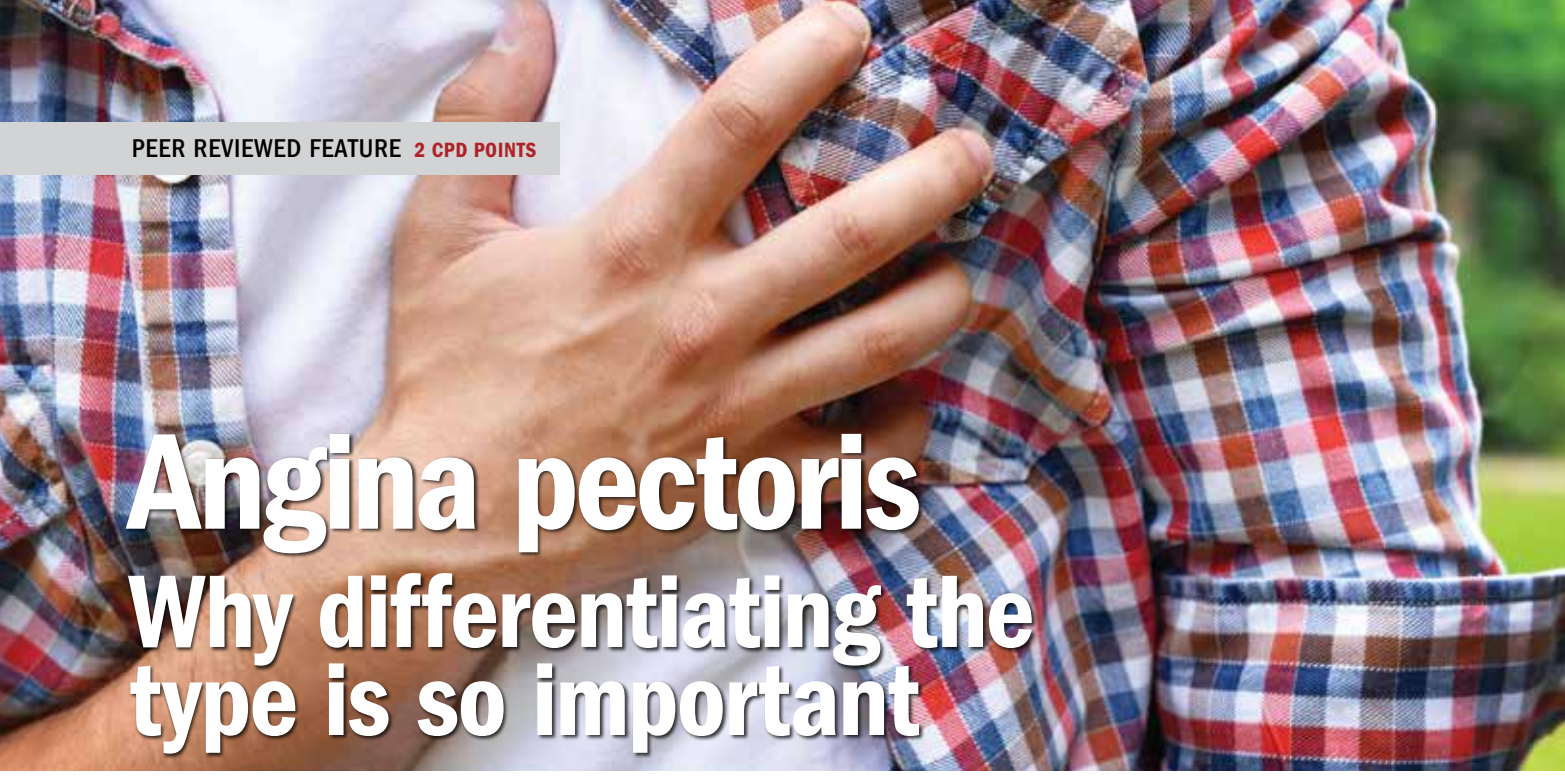

Angina pectoris
Why differentiating the type is so important

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Apart from the traditionally recognised conditions of stable and unstable angina, many other disease entities produce anginal-type chest pain. Each of these presents its own diagnostic challenges.

KEY POINTS

- It has now emerged that apart from the traditionally recognised conditions of stable and unstable angina, many other disease entities produce anginal-type chest pain.
- Angina can be classified by type, taking into account the pathogenesis and clinical features in each patient and thus guiding management, or, for predominantly exertional angina, by severity, thus indicating the urgency for treatment.
- The diagnosis of angina is mainly clinical; investigations are available to confirm the diagnosis but should be used only if the history is not clear-cut, or if there is a reason to evaluate the extent and localisation of ischaemia.
- Although routine exercise stress testing rarely provides information on the presence of serious coronary disease, exercise perfusion imaging with various radionuclides yields more reliable data, including localisation and severity of reversible ischaemia.
- It is vital not to miss a diagnosis of unstable angina because of the associated risk of the development of infarction.
- Disorders of coronary vasomotor tone producing angina are often misdiagnosed as noncardiac chest pain.

What is angina and what are its causes?

Definition

Although angina pectoris means 'pain in the chest', in practice the term denotes pain resulting from myocardial ischaemia, which is usually, but not always, mainly in the chest. Typically, angina is precipitated by exertion or emotional stress, and involves a sensation of tightness and/or pressure across the patient's chest that resolves with rest. Angina pain frequently extends beyond the front of the chest, often into the jaw, the left shoulder and arm, and, more rarely, into the upper abdomen and back. The pain causes a feeling of apprehension (*anguor animi*) and is often preceded slightly by dyspnoea. In the elderly and patients with diabetes, dyspnoea may be the predominant symptom ('defective anginal warning syndrome' or DAWS). In most cases, patients' symptoms rapidly resolve after taking sublingual glyceryl trinitrate.

Causes of angina

Historically, it was considered that all cases of angina pectoris were reflected (reversible) myocardial ischaemia, with underlying obstructive acute or chronic coronary artery disease. Thus angina was thought to be largely predictable and precipitated mainly by exertion, with underlying stable, severe coronary stenosis, whereas in the presence of underlying but nonocclusive coronary thrombus, angina might rapidly occur at lower levels of physical activity, and also at rest. Although these principles remain largely correct today, the nexus between angina and 'fixed' coronary artery disease has turned out to be less consistent.

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Why classify angina?

There are two major reasons supporting the classification of angina. First, and most importantly, classification according to type of angina is necessary because both its pathogenesis and associated clinical features vary between patients and influence the choice of treatment (Table 1). Second, in the case of predominantly classic (exertional) angina, classifying angina by its severity is important in determining the urgency for treatment. The Canadian Cardiovascular Society grading of angina classifies exertional angina according to symptom severity, as shown in the Box.[1]

Bases for delineating the type of angina

It has now emerged that apart from the traditionally recognised entities of stable (exertional, classic) and unstable angina, many other disease entities produce anginal-type chest pain. These 'new' types of angina vary substantially from exertional angina and reflect coronary artery constriction, either predominantly or entirely. Patients with these types of angina experience anginal-type pain that is often, regrettably, dismissed as 'noncardiac pain' when initial tests fail to establish any abnormalities. As the outlook for these patients is one of substantial morbidity (and sometimes mortality), it is critically important to ensure that the diagnosis is precise.

The major developments in understanding the pathogenesis of the 'new'

TABLE 1. CLASSIFICATION OF TYPE OF ANGINA ACCORDING TO TYPICAL CLINICAL PRESENTATION

Predominant clinical presentation of angina	Type of angina	Pathogenesis	Usual anginal pattern	First-line treatments
Predictable with exertion	Classic angina	'Fixed' coronary stenosis	Stable pattern of precipitation with exertion/emotional stress	Organic nitrates β-adrenoceptor antagonists Nondihydropyridine calcium antagonists Revascularisation
	Cardiac syndrome X	Coronary microvascular dysfunction (failure to dilate with exertion)	Exertional symptoms	Uncertain
	Mixed pattern angina	Combination: coronary stenosis plus associated coronary vasoconstriction	Angina mainly on exposure to cold	Nondihydropyridine calcium antagonists Organic nitrates
	Angina precipitated by left ventricular hypertrophy	Increased myocardial oxygen demand ? Impaired diastolic coronary flow	Associated with aortic stenosis or hypertrophic cardiomyopathy	Uncertain
Transition (over days) from exertional to resting angina, or new onset severe angina	Unstable angina	Ruptured coronary plaque: incipient thrombosis	May present entirely with rest pain, or with rapid worsening of symptoms	Anticoagulants Antiaggregatory agents Nondihydropyridine calcium antagonists Revascularisation
Occurring predominantly at rest	Variant (Prinzmetal) angina	Large coronary artery spasm	Cyclical symptoms Prolonged episodes Good response to organic nitrates	Nondihydropyridine calcium antagonists Organic nitrates
	Coronary slow flow phenomenon	Small coronary artery spasm	Cyclical symptoms Pain duration up to 12 hours Poor response to organic nitrates	Nondihydropyridine calcium antagonists ? Organic nitrates Organic nitrates plus N-acetylcysteine (intravenous)
	Nitrate-withdrawal angina	Sudden cessation of nitrate vasodilation	Occurs at time of cessation of nitrate effect: mainly resting symptoms	Adjust organic nitrates
	Decubitus angina	Increased venous return in presence of severe heart failure	Relieved by changing from lying down to sitting up Severe dyspnoea	Treat heart failure Initial therapy includes organic nitrates

forms of angina are summarised below.

- Abnormalities of coronary artery reactivity, with resultant constriction or spasm of the large or small coronary arteries, often contribute to angina occurrence, especially when symptoms occur predominantly randomly and at rest.
- Angina need not reflect underlying coronary artery disease in patients in whom myocardial oxygen demand is increased substantially by the presence of gross global or regional left ventricular hypertrophy.
- In patients with severe systolic heart failure, angina may be precipitated by increases in cardiac work triggered by increased venous return – for example, associated with lying down horizontally.

Diagnosing angina: clinical considerations

The diagnosis of angina is basically clinical. Patients should be asked to describe a typical episode, including its precipitating factors and diurnal variability. Key questions include:

- What is the relation between the angina and long-acting nitrate therapy?
- What is the response of symptoms to sublingual nitrate administration?
- What is the duration of typical episodes?
- Is there a cyclical pattern to the symptoms?
- What is the severity of associated dyspnoea?

As a common differential diagnosis of angina is chest-wall pain, examination should include determining whether pressure on the chest wall precipitates identical symptoms.

An electrocardiogram (ECG) taken during an episode of pain is potentially useful if ST segment depression or elevation occurs at this time. However, having patients perform an exercise stress test (EST) to establish a diagnosis of angina is rarely ideal. This test is only relevant for patients who have exertional symptoms; however, the diagnosis in these patients can usually be made via history alone, and exercise-testing results are rarely definitive.[2] Although routine exercise testing rarely yields new insights into the presence of serious coronary disease, exercise perfusion imaging with various radionuclides, including ^{99m}Tc-sestamibi, produces more reliable information, including localisation and severity of reversible ischaemia.

Diagnosing angina: investigations

The appropriate investigations to diagnose angina depend on the type of angina suspected. For example, an exercise test to precipitate angina is of no use for patients who experience symptoms entirely at rest. Appropriate investigations are discussed below according to specific causes.

Diagnosis of predominantly exertional angina

As noted above, the diagnosis of angina is essentially clinical. Accessory procedures are available to confirm the diagnosis, but should be used only if the history is not clear-cut or if there is a reason to evaluate the extent and localisation of ischaemia. For example, coronary angiography can be used to determine the extent of concomitant fixed coronary disease; it is not useful in the diagnosis of exertional angina, rather it identifies management options.

Classic angina

Exercise stress test. The EST is a readily available test for patients with exertional angina in whom the resting ECG is normal, providing they can achieve an adequate workload. However, before performing an EST, physicians must be confident that the test will provide information necessary to guide clinical decision-making.

For example, it is not necessary to perform an EST for diagnostic purposes in a patient with *a priori* high probability of symptomatic coronary artery disease, as the result will not influence the next management step – i.e. antianginal treatment.

CANADIAN CARDIOVASCULAR SOCIETY'S GRADING OF ANGINA OF EFFORT[1]

Grade I
'Ordinary physical activity does not cause angina', such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.

Grade II
'Slight limitation of ordinary activity'. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

Grade III
'Marked limitation of ordinary physical activity'. Walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace.

Grade IV
'Inability to carry on any physical activity without discomfort – anginal syndrome may be present at rest'.

In contrast, it is useful to perform an EST for prognostic purposes in a patient who has had an acute coronary event, or in someone with chronic angina whose functional capacity has diminished for unknown reasons. Objective evaluation of exercise ability in such cases may provide useful information that guides management and indicates prognosis.

Perhaps the only time the EST should be considered as a diagnostic tool is when a patient with minimal or no risk factors presents with an equivocal history, and that due to high occupational risks, an objective investigation of the pain is necessary. Apart from the case of patients with severe inducible ischaemia (e.g. left main coronary artery stenosis; Figure 1), when the EST result is strongly positive, the gain from EST is mostly minimal.[2]

Stress echocardiography. Two-dimensional stress echocardiography can be performed with either exercise or pharmacological agents, depending on

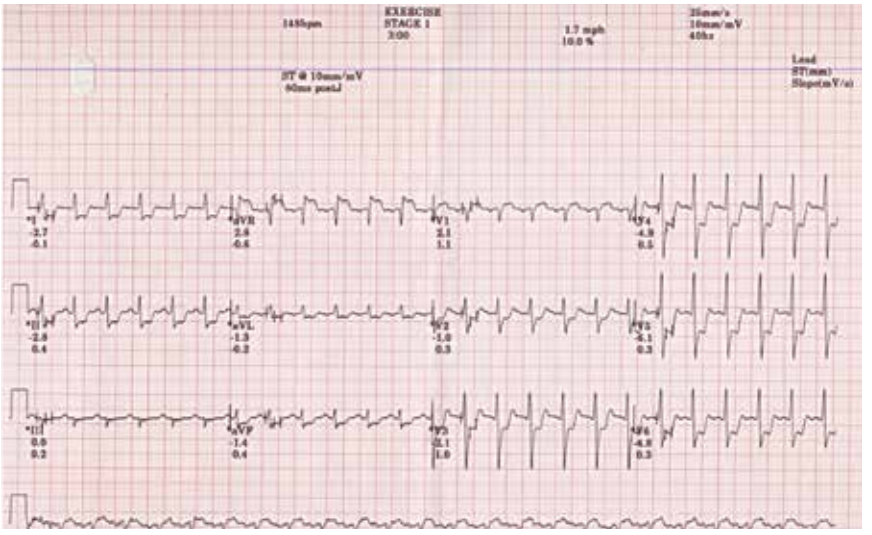


Figure 1. ECG during exercise of a man with left main coronary artery disease. Note the precipitation of marked and extensive ST segment depression in most leads, but ST elevation in aVR.

the patient's exercise capacity. Exercise is usually preferred, as it provides a more physiological environment and additional data on haemodynamic changes. Pharmacological testing can be used when a patient's exercise capacity is limited by mobility or other noncardiac issues.

Stress echocardiography is useful not only in the diagnosis of regional myocardial ischaemia, but also in allowing the quantification of the extent of ischaemia. Its main limitation is poor visualisation of endocardial borders in certain subgroups, including patients who are obese and those with chronic lung disease. Furthermore, the quality of data generated is strongly operator-dependent. Finally, chemical stress echocardiography data are somewhat less specific than those obtained with exercise testing (Table 2).[3]

Myocardial perfusion scintigraphy. The use of nuclear medicine procedures such as single photon emission computed tomography (SPECT) combines the artificial induction of ischaemia (again via exercise or chemical stimuli) with nuclear medicine perfusion imaging, typically with ^{99m}Tc-sestamibi injection after induction of potential ischaemia and its repetition at rest. Advantages of the resultant paired imaging of regional myocardial perfusion include greater diagnostic accuracy than that achieved with ECG interpretation alone; however, its main advantages are of localisation and quantitation of the induced ischaemia (Figure 2).

Given the incremental cost of the procedure and associated (if minor) radiation exposure, the use of SPECT in patients with suspected exertional angina should be restricted to 'complex' cases. Examples are patients with both ischaemia and previous myocardial infarction in whom invasive intervention is contemplated, or patients in whom it is desirable to localise the major site of ischaemia for potential angioplasty to the responsible lesion.

Exercise SPECT is preferable to chemical procedures, which carry the potential for missing the diagnosis of 'global' ischaemia due to left main coronary stenosis.

Coronary angiography. Definitive diagnosis and precise assessment of underlying coronary artery disease still requires cardiac catheterisation and coronary angiography. Patients in whom a high likelihood of coronary artery disease is suspected clinically or in whom ischaemia has been demonstrated on imaging modalities can be managed in the first instance with optimal medical therapy. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial has shown that percutaneous coronary intervention in addition to optimal medical therapy does not provide incremental cardioprotection.[4]

In patients with suspected exertional angina, coronary angiography has virtually no diagnostic role: it defines coronary anatomy, not myocardial physiology. However, it is important in the early assessment of other forms of angina (see below) and is critical to the selection of invasive modes of treatment (e.g. coronary angioplasty/stent insertion or coronary bypass surgery) in patients with exertional angina whose symptoms have failed to resolve with medical therapies.

TABLE 2. SENSITIVITIES AND SPECIFICITIES OF TESTS TO DIAGNOSE INDUCIBLE ISCHAEMIA DUE TO 'FIXED' CAD[3]

Test	Diagnosis of coronary artery disease	
	Sensitivity (%)	Specificity (%)
Exercise stress test*	45–50	85–90
Exercise stress ECHO	80–85	80–88
Exercise MPS	73–92	63–87
Dobutamine stress ECHO	79–83	82–86
Vasodilator stress ECHO	72–79	92–95

* Results without minimal referral bias.

Abbreviations: CAD = coronary artery disease; ECHO = echocardiography; MPS = myocardial perfusion scintigraphy.

Data from reference 3 (2013 ESC guidelines on the management of stable coronary artery disease: the task force on the management of stable coronary artery disease of the European Society of Cardiology).

Cardiac syndrome X

Cardiac syndrome X occurs particularly in ageing women with associated hypertension. Affected patients have symptoms suggestive of exertional angina, which can sometimes be shown on coronary angiography to occur in the absence of haemodynamically significant coronary stenoses. Unfortunately, cardiac syndrome X, a presumptive disorder of the small coronary vessels, can only be diagnosed by angiography.

Mixed pattern angina

Mixed pattern angina (angina with variable exercise threshold) is caused by episodic increases in coronary tone, largely modulated by sympathetic activation causing transient spasm at sites of fixed, but limited, coronary artery disease. Its diagnosis is made mainly from patients' histories. Patients may say, for example: 'In warm weather, I experience angina only with severe exertion, but I avoid exercise of any type on cold, windy days, when I would develop angina readily'. The implications of such a history are:

- exercise testing (at room temperature) may not capture the severity of potential ischaemia
- in the choice of pharmacotherapy, there is a strong argument to avoid use of beta-adrenoceptor antagonists, as these may worsen coronary vasoconstriction.[5]

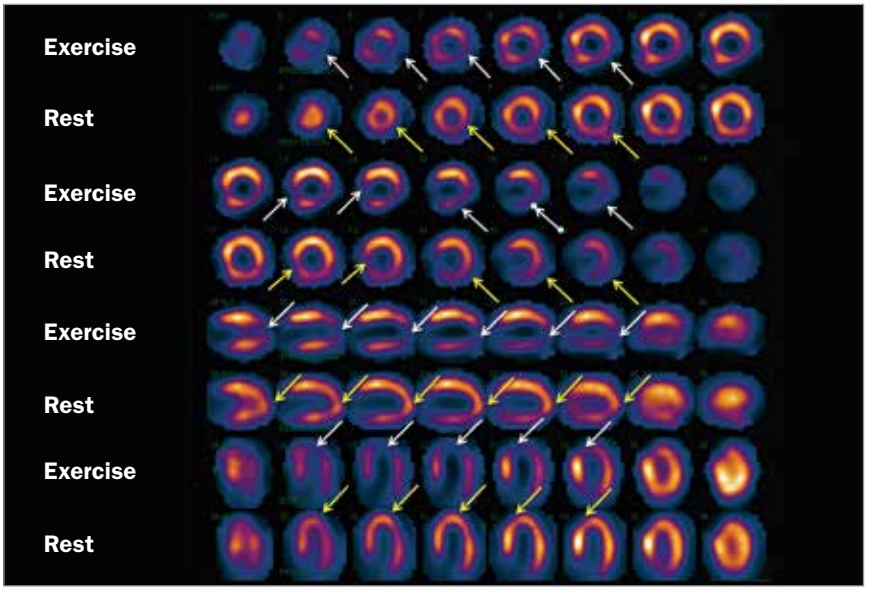


Figure 2. Myocardial perfusion imaging generated at peak exercise and at rest. Exercise has induced a substantial degree of myocardial ischaemia, probably corresponding to the distribution of the distal left anterior descending and right coronary arteries. White arrows indicate a large perfusion defect involving apical and distal anterior and inferolateral walls on exercise images. Yellow arrows indicate significant reversibility of abnormalities on rest images, demonstrating ischaemia rather than infarction.

Image courtesy of Dr S. Unger, Adelaide.

Diagnosis of unstable angina

Given that unstable angina results primarily from the rupture or fissure of a coronary plaque with associated platelet aggregation and thrombus formation, a 'grey area' has developed between unstable angina and (small) myocardial infarction. It is vital not to miss a diagnosis of unstable angina, because of the associated risk of the development of infarction. Beyond a characteristic history of rapidly worsening symptoms or new onset of severe symptoms, the most useful diagnostic finding is that of marked ST segment depression on ECG during spontaneous pain. A blood sample should be taken for measurement of (high sensitivity) cardiac troponin levels: elevation of these is strongly suggestive of myocardial infarction. Irrespective of troponin elevation, patients should be transferred urgently to an appropriately equipped hospital.

It is often difficult, however, at the time of a patient's first presentation, to distinguish unstable angina from the various forms of coronary artery spasm, as discussed below.

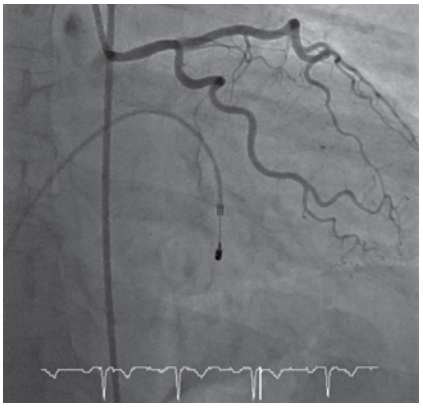
Diagnosis of angina occurring predominantly at rest

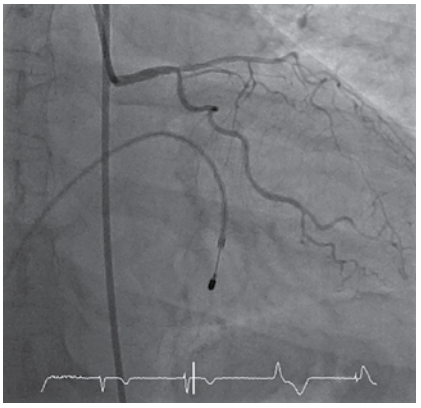
Potential diagnoses of angina occurring mainly at rest include various forms of coronary spasm (variant angina, coronary slow flow phenomenon, nitrate-withdrawal angina) and decubitus angina, reflecting systolic heart failure. Each presents its own diagnostic challenges.

Variant angina and coronary slow flow phenomenon

Variant angina (VA) and coronary slow flow phenomenon (CSFP) represent a spectrum of coronary artery spasm. VA affects mainly the large coronary arteries, whereas CSFP results from spasm of the smaller vessels. Symptoms may be precipitated by exposure to cold or by hyperventilation. Many doctors consider these to be relatively rare conditions, occurring mainly in Japanese patients; however, the problem is that they are poorly diagnosed by most Western physicians.[6] This is despite patients presenting recurrently to emergency departments with prolonged episodes of anginal-type chest pain. The confusion seems to arise from patients having prolonged ischaemia but little change on ECG and no increase in troponin level. Such patients are often treated with nitrates and heparin, and then discharged with a diagnosis of 'atypical chest pain'. Although cardiac death due to VA and CSFP is relatively rare, these conditions are usually debilitating, and failure to diagnose and treat them appropriately is regrettable.

The diagnosis of both VA and CSFP





Figures 3a and b. Coronary arteriography of a patient with variant angina who presented with frequent prolonged episodes of angina at rest.
a (far left). Left coronary artery at rest.
b (left). Induction of severe diffuse coronary vasoconstriction (especially in the left anterior descending coronary artery) after intracoronary injection of acetylcholine. Both vasoconstriction and associated angina resolved rapidly after intracoronary injection of glyceryl trinitrate.

requires coronary angiography, both to exclude the presence of severe coronary stenoses and to demonstrate the spastic condition. Coronary angiography in patients with CSFP will reveal marked slowing of flow of contrast agent down one or more coronary arteries in the absence of significant narrowing in the proximal vessel. Flow can be improved by the use of selective small coronary artery dilators.

In the case of patients with VA, the coronary vessels usually look completely normal in the absence of symptoms, and a provocative test needs to be performed to elicit the diagnosis.[7] Low-dose acetylcholine is injected into a coronary artery, producing localised or generalised spasm of the epicardial vessels in susceptible patients (Figures 3a and b).

Nitrate-withdrawal angina

Many patients receiving long-acting nitrate preparations, especially high-dose isosorbide mononitrate or glyceryl trinitrate patches, are at risk of nitrate-withdrawal angina. This occurs due to the imbalance in coronary vasomotor tone engendered by the sudden withdrawal of nitrate-related vasodilatation, and the persistent presence of increased (reflex) vasoconstrictor tone.

Diagnosis is made predominantly on the basis of history. Patients present with angina at rest, occurring regularly one to eight hours after the beginning of their 'nitrate-free period'. For example, in a patient who takes isosorbide mononitrate at 8 am, angina occurring regularly between midnight and 8 am probably represents nitrate withdrawal, rather than unstable angina.

Decubitus angina

Given that decubitus angina occurs due to increased venous return associated with a horizontal recumbent position in the presence of severe systolic heart failure, the diagnosis should be suspected on the basis of history alone. Symptoms will be improved when the patient sits up in bed, thus decreasing venous return. Physical examination will usually reveal evidence of cardiomegaly and pulmonary congestion, indicating that the underlying major problem is uncontrolled heart failure.

Conclusion

Although the diagnosis of angina pectoris is essentially based on clinical information, it is equally important to diagnose the type of angina. This often requires additional evaluation, and sometimes both noninvasive and invasive diagnostic evaluation. Treatment of angina will depend very much on the type of disorder involved. MT

Acknowledgment

We are grateful to Dr S. Unger for the material for Figure 2.

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