

Vasospastic Angina (Prinzmetal Angina) — Definition and Treatment

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Vasospastic angina is a variety of angina pectoris (chest pain) occurring at rest in which myocardial ischemia is due to transient vasospasm, with or without any underlying pathology. It is one of the syndromes that cause ischemic myocardial pain (angina pectoris), the other two being stable and unstable angina. Although rare in comparison, students are expected to know about it for the purposes of USMLE, as well as for their clinical knowledge.



Definition of Vasospastic Angina

A **sudden coronary artery spasm** leading to a **reduction in coronary blood flow** and causing **severe chest pain** (angina) at rest is called vasospastic, Prinzmetal, or variant angina. This type of angina occurs at rest, rather than on exertion, without any initiating factors.

Usually, a cardiovascular event is associated with the [atherosclerosis](#) of a major coronary artery but, in this case, the causative mechanism is '**vasospasm**' which may or may not occur at the site of atherosclerosis. Multifocal spasms can also occur in the coronary system. An ECG at the time of the chest pain due to vasospastic angina may show ST-segment elevation.

Epidemiology of Vasospastic Angina

Spread of vasospastic angina

Vasospastic angina is an uncommon cause of myocardial ischemia, responsible for approx. 5% of angina cases. Patients are generally **younger** than those with stable or unstable angina secondary to coronary artery atherosclerosis. Variant angina more commonly affects **women**.

This syndrome has a higher incidence in **Japan**, compared to Western countries. The overall incidence has decreased significantly over the past 30 years. It is believed that this decline is because of the increased use of calcium antagonists to treat hypertension.

Etiology of Vasospastic Angina

Causes of vasospastic angina

Vasospastic angina is caused by the **spasm of the coronary arteries**, which are the arteries supplying the heart. Coronary artery spasm can occur as a result of various risk factors, such as **stress, smoking, cocaine use, insulin resistance, and medications** that have the effect of constricting [blood vessels](#), such as triptans.

Rarely, coronary artery vasospasm may be triggered after coronary artery bypass surgery or near a drug-eluting stent. Generally, the specific trigger is unknown. Many patients do not usually display classical coronary risk factors, apart from heavy smoking.

Risk Factors and Associations of Vasospastic Angina

Risk factors for vasospastic angina

- Smoking
- Substance abuse
- Alcohol
- Cocaine
- Sumatriptan
- 5-fluorouracil
- Insulin resistance

Associations

Rarely, variant angina is associated with **systemic vasomotor disorders** such as migraine and Raynaud's phenomenon. This suggests the presence of a general vascular disorder.

Pathology and Pathophysiology of Vasospastic Angina

The underlying mechanism causing vasospasm in vasospastic angina is debatable, and many theories have been put forward in recent years. Vasospasm occurs in response to local **vasoconstrictor stimuli** in the coronary segment. Impaired regulation of myofibril contraction in the smooth muscle cells of coronary vessels causes smooth muscle

hyperactivity, resulting in vasospasm.

Other abnormalities of the endothelium, such as **defects in the enzyme** - endothelial nitric oxide synthetase - can lead to reduced levels of nitric oxide. Nitric oxide is a natural vasodilator, and its decreased synthesis can lead to vasoconstriction. Current studies also show that coronary artery vasospasm can result from the impairment of K⁺ ATP-dependent channels and hyperactivity of an intracellular enzyme - Rho-kinase.

Sudden vasoconstriction resulting from any of the aforementioned phenomena leads to decreased coronary blood flow which causes myocardial hypoxia and triggers angina.

In vasospastic angina, **focal coronary artery spasm** occurs and significantly reduces the diameter of the coronary artery lumen, causing temporary occlusion and leading to myocardial ischemia. This vasospasm can occur in arteries that appear normal, or in arteries affected by atherosclerosis. The most common artery affected is the right coronary artery; the second most commonly affected is the left anterior descending artery.

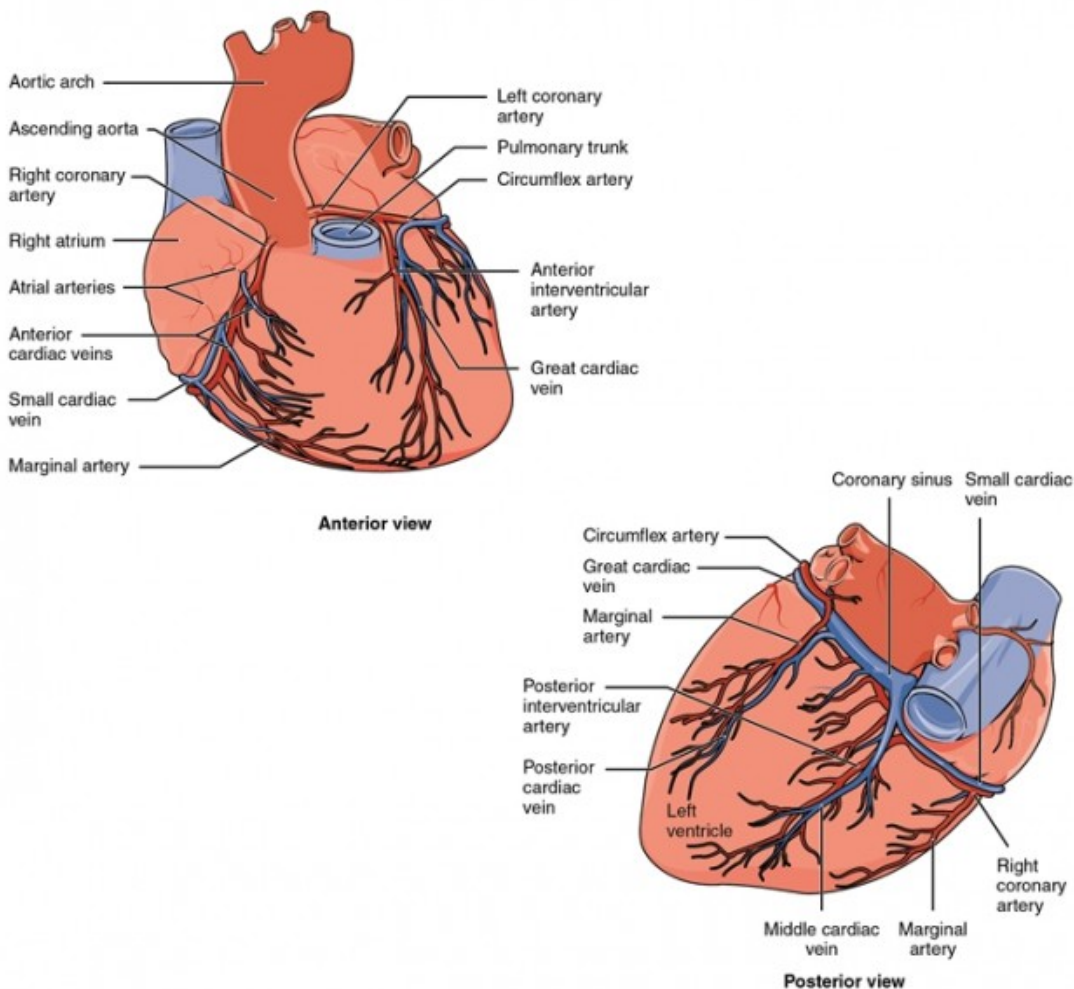


Image: Coronary Circulation By PhilSchatz, License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

The exact mechanisms that cause coronary artery spasm are not well understood. Some theories that have been proposed are related to **endothelial dysfunction** and **increased contractility of vascular smooth muscle**. With endothelial dysfunction, there is an imbalance between relaxing and contracting factors that are produced by the endothelium.

One important mechanism is related to **decreased nitric oxide production** by the dysfunctional endothelium, which is normally produced from L-arginine by endothelial nitric oxide synthase. As nitric oxide has potent smooth muscle relaxation and vasodilator effects, reduced levels can contribute to vasoconstriction. **Increased activity of phospholipase C** has also been reported, which is an enzyme that mobilizes intracellular calcium and may cause smooth muscle contraction.

Another theory is that repeated episodes of coronary vasospasm may cause neointimal hyperplasia, contributing to stenosis in the artery. Rho-kinase is also believed to play a role in the pathogenesis of this condition, being involved in regulating vascular smooth muscle contractility.

It is important to note that patients with the variant coronary syndrome may have significant **atherosclerosis** of their coronary arteries. However, the episodes of pain they experience are not related to increased oxygen demand (which occurs with changes in activity, heart rate, or blood pressure).

Other factors that have been suggested to contribute to the pathogenesis of coronary artery spasm include **autonomic nervous system dysfunction, magnesium deficiency, chronic low-grade inflammation, and increased oxidative stress** (with smoking). **Genetic factors** may be involved, as there is a 3-fold greater incidence in Japanese people, compared to Caucasians. It is possible that certain genetic mutations predispose to coronary artery spasm, such as those affecting the endothelial *NOS* gene.

Clinical Presentation and Diagnosis of Vasospastic Angina

Symptoms of vasospastic angina

Patients experience **very severe central chest pain**, which is the same type of pain in classic angina. These attacks tend to happen at **rest**, or during normal activity, but some patients may also experience these attacks during or after exercise, including those who have coexisting fixed coronary artery stenosis.

Patients typically experience attacks of angina in **clusters, from midnight to early morning** (midnight - 8.00 am). Patients with the variant coronary syndrome may also experience **asymptomatic ischemic episodes**. If coronary artery spasm causes a prolonged disturbance of coronary blood flow, it can cause a **myocardial infarction**.

Syncope may also occur if there are disturbances of heart rhythm, such as asystole, atrioventricular block, or ventricular tachyarrhythmias. **Fatal arrhythmias** and **sudden cardiac death** can also occur.

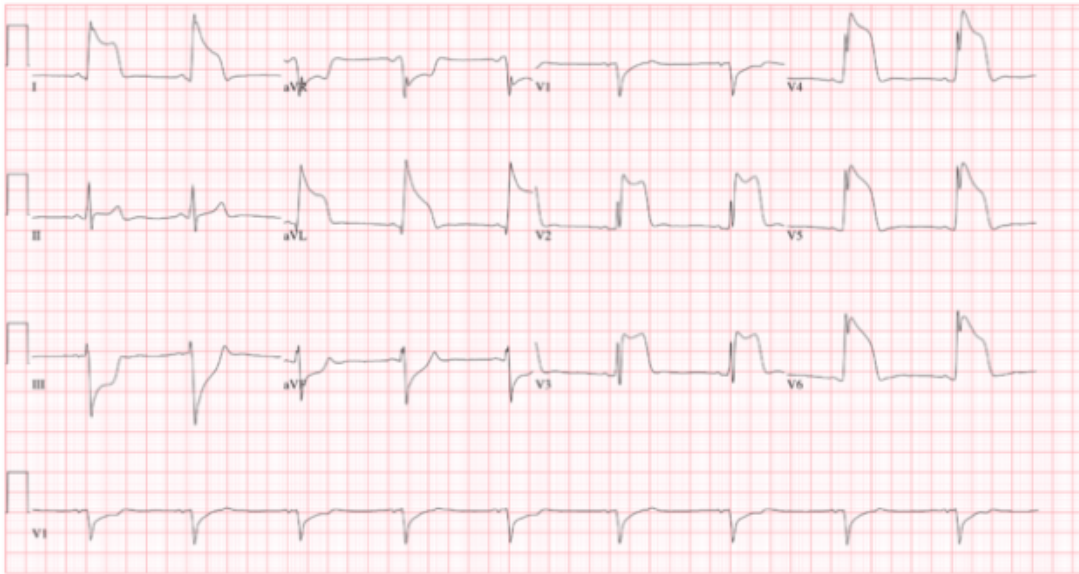
Symptoms include:

- Chest pain at rest
- Shortness of breath
- Palpitations

Diagnosis of vasospastic angina

Diagnosis can be confirmed by an ST-segment elevation (> 1 mm) on the **ECG** recorded immediately after or during chest pain. A 24-hour ambulatory ECG recording is performed

to identify any ECG changes in order to rule out angina pectoris. Holter monitoring for 24 hours can even detect any silent ischemic episodes occurring during the day.



[Image](#): ECG of a patient with Prinzmetal's angina. By Gogradgme, License: [CC BY-SA 3.0](#)

Electrocardiography is the **key to diagnosing vasospastic angina**. ECG changes demonstrate **transient ST-segment elevation** during episodes of chest pain, which elevation resolves when the pain settles. ST-segment elevation represents transmural myocardial ischemia and is accompanied by **reciprocal ST depressions**.

Other changes in ECG that may be detected include a **taller T wave**, a **taller and wider R wave**, and **loss of the S wave**. Occasionally, negative U waves may present in the same leads as the ST-segment elevation, after the ST elevation starts to resolve. In addition, arrhythmias may be detectable during an episode of variant angina, such as [ventricular tachycardia](#), atrioventricular block, and [bradyarrhythmia](#).

If silent episodes of coronary spasm or arrhythmias are suspected, **ambulatory electrocardiographic monitoring** with a Holter monitor should be utilized. This is also helpful for recording ECG changes during symptomatic episodes.

Serum cardiac enzymes are typically within normal limits, and coronary artery catheterization often reveals normal coronaries.

The gold standard for diagnosis - Induction of vasospasm during angiography:

Intracoronary or intravenous administration of ergonovine or intracoronary infusion of acetylcholine can be used to induce coronary spasm during angiography confirming vasospastic angina.

Intravenous ergonovine test: Non-invasive induction of vasospasm can be achieved by the administration of ergonovine intravenously with 12-lead ECG monitoring. ST-segment elevation and induction of angina confirm vasospastic angina.

Exercise testing

Exercise testing with ECG monitoring has variable results. Changes that can be detected in response to exercise include **ST elevation**, **ST depression**, or no change. ECG changes may point to fixed artery stenosis, coronary artery spasm, or an absence of

problems.

Coronary angiography

In many cases of variant angina, there is usually an absence of organically stenosed arteries detected on an angiography. However, some patients have coronary artery stenosis coexisting with coronary artery spasm.

Provocation testing can be used for the definitive diagnosis of the coronary variant syndrome. Coronary vasospasm can be provoked during an angiography by injecting acetylcholine and ergonovine into the coronary arteries.

Blood tests

With vasospastic angina, blood tests are generally negative for cardiac enzymes, including troponins and CK-MB.

Major Clinical Complications of Vasospastic Angina

In a few patients, variant angina may lead to complications, such as **severe ventricular tachyarrhythmias** or **bradyarrhythmias**, **sinus arrest**, or even **AV block** resulting from a severe ischemic episode following vasospasm. **Sudden cardiac arrest**, with or without syncope, can occur due to ischemia-induced ventricular fibrillation.

Atherosclerosis can also occur later at the site of vasospasm leading to **local coronary thrombosis**.

Differential Diagnosis of Vasospastic Angina

Most common clinical pictures similar to vasospastic angina

- **Angina pectoris** (stable angina is exercise-induced, demonstrates ST depression and fixed narrowing are usually present).
- **Myocardial infarction** (vasospastic angina can lead to myocardial infarction if prolonged – an acute myocardial infarction causes prolonged, more severe pain, with positive cardiac enzymes).
- **Pulmonary embolism** (pain is pleuritic in nature – worse on inspiration, associated with specific risk factors, no ST elevation).
- **Pericarditis** (pleuritic pain, improved on sitting up and leaning forward).

Other clinical pictures similar to vasospastic angina

- Anxiety disorders
- [Aortic dissection](#)
- Cocaine toxicity
- Coronary artery [atherosclerosis](#)
- Esophageal motility disorders
- Esophageal spasm
- [Gastroesophageal reflux disease \(GERD\)](#)
- Isolated coronary artery anomalies
- Panic disorder
- Unstable angina

Treatment and Management of Vasospastic Angina

Treatment of vasospastic angina

Patients identified to have variant coronary syndrome should be started on treatment **as early as possible**. This is very important in order to prevent complications such as myocardial infarction, serious arrhythmias, and cardiac death. In the acute setting, **nitrate** can be administered to relieve an attack of angina. In the long-term setting, patients who smoke are strongly advised to **stop smoking**.

The main drug used to treat variant coronary syndrome is a **calcium channel blocker** such as diltiazem. Calcium channel blockers are very effective in the prevention of ischemia. They may be given alone or together with isosorbide mononitrate, a **long-acting nitrate**. Beta-blockers are contraindicated as they reduce the dilatation of the smooth musculature by blocking the β_2 receptors and would, therefore, further increase the tone of the coronary vessels.

It has also been suggested that a **statin** can be given alongside a calcium channel blocker to suppress acetylcholine-induced coronary artery spasm. Statins achieve this effect by inhibiting the Rho-associated kinase pathway.

If a patient experiences arrhythmias secondary to the effects of coronary vasospasm, a **pacemaker or automatic defibrillator** may be needed.

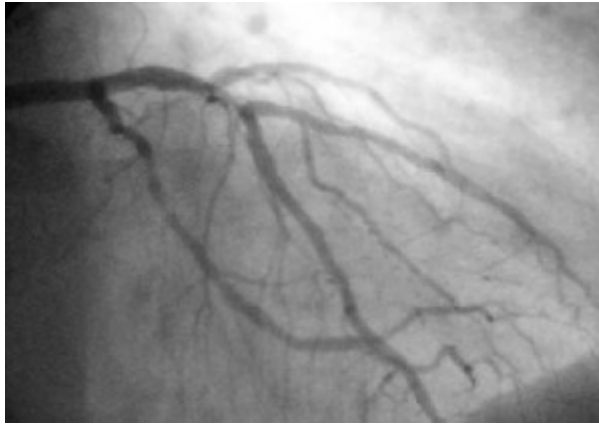
Medical treatment of vasospastic angina

- Commonly, nitrates (isosorbide mononitrate) and calcium channel blockers (Diltiazem) are prescribed for a patient with Prinzmetal angina. Beta-blockers are contraindicated.
- Use of antioxidants like vitamin C and E directly improves endothelial function and enhances the effect of vasodilators.

New drugs:

- Nicorandil: A K⁺ channel agonist can be added in recurrent cases.
- Fasudil is a novel drug that inhibits Rho-kinase, preventing acetylcholine-induced vasospasm.

Coronary intervention in vasospastic angina



- [Image](#): A Coronary Angiogram. By [Bleiglass](#), License: [CC BY-SA 3.0](#)

In refractory cases of variant angina, angioplasty with stenting may improve the condition.

- Complete cardiac denervation with plexectomy, with or without coronary artery bypass surgery, is an option for resistant cases; however, procedural risks are high and results have been inconsistent.

Lifestyle modification

A person should also:

- Eat a healthy balanced diet and exercise regularly
- Quit smoking and limit the use of alcohol
- Immediately report any change in the pattern or severity of chest pains to his or her healthcare provider.

Regular follow-up investigations include:

- Blood tests
- [ECG](#)

Cardiac stress tests or an ECG of the heart's function during exercise.

Progression and Prognosis of Vasospastic Angina

If the condition is controlled from early on, it can have a favorable prognosis. Complications such as acute myocardial infarction, coronary artery bypass grafting, and cardiac death, typically occur early after the onset of angina. Patients who have coronary spasm in multiple arteries are prone to fatal arrhythmias.

Survival rates for vasospastic angina are **over 90% at 5 and 10 years**. Individuals, who do not have coexisting coronary artery stenosis, generally have a more benign prognosis and better survival than those who have severely diseased arteries and coronary artery vasospasm.

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