# Angina Pectoris with a Normal Coronary Angiogram

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**Abstract**
Angina in the setting of a normal angiogram (NOCAD) occurs in 20–30% of patients undergoing coronary angiography. The etiologies of NOCAD can be anatomically classified into three groups: epicardial disease, coronary microvascular dysfunction, and noncoronary disease. Epicardial disease resulting in NOCAD includes endothelial dysfunction, coronary artery spasm, and coronary artery bridging. Microvascular dysfunction may be secondary to hypertension, cardiomyopathy, infiltrative disease, valvular disease, or idiopathic. Noncoronary artery disease states involving other organs systems such as the pulmonary, gastrointestinal, or musculoskeletal systems can also result in NOCAD. This review focuses on the coronary etiologies of NOCAD. The pathophysiology of disease is discussed as well as a systematic diagnostic strategy. Potential therapeutic options and prognosis are also reviewed.

**Key Words:** Angina · Normal angiogram · Endothelial dysfunction · Coronary spasm · Microvascular dysfunction

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## Angina pectoris bei normalem Koronarangiogramm

**Zusammenfassung**
Die Angina pectoris bei normalem Koronarangiogramm (NOCAD) ist bei 20–30% der Patienten festzustellen, die koronarangiographiert werden. Die Ätiologie dieser NOCAD kann anatomisch in drei Gruppen klassifiziert werden: epikardiale Erkrankungen, koronare mikrovaskuläre Erkrankungen und nichtkoronare Erkrankungen. Epikardiale Erkrankungen, die eine NOCAD verursachen können, müssen in endotheliale Dysfunktion, Koronararterienspasmen und Myokardbrücken unterschieden werden. Die mikrovaskuläre Dysfunktion kann als Folge einer arteriellen Hypertonie, einer Kardiomyopathie, einer infiltrativen Herzerkrankung, einer Herzklappenerkrankung oder idiopathisch auftreten. Grundsätzlich muss bei NOCAD eine Erkrankung anderer Organe ausgeschlossen werden. An erster Stelle stehen pulmonale und gastrointestinale Erkrankungen sowie Erkrankungen des muskuloskelettalen Systems. Diese Übersichtsarbeit konzentriert sich auf die Darstellung koronarer Ätiologien der NOCAD. Die Pathophysiologie der Erkrankung wird diskutiert und eine diagnostische Strategie vorgestellt. Mögliche therapeutische Optionen werden beschrieben, und die Prognose dieser Patienten wird dargestellt.

**Schlüsselwörter:** Angina pectoris · Normales Koronarogramm · Endotheliale Dysfunktion · Koronare Spasmen · Mikrovaskuläre Dysfunktion

## Introduction

Chest pain is one of the most common chief complaints encountered by physicians [1]. Although the etiology of chest pain can be diagnosed without the use of invasive testing in the majority of cases, some patients proceed to coronary angiography. Previous studies have shown that 20–30% of patients undergoing angiography for angina-like symptoms have nonobstructive coronary artery disease [2, 3]. Compared to those with obstructive coronary disease, these patients tend to be younger and are more likely to be female [4, 5]. Several conditions can result in angina in the setting of a normal coronary angiogram (NOCAD). This review focuses on the coronary etiologies of NOCAD. The pathophysiology of

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disease is discussed as well as a systematic diagnostic strategy. Potential therapeutic options and prognosis are also reviewed.

## Classification and Pathophysiology

As shown in Table 1, the etiologies of NOCAD can be anatomically classified into three groups: epicardial disease, coronary microvascular dysfunction, and noncoronary disease. Epicardial disease resulting in NOCAD includes endothelial dysfunction, coronary artery spasm, and coronary artery bridging. Microvascular dysfunction may be secondary to hypertension, cardiomyopathy, infiltrative disease, valvular disease, or idiopathic. Noncoronary artery disease states involving other organs systems such as the pulmonary, gastrointestinal, or musculoskeletal systems can also result in NOCAD.

**Table 1.** Anatomic classification of the etiologies of chest pain in the setting of a normal epicardial coronary angiogram.

**Tabelle 1.** Anatomische Klassifikation der Ätiologie des Brustschmerzes bei normalem Koronarangiogramm.

| |
|---|
| **Coronary etiology** |
| A. Epicardial disease |
| 1. Endothelial dysfunction |
| 2. Coronary spasm |
| 3. Coronary bridging |
| B. Microvascular dysfunction |
| 1. Secondary to hypertension |
| 2. Secondary to cardiomyopathy |
| 3. Secondary to infiltrative disease |
| 4. Secondary to valvular disease |
| 5. Idiopathic |
| **Noncoronary etiology** |
| A. Gastrointestinal |
| B. Pulmonary |
| C. Musculoskeletal |
| D. Psychological |

### Epicardial Disease

**Endothelial dysfunction.** The endothelium consists of a monolayer of endothelial cells that line the intima of blood vessels. It plays an important role in the regulation of vascular tone via the production and release of vasodilating and vasoconstricting factors. The most potent dilators are:

1. *Nitric oxide:* nitric oxide (NO) is a molecule with a short half-life and is derived from the oxidation of the *N*'-terminal of arginine [6]. The reaction is catalyzed by the enzyme endothelial nitric oxide synthase (eNOS), which is constitutively expressed in endothelial cells [6]. The expression of eNOS in endothelial cells can be upregulated by shear stress [7]. NO is a potent vasodilator whose effects are mediated by the secondary messenger cyclic 3'5'-guanosine monophosphate (cGMP) [8].
2. *Prostacyclin $I_2$:* prostacyclin $I_2$ ($PGI_2$) is a compound synthesized from arachidonic acid by the sequential actions of cyclooxygenase and prostacyclin synthase [9]. It causes vasodilation by increasing the production of cyclic 3'5'-adenosine monophosphate (cAMP) in platelets and smooth muscle cells [10].

The most potent vasoconstricting agents produced by the endothelium are:

1. *Endothelin-1:* three isoforms of endothelin exist, endothelin-1, endothelin-2, and endothelin-3 [11]. Endothelin-1 is the product of endothelial cells and is produced from the cleavage of a propeptide by endothelin-converting enzymes I and II [12–14]. Production of endothelin-1 is stimulated by epinephrine, angiotensin II, and vasopressin [12]. Vasoconstriction occurs when the compound binds to the ETA receptor located on smooth muscle cells [15, 16]. Another endothelin receptor, ETB, is located on endothelial cells and when stimulated increases the production of vasodilating factors such as NO and $PGI_2$ [15, 16].
2. *Thromboxane $A_2$:* thromboxane $A_2$ is a cyclooxygenase-derived compound that causes vasoconstriction. Its actions are mediated through the thromboxane receptor located on vascular smooth muscle cells [17].

The increase in coronary blood flow (CBF) in response to an increase in myocardial oxygen demand is dependent on healthy endothelium. Abnormalities in vasomotor tone and CBF can occur in the presence of endothelial dysfunction. Angina occurs if there is a mismatch between cardiac oxygen supply and demand.

Intracoronary acetylcholine can be used to assess endothelial function [18–20]. The direct response to acetylcholine is smooth muscle cell contraction and vasoconstriction. However, in patients with normal endothelial function this effect is counterbalanced by vasodilation due to the release of NO from the endothelium. According to our previous studies, endothelial dysfunction is defined as an increase in CBF ≤ 50% or an increase in epicardial coronary artery diameter ≤ 20% in response to acetylcholine [21, 22].

**Coronary artery spasm.** Prinzmetal et al. first described chest pain secondary to coronary artery spasm in 1959 [23]. Symptoms are similar to angina caused by coronary artery disease but tend to occur at rest and between midnight and 8 a.m. [24]. The episodes can last from 30 to 60 min and may be associated with ischemic

changes on the electrocardiogram [25]. The actual mechanism is not known, but most likely involves endothelial dysfunction as well as an increased response to vasoconstrictor agents such as catecholamines, endothelin, serotonin, arginine vasopressin, and thromboxane $A_2$ [25–28]. Increased autonomic tone may also play a role [29].

Since endothelial dysfunction is involved, provocative testing with intracoronary acetylcholine can be used to diagnose coronary spasm [26]. Unlike patients with diffuse endothelial dysfunction, patients with spasm tend to have focal vasoconstriction. Direct constricting agents such as ergonovine maleate, which stimulates α- and serotonin receptors, can also be used for provocative testing [30]. Although many patients will have some degree of vasoconstriction, spasm is defined as a > 50% reduction in luminal diameter that is reversed with intracoronary nitroglycerin [31].

**Myocardial bridging.** Myocardial bridging is the term used to describe systolic compression of a coronary artery by the myocardium. It was first described by Reyman in 1737 and occurs when a segment of artery is tunneled in the myocardium [32]. Its prevalence in autopsy studies ranges from 5% to 86%, but angiographic studies have shown a lower rate of 0.5–33% [33]. Although the left anterior descending artery is involved in the majority of cases, reports have shown that bridging can be present in any of the major epicardial arteries. Patients with myocardial bridging and otherwise normal epicardial coronary arteries can experience ischemic chest pain. The mechanism is not completely understood. Intravascular ultrasound studies have shown that there is some compression which extends into early diastole [34]. In addition, intracoronary flow wire studies have shown that bridging results in a much greater dependence on diastolic blood flow [34]. Although these changes may not be significant at rest, they can result in ischemia during tachycardia because of the shortened diastolic time period. Some studies have shown that myocardial bridging can also result in endothelial dysfunction and coronary spasm [33, 35]. Myocardial bridging can also result in a greater coronary artery wall shear rate which along with endothelial dysfunction and mechanical compression causes angina [35].

### Microvascular Dysfunction

The coronary artery tree can be divided into three components: the large conductance vessels, the intermediate-sized prearteriolar vessels, and the small arteriolar vessels. Various definitions have been given to the term "microcirculation", but for the purpose of this review the term refers to arteriolar vessels < 300 μm in diameter. Since approximately 80% of the coronary resistance is determined by the microcirculation, it plays a major role in the regulation of CBF. The microcirculation is tightly regulated by four control mechanisms (Figure 1):

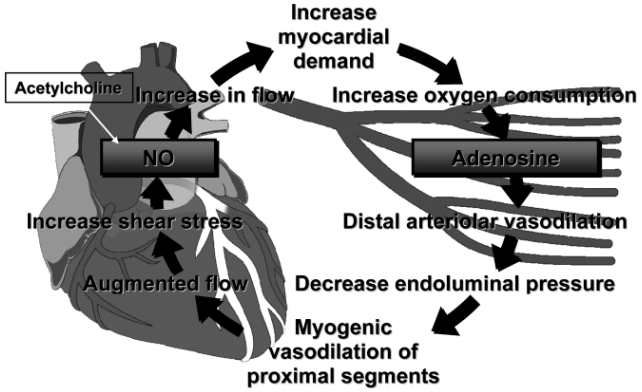


**Figure 1.** Normal regulation of coronary artery endothelial and microvascular function. NO: nitric oxide.

**Abbildung 1.** Regulationsschema der koronaren endothelialen und mikrovaskulären Funktion. NO: Stickstoffmonoxid.

1. *Myogenic control:* luminal pressure on the microcirculation from the surrounding myocardium produces an intrinsic vascular tone. An increase in luminal pressure results in vasoconstriction followed by an increase in coronary resistance and a decrease in CBF. The purpose of myogenic control is to maintain the intraluminal pressure within a physiological range to allow for the optimal transport of metabolic substrates across capillary membranes [36].
2. *Flow-mediated control:* CBF is self-regulating and an increase in CBF results in a reduction in microcirculatory vasomotor tone [37]. This occurs in order to maintain intracoronary pressure and to prevent shear stress-mediated injury. The mechanism is endothelium-dependent and most likely involves shear stress-mediated release of NO [38].
3. *Metabolic control:* since the main function of the microcirculation is to deliver oxygen and metabolic substrates, the metabolic state of the myocardium plays an important role in the regulation of microvascular blood flow. Oxygen consumption appears to be the major regulating factor and may involve mediators such as adenosine, prostacyclin, and carbon dioxide. Potassium and $K_{ATP}$ channels may also be involved [39, 40].

4. *Neurohormonal regulation:* neural regulation of CBF is made possible through sympathetic and parasympathetic innervation of the coronary circulation. Anatomic studies have shown that the microcirculation is more heavily innervated than the larger epicardial conductance vessels [41]. Neurotransmitters such as acetylcholine, norepinephrine, and neuropeptide Y help mediate the response [42].

Microvascular dysfunction can occur when the regulatory mechanisms do not function properly. In the presence of normal epicardial coronary arteries, a reduced coronary flow reserve (CFR) indicates microvascular dysfunction. CFR is the ratio of the average peak velocity (APV) during maximal hyperemia to the APV at baseline [43]. It can be measured invasively with a Doppler flow wire or noninvasively with transthoracic echocardiography. Patients with normal microvascular function should have a CFR > 2.5.

**Hypertension and microvascular dysfunction.** A substantial proportion of patients with hypertension experience chest pain in the setting of normal epicardial coronary arteries. A combination of increased myocardial oxygen demand and a decrease in oxygen delivery can result in myocardial ischemia. The decrease in oxygen delivery may be the result of microvascular dysfunction. Although the mechanism is not completely understood, it may involve an increase in microvascular resistance [44, 45]. This change in resistance could be due to increased myogenic tone caused by the elevated diastolic pressures and/or compression of the microcirculation by the hypertrophied myocardium. A previous study suggests that left ventricular hypertrophy plays an important role in microvascular dysfunction, since hypertensive patients without left ventricular hypertrophy did not appear to have an abnormal CFR [46].

**Cardiomyopathy and microvascular dysfunction.** Approximately 50% of patients with dilated cardiomyopathy can have NOCAD [47]. Studies have shown that these patients have microvascular dysfunction and a reduced CFR [48, 49]. The mechanism is not completely understood, but may be due to myogenic compression caused by the elevated filling pressures and/or microvascular endothelial dysfunction. Patients with hypertrophic cardiomyopathy can also have ischemic symptoms in the presence of normal coronary angiograms [50–52]. Several studies have demonstrated a reduced CFR in these patients [52–54]. The mechanism of microvascular dysfunction is not clear. Previously proposed mechanisms have included narrowing of intramyocardial small arteries and compression of the microcirculation [55–58]. An alternative mechanism for the reduction in CFR may be that the microcirculation is already near maximal dilation in the basal state and is therefore limited in its ability to further dilate and compensate for the increase in myocardial demand [59].

**Infiltrative disease and microvascular dysfunction.** Patients with cardiac amyloidosis can experience angina in the setting of normal epicardial coronary arteries [60]. Several autopsy studies have shown that amyloid deposits in the microcirculation result in a narrowing of the lumen [60–65]. These deposits appear to be located in the tunica media [61]. The resulting ischemia from the microvascular dysfunction may be one of the factors responsible for the sudden cardiac death that occurs in these patients.

**Valvular disease and microvascular dysfunction.** Some patients with valvular heart disease can have angina in the setting of normal epicardial coronary arteries. The specific disorders associated with this are aortic stenosis, aortic regurgitation, and mitral regurgitation [66–69]. Several studies have shown that these types of valvular lesions are associated with a reduction in CFR [69–72]. The mechanisms may involve an increase in oxygen demand as a result of the increase in wall stress caused by the valvular disease. In addition, the increase in left ventricular diastolic pressures may increase myogenic tone and result in compression of the microcirculation. It appears that the microcirculation dysfunction improves after mitral and aortic valve replacement or repair [69, 73, 74].

**Idiopathic microvascular dysfunction.** Patients with microvascular dysfunction not secondary to another disease are said to have idiopathic microvascular dysfunction. The term *syndrome X* has been used to describe these patients; however, it is not specific and does not define the mechanism. Proposed mechanisms of microvascular dysfunction have included primary smooth muscle cell dysfunction resulting in an impaired response to vasodilatory stimuli and microvascular endothelial dysfunction [75–77]. Enhanced sodium-hydrogen transport activity may also play a role [78]. Increased activity of this ion channel produces a greater concentration of intracellular calcium, which may in turn result in vasoconstriction of the microvascular vessels.

### Noncoronary Etiologies

Previous studies have shown that approximately 42% of patients with NOCAD have a noncoronary etiology

[79]. As shown in Table 1, noncoronary etiologies can be classified by the organ system involved. Although it is beyond the scope of this review to discuss these etiologies, clinicians should be aware of them when assessing patients with NOCAD.

### Diagnosis in the Cardiac Catheterization Laboratory

Determination of the etiology of angina in the setting of normal epicardial coronary arteries is essential for management and prognosis. Since the majority of these patients will undergo coronary angiography, the diagnostic strategy should include the use of invasive coronary hemodynamics to determine endothelial and microvascular function. This so-called functional angiogram (Figure 2) is routinely used at our institution to assess patients with NOCAD.

#### Mayo Protocol

After coronary angiography, a guiding catheter is placed into the left main coronary artery. A 0.014-inch Doppler guide wire is placed within a 2.2-F coronary infusion catheter and the system is advanced through the guiding catheter into the middle portion of the left anterior descending coronary artery [21, 22]. The Doppler wire is then positioned 2–3 mm distal to the tip of the infusion catheter, and a baseline APV is obtained. Coronary artery diameter is measured 5 mm distal to the tip of the Doppler wire and baseline CBF is calculated with the following equation:

$$CBF = \pi\ (coronary\ artery\ diameter/2)^2 \times (APV/2).$$

Microvascular function is assessed with the use of an intracoronary adenosine (18–42 µg) bolus. CFR is calculated as the ratio of the APV during maximal hyperemia to the APV at baseline. We define a normal CFR as > 2.5. Endothelial function is then assessed with the use of acetylcholine. Intracoronary acetylcholine is infused through the infusion catheter at three different doses: $10^{-6}$, $10^{-5}$, and $10^{-4}$ M for 3 min each followed by 200 µg of intracoronary nitroglycerin. APV and coronary diameter are measured before and after each infusion. Based on our prior studies, an abnormal response to acetylcholine is an increase in CBF ≤ 50% or an increase in epicardial coronary artery diameter ≤ 20% [21, 22].

#### Interpretation of Results

The diagnostic angiogram is carefully reviewed to ensure no significant epicardial stenosis or myocardial bridging is present. As shown in Table 2, patients can be classified into one of four groups based on the results of the invasive functional study. Patients with normal CFR and an abnormal acetylcholine response have endothelial dysfunction. If there is a > 20% reduction in coronary artery diameter during acetylcholine infusion, coronary spasm can be diagnosed. Those with normal acetylcholine responses and abnormal CFR have non-endothelial-dependent microvascular dysfunction. These patients should also undergo echocardiography to help determine the etiology of their microvascular dysfunction. An abnormal acetylcholine response and CFR indicate both endothelial and microvascular dysfunction. Finally, patients with normal angiograms and no evidence of microvascular or endothelial dysfunction have a noncoronary etiology of angina. These patients should be evaluated for other etiologies of chest pain such as gastrointestinal, pulmonary, or musculoskeletal disease.

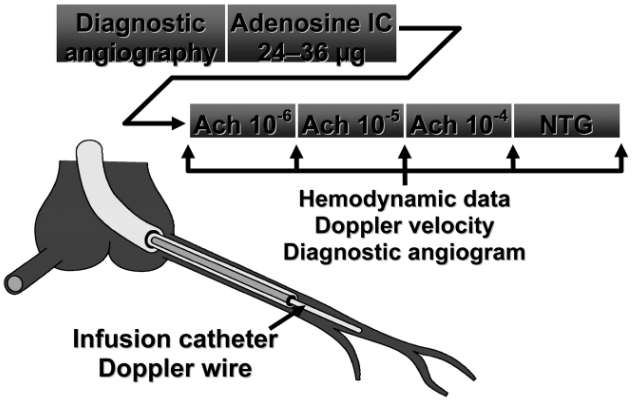


**Figure 2.** Functional angiogram protocol to assess coronary endothelial and microvascular function. Ach: acetylcholine; IC: intracoronary; NTG: nitroglycerin.

**Abbildung 2.** Testprotokoll für die Erfassung der koronaren endothelialen und mikrovaskulären Dysfunktion. Ach: Acetylcholin; IC: intrakoronar; NTG: Nitroglycerin.

**Table 2.** Interpretation of results from a functional angiogram.

**Tabelle 2.** Interpretationen von Ergebnissen der funktionellen Angiographie.

| Diagnosis | Response to acetylcholine[a] | Response to adenosine[b] |
|---|---|---|
| Endothelial dysfunction | Abnormal | Normal |
| Microvascular dysfunction | Normal | Abnormal |
| Endothelial and microvascular dysfunction | Abnormal | Abnormal |
| Normal functional angiogram | Normal | Normal |

[a] A normal response to acetylcholine infusion is an increase in coronary blood flow by > 50% and an increase in coronary artery diameter > 20%

[b] A normal response to adenosine is a coronary flow reserve > 2.5

## Treatment

### Endothelial Dysfunction

Endothelial dysfunction is potentially reversible if the proper therapy is initiated. The first step in treating these patients is lifestyle modification. Previous studies have shown improvements in endothelial function with physical exercise and smoking cessation [80, 81]. Risk factor modification with cholesterol-lowering agents is also important. Evidence exists suggesting that the benefits of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors extend beyond their ability to lower cholesterol. These agents may improve endothelial function through their antioxidant and anti-inflammatory properties [82]. In addition, statins may be able to restore vascular NO bioavailability [82].

Blood pressure management is also essential in the treatment of endothelial dysfunction. Angiotensin-converting enzyme (ACE) inhibitors have been shown to improve coronary and systemic endothelial function [83–86]. The mechanism appears to involve their ability to inhibit angiotensin II production and inhibition of the degradation of bradykinin [87]. Nifedipine also improves endothelial function through mechanisms that are independent of its blood pressure effects [88]. Other therapies which have been shown to improve endothelial function included L-arginine, folic acid, and estrogen replacement therapy in postmenopausal women [89–91]. Initial studies with peroxisome proliferator-activated receptor-γ agonists such as rosiglitazone have shown that these agents have beneficial effects on endothelial function [92, 93].

### Coronary Spasm

Nondihydropyridine calcium channel blockers and long-acting nitrates are the first-line therapy for coronary spasm [94]. Additional therapy with nifedipine and α-blocking agents can also be used [95, 96]. Therapy with nonselective β-blocking agents such as propranolol should be avoided because of their potential to exacerbate spasm [97]. Aspirin should also be used with caution, since it inhibits production of the vasodilator prostacyclin [98]. Coronary artery stenting has been reported to be of benefit in patients that are refractory to medical therapy [99]. Finally, since coronary spasm involves endothelial dysfunction, the therapies used to treat endothelial dysfunction should be considered.

### Myocardial Bridging

Patients with angina secondary to myocardial bridging should be treated with β-blockers. These agents have been shown to improve CBF by increasing the amount of time in diastole and reducing the amount of myocardial bridging [100]. Patients who do not improve with medical therapy can be treated with more invasive strategies such as coronary artery stenting, surgical myotomy, and coronary artery bypass surgery [101–103]. If stent placement is considered, patients should be informed of the high risk of restenosis in the bridging segment [104].

### Microvascular Dysfunction

Therapy for microvascular dysfunction focuses on treatment of the underlying etiology. Patients with microvascular dysfunction secondary to hypertension benefit from blood pressure control. Those with cardiomyopathy may improve with treatment for heart failure. These therapies reduce left ventricular filling pressures and wall stress, which in turn improve microvascular function. Valvular replacement or repair has been shown to improve endothelial function in patients with valvular disease [69, 73, 74]. It is currently unknown if myectomy or septal ablation improves microvascular function in patients with hypertrophic obstructive cardiomyopathy. Microvascular dysfunction secondary to infiltrative disease is a difficult issue and no current therapies are available.

Numerous therapies have been investigated for the treatment of patients with idiopathic microvascular dysfunction. Since this group consists of a heterogeneous population of patients, it is difficult to determine the efficacy of these therapies. β-blockade appears to reduce angina symptoms, but no large randomized studies have been performed. Treatment with ACE inhibitors and HMG-CoA reductase inhibitors also results in some benefit [76, 105]. Imipramine, a tricyclic antidepressant, has been shown to reduce anginal pain in patients with idiopathic microvascular dysfunction [106]. The mechanism is not completely understood, but may involve inhibition of pain-modulating neurons by blockade of norepinephrine reuptake [107].

## Prognosis

### Endothelial Dysfunction

Endothelial dysfunction is felt to represent the early stages of coronary atherosclerosis and has been shown to be associated with an increase in cardiac events such as myocardial infarction, revascularization, and cardiac death [108]. The mechanism may involve ischemia and accelerated atherosclerosis.

### Coronary Artery Spasm

In general, patients with coronary spasm who are treated have a good prognosis. There is an initial active phase during the first 6 months when patients experience frequent angina and are at increased risk of adverse cardiac events. Long-term studies have shown that the 5-year survival in these patients is excellent and with the exception of the initial active phase there is no increased risk for cardiac events [109, 110].

### Myocardial Bridging

Several studies have shown that patients with myocardial bridging have a good long-term prognosis [111–113]. These studies showed no increased risk of cardiac events and a normal survival rate. Pediatric patients with hypertrophic obstructive cardiac myopathy and myocardial bridging, however, may have an increased risk of death and cardiac events [114]. A study in adult patients with hypertrophic obstructive cardiomyopathy and myocardial bridging showed no increased risk of adverse cardiac events or death [115].

### Microvascular Dysfunction

The long-term prognosis of patients with microvascular dysfunction, but otherwise normal coronary arteries is not known. A possible explanation for the lack of data is the ability to assess microvascular function has not been available until recently. Microvascular dysfunction may interact with other underlying diseases. For example, a study of patients with hypertrophic cardiomyopathy showed that the presence of microvascular dysfunction results in an increase in adverse clinical events [116].

## Conclusion

20–30% of patients undergoing coronary angiography for angina will have normal epicardial arteries. The etiology of angina in these patients is diverse and can be diagnosed with a functional angiogram. This procedure evaluates coronary endothelial and microvascular function. A proper diagnosis will help guide the treatment and prognosis of these patients.

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