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Non-Acute Coronary Syndrome Anginal Chest Pain

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Abstract

Anginal chest pain is one of the most common complaints in the outpatient setting. While much of the focus has been on identifying obstructive atherosclerotic coronary artery disease (CAD) as the cause of anginal chest pain, it is clear that microvascular coronary dysfunction (MCD) can also cause anginal chest pain as a manifestation of ischemic heart disease (IHD), and carries an increased cardiovascular risk. Epicardial coronary vasospasm, aortic stenosis, left ventricular hypertrophy, congenital coronary anomalies, mitral valve prolapse and abnormal cardiac nociception can also present as angina of cardiac origin. For non-acute coronary syndrome (ACS) stable chest pain, exercise treadmill testing (ETT) remains the primary tool for diagnosis of ischemia and cardiac risk stratification; however, in certain subsets of patients, such as women, ETT has a lower sensitivity and specificity for identifying obstructive CAD. When combined with an imaging modality, such as nuclear perfusion or echocardiography testing, the sensitivity and specificity of stress testing for detection of obstructive CAD improves significantly. Advancements in stress cardiac magnetic resonance imaging (MRI) enables detection of perfusion abnormalities in a specific coronary artery territory, as well as subendocardial ischemia associated with MCD. Coronary computed tomography angiography (CCTA) enables visual assessment of obstructive CAD, albeit with a higher radiation dose. Invasive coronary angiography (CA) remains the gold standard for diagnosis and treatment of obstructive lesions that cause medically refractory stable angina. Furthermore, in patients with normal coronary angiograms, the addition of coronary reactivity testing (CRT) can help diagnose endothelial dependent and independent microvascular dysfunction. Life-style modification and pharmacologic intervention remains the cornerstone of therapy to reduce morbidity and mortality in patients with stable angina. This review focuses on the pathophysiology, diagnosis, and treatment of stable, non-ACS anginal chest pain.

Keywords

chronic stable angina; chest pain; stress testing; atherosclerosis; microvascular angina

Introduction

Anginal chest pain is the most common complaint encountered by family physicians, internists, and emergency room physicians. Patients with escalating chest pain symptoms,

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electrocardiographic (ECG) abnormalities consistent with acute myocardial ischemia or infarction, and/or hemodynamic instability suggestive of an acute coronary syndrome (ACS), that includes unstable angina (UA), ST elevation (STEMI), and non-ST elevation myocardial infarction (NSTEMI), should be triaged to the emergency department. Non-ACS anginal chest pain, termed chronic stable angina (CSA), can also have devastating consequences; therefore, a considerable amount of time and resources is appropriately spent in risk stratifying the patient who complains of chest pain in an office-based setting. The challenge for the clinician is to determine cardiac from non-cardiac chest pain, and use a systematic approach for testing and therapy based on patient risk factors and characteristics. This review will focus on our current understanding of non-ACS anginal chest pain, its pathophysiology, diagnostic modalities, and treatment.

Pathophysiology

The reduction in coronary blood flow (CBF) leads to a decline in oxygen supply, resulting in development of an ACS. Similarly, a chronic limited ability to increase oxygen supply to the myocardium in the setting of increased oxygen demand results in CSA¹. Since myocytes already extract about 75% of the oxygen in coronary blood at rest, a higher demand is primarily met by increasing CBF²⁻³. Myocardial ischemia results from hypoxia which disrupts oxidative metabolic pathways; cellular anaerobic pathways are activated and mediators such as lactate are produced, which results in the sensation of pain⁴.

Coronary Atherosclerosis and Obstructive Coronary Artery Disease

In the largest diameter epicardial coronary vessels, CBF is primarily limited due to obstructive atherosclerotic coronary artery disease (CAD). Originally thought to be dominantly a lipid storage disease, our current understanding of the pathogenesis of atherosclerosis implicates endothelial injury and inflammation⁵⁻⁹. Inflammation-induced atherosclerosis does not occur linearly¹⁰. Instead, bursts of atherosclerotic plaque progression occur and are triggered by physical disruption to endothelial cells, hemorrhage into the plaque, clot formation, and vascular remodeling. Studies of vessels at autopsy show that as atheromatous plaques continue to increase, deposition occurs principally within the vascular wall, with compensatory enlargement of the external vessel¹¹. This permits maintenance of the lumen size. Once this compensatory mechanism is exhausted, the plaque begins to bulge into the lumen, causing obstruction to CBF during periods of increased oxygen demand^{1, 6, 11}. As a result, atherosclerosis produces symptomatic chest pain relatively later in its course of development.

While elevated low density lipoprotein (LDL) cholesterol still remains a major contributor to atherosclerosis and adverse ischemic heart disease (IHD) events, effective therapies which target LDL reduce coronary events by only 33% over a five-year treatment period⁶. This observation has led to the conclusion that additional chemical and mechanical insults also trigger endothelial injury, including altered shear stress, high oxidative stress, smoking, and insulin resistance⁸⁻⁹.

Microvascular Coronary Dysfunction

Myocardial ischemia can produce anginal chest pain without angiographically obstructive CAD, often due to microvascular coronary dysfunction (MCD). A relatively common occurrence of MCD appears to be in women who present with evidence of myocardial ischemia, identified by a myocardial infarction (MI) or abnormal stress testing in the absence of obstructive CAD. Autopsy reports in patients with normal angiograms and angina have revealed myointimal proliferation, endothelial degeneration, and lipid deposits in the microvasculature¹². Multiple angiographic studies have demonstrated abnormal endothelium-dependent function in subjects with angina, evidence of ischemia, and no obstructive CAD

13–15. Patients with angina and MCD have elevated levels of serum inflammatory markers, such as C-reactive protein, suggesting an underlying inflammatory process as well.¹⁶ There is a significant peri- and post-menopausal female predominance in this condition, leading to a suspected pathogenic role of estrogen deficiency¹⁷; however, this remains controversial.

Coronary Artery Spasm

Additional etiologies of anginal chest pain to consider include coronary artery vasospasm (CAS),¹⁸ also known as Prinzmetal's angina,^{19–21} which involves epicardial coronary vasoconstriction secondary to smooth muscle dysregulation, and may lead to transient reduction in myocardial oxygen supply. Again, inflammation is thought to initiate damage as patients with CAS tend to have higher levels of circulating leukocytes, C-reactive protein (CRP), and interleukin-6 (IL-6), as compared to control populations^{22–23}. Inflammatory mediators promote smooth muscle cell (SMC) migration into the intima. Endothelial damage exposes SMC to agents that cause vasoconstriction²⁴. Of note, intimal thickening in CAS patients is not a localized phenomenon, as intravascular ultrasound images and angiography have shown diffuse intimal thickening in patients with spasm²⁵.

Aortic Stenosis and Left Ventricular Hypertrophy

Aortic stenosis (AS) can indirectly impact CBF in normal arteries and produce CSA in 30–40% of patients^{25–26}. Physiologic hypertrophy of cardiac myocytes occurs to generate enough force to maintain cardiac output against the restricted valvular diameter^{26–27}. Because patients may develop severe AS and not manifest symptoms, it is difficult to associate a degree of hypertrophy to development of anginal chest pain. Pressure overload resulting in compensatory left ventricular hypertrophy (LVH) results in impaired diastolic relaxation, increased end-diastolic pressure, and reduced gradient driven CBF, especially to the subendocardium²⁸. CBF is further compromised due to tachycardia-induced decreased diastolic filling times and decreased capillary density in hypertrophied myocardium^{29–30}. Impaired flow leads to ischemia, necrosis and fibrosis primarily in the subendocardial layer²⁷. Weidemann et al. reported severe myocardial fibrosis in this layer and observed an association with reduced stroke volume in these patients³¹, which further exacerbates reductions in CBF.

Congenital Coronary Anomalies

Congenital coronary anomalies such as pre-capillary fistulas, myocardial bridging, where coronary arteries are embedded in contractile myocardial tissue, and most commonly, aberrant origins of coronary vessels (e.g. ectopic origin of the right coronary artery, or the left coronary artery originating from the right coronary ostia and vice-versa) can lead to angina³². Often not discovered well into adulthood, it has been speculated that coronary anomalies produce symptoms by local compression and cessation of distal flow or even CAS^{33–34}. Chest pain may occur due to left-to-right shunting and/or a coronary steal phenomenon, which supplies the myocardium with poorly oxygenated blood at low perfusion pressures³⁴. Presentation can range from reproducible typical angina, sudden death, cardiomyopathy, or lethal arrhythmias³².

Mitral Valve Prolapse

Mitral valve prolapse (MVP) has a population incidence of 1%, with 11–15% of those patients exhibiting symptoms of chest pain and dyspnea³⁵. The pathophysiologic mechanisms behind chest pain in MVP have proven to be elusive. Vavuranakis et al. conducted left ventricular hemodynamic studies in patients with MVP and control subjects, and found little differences between the two groups³⁶. One study compared panic disorders to MVP and found many similarities in the nature and frequency of the pain, which suggests that a component of the

pain may be related to panic disorders³⁷. MVP is currently not considered a diagnostic etiology for anginal chest pain.

Abnormal Cardiac Nociception

Patients can have a heightened perception of cardiac pain due to abnormalities in cardiac neural nociception pathways. This has been documented when anginal chest pain was reproduced during right heart stimulation with intra-cardiac infusion of saline^{38–40}. In one study, the perception of pain occurred in the absence of ECG changes or evidence of left ventricular (LV) dysfunction, suggesting a non-ischemic etiology of pain⁴⁰. Other studies even suggest altered central nervous system processing in these patients^{41–42}. Because the atria and ventricles have dense sensory innervations, heightened sensitivity of chemical and mechanical receptors may be leading to the false sensation of ischemia⁴⁰. This abnormality in cardiac nociception may require medications to treat neuropathic pain (such as imipramine).

Diagnosis

Diagnosis of cardiac chest pain relies on history and physical, patient characteristics, and identification of coronary heart disease (CHD) risk factors⁴³. Using age, sex, and characteristics of pain the pre-test probability of having obstructive CAD can be determined (Table 1)⁴³. If there is a low pre-test probability of having CAD (<10–20%), further work up should focus on non-coronary causes of pain. The intermediate risk group benefits the most from noninvasive testing, while further work-up in high probability patients should place more focus on prognostication instead of diagnosis, since CAD is likely based on history and risk factors (Figure 1)^{43–44}. High risk patients benefit more from coronary angiography rather than non-invasive testing first^{43, 45–49}. However, it should be noted that regardless of the patient's pre-test probability of CAD, further testing is not recommended if life expectancy is limited⁴⁸.

Electrocardiogram

The electrocardiogram (ECG) remains the most convenient, albeit a relatively insensitive method of diagnosing myocardial ischemia. It is most useful when compared to a prior ECG when the patient was asymptomatic. A resting ECG may be normal in 50% of patients with CSA⁵⁰; however, certain ECG patterns are suggestive of ischemia or an increased likelihood of morbidity and mortality from IHD. In both men and women, LVH as determined by ECG is associated with the development of CHD,^{51–52} and serves as a strong, independent prognostic marker in patients with angina⁵². In a 30-year follow-up of the Framingham study, Kannel and colleagues also found that non-specific ST-T wave abnormalities were associated with a two-fold increase in the risk for IHD morbidity and mortality in both men and women⁵³.

DeBacquer et al. further separated ECG findings into major and minor ECG criteria. They found that severe/moderate ST depression, deep or moderate T wave inversions, complete or 2nd degree atrio-ventricular (AV) block, complete right and left bundle branch block (RBBB and LBBB), frequent premature beats and atrial fibrillation and flutter on ECG were highly predictive of all cause mortality⁵⁴. ST-T wave changes are non-specific, but in the setting of anginal chest pain may indicate ischemia. In addition, if ST-T wave changes occur at rest, this suggests the presence of significant obstructive CAD and/or an ACS⁴⁸. Similarly, conduction defects are nonspecific, but may indicate multivessel disease.

Stress Testing

Stress testing is most often utilized to diagnose ischemia and to detect the amount of myocardium at risk. The main contraindications to stress testing include, acute MI within two

days of stress testing, symptomatic cardiac arrhythmia, severe aortic stenosis, and/or decompensated heart failure⁴⁷. Without contraindications the choice of stress test is dictated by prior cardiac history, baseline ECG, ability to exercise, as well as local expertise and availability

Exercise Treadmill Testing

Exercise treadmill testing (ETT) is the recommended initial non-invasive test for risk stratification and diagnosis of CAD in intermediate probability patients who are able to exercise and have no abnormalities on resting ECG⁴⁷. ETT is widely available at a low cost⁵⁵, and is useful because of its convenience and relative accuracy. The presence of LBBB, LVH, paced rhythm, intraventricular conduction delay, digoxin use, and Wolf-Parkinson's White (WPW) on ECG^{47, 49} render an ETT non-diagnostic for ischemia detection. A cardiac imaging study typically is added to the ETT in these patients to enhance diagnostic sensitivity and specificity for detection of obstructive CAD.

ETT alone has a moderate sensitivity and specificity for obstructive CAD. A normal test may not exclude ischemia^{48, 56}, particularly in low risk populations, such as women⁴⁷. Sex-related hormonal and anatomical differences between men and women may contribute to this difference, as well as the presence of MCD, which can cause ischemia in the absence of obstructive CAD^{55, 57}. Even after using a modified ETT protocol to account for some of the gender differences, the test remains of moderate diagnostic value in this sub-group⁵⁷. Therefore, intermediate-risk female patients may be better suited to receive an imaging study^{55–56}.

Stress Imaging

When imaging is added to ETT, via myocardial perfusion studies (MPS) or stress echocardiogram (SE), sensitivity is improved⁴⁹. Imaging is preferred in patients with a history of prior revascularization as this allows localization of the myocardial ischemia⁴⁷. Both imaging studies are superior to ETT due to their ability to quantify and localize ischemia, offer diagnostic data in patients with resting ECG abnormalities, and in patients who cannot exercise. The two imaging modalities are comparable, and usage is primarily dependent on availability and local expertise; however, imaging studies are more expensive than ETT and less readily available⁴⁹.

Stress Echocardiography

SE remains an easily available, widely used method to determine left ventricular (LV) wall motion and valvular abnormalities. The addition of advanced echocardiographic techniques such as tissue doppler and strain imaging allows for assessment of diastolic function. It is limited by patient characteristics (obesity, COPD) which limit image quality. This occurs in 5–10% of patients⁴⁹, and is often technician dependent. SE has a higher specificity but is less sensitive compared to MPS for detecting ischemia⁴⁹.

Stress Myocardial Perfusion Study

A stress MPS with nuclear imaging identifies focal regions of hypoperfusion in the myocardium. It is especially preferred in women, obese patients, and patients with LBBB. However, MPS does expose patients to a moderate amount of ionizing radiation^{47, 49, 56}.

Modalities of Stress

Both SE and MPS can be utilized with exercise or pharmacologic agents as a cardiac stressor; and both methods are equally accurate and safe in the diagnoses of ischemia⁵⁸. If a patient is able to reach 85–90% of their predicted maximal heart rate with exercise, this form of stress

is preferred as it provides information regarding patient's functional capacity. If unable to exercise, a pharmacologic agent is preferred. Two main categories of pharmacologic stress are utilized: coronary vasodilators (adenosine and dipyridamole) and positive inotropic agents (dobutamine). Vasodilators dilate coronary arteries directly to increase flow. Inotropic agents indirectly increase coronary flow by increasing myocardial work load and oxygen requirements, mimicking the effects of physical exercise.

Coronary Vasodilators

Pharmacological vasodilators provide the largest increase in CBF⁵⁹. With adenosine, this effect is short lived. Dipyridamole inhibits adenosine metabolism, therefore the vasodilatory effect lasts longer. Adenosine can cause AV block, which is rare with dipyridamole because inhibition of adenosine metabolism doesn't produce a sufficient enough concentration to induce AV block. Secondly, adenosine is known to induce bronchospasm in asthmatics. Dipyridamole, instead, is safe in patients with reactive airways producing no evidence of wheezing^{47, 49, 58}.

Positive Inotropic Agents

Dobutamine is the preferred positive inotropic agent for patients who have had recent respiratory failure or bronchospasm^{47, 49, 58}. It accelerates conduction through the sino-atrial (SA) and AV nodes⁵⁸ and is, therefore, contraindicated in patients with supraventricular and ventricular tachycardias⁴⁷. Further, dobutamine promotes myocardial ectopy, and is unsafe in acute post-MI patients⁶⁰⁻⁶¹.

Advanced Cardiac Imaging

Advanced cardiac imaging allows assessment not only of obstructive and non-obstructive CAD, but also of plaque composition, subendocardial myocardial perfusion, coronary flow reserve, myocardial metabolism, and left ventricular function. Cardiac magnetic resonance imaging (CMRI), positron emission tomography (PET), and coronary computed tomography angiography (CCTA), have transformed clinical cardiology. Even single photon emission computed tomography (SPECT) has evolved with improved resolution cameras and more sensitive tracers. The clinician's challenge is determining which test is appropriate for an individual patient and whether advanced imaging adds further to risk stratify the patient.

Cardiac Magnetic Resonance Imaging

Stress CMRI is done with a vasodilatory pharmacologic agent, usually adenosine, and provides comprehensive assessment of myocardial function, perfusion, and provides structural details. In addition to very high spatial and temporal resolution images, CMRI can detect and quantify areas of necrosis and scar tissue, quantify perfusion deficits at the level of the subendocardium (Figure 2), define structural abnormalities and evaluate ventricular function⁶². Patterns of enhancement can identify myocarditis, significant epicardial coronary disease, and/or subendocardial ischemia secondary to MCD, which may be missed by other stress tests. The test does not expose the patient to ionizing radiation⁶³. CMRI is limited in patients with metallic hardware such as pacemakers, and has long acquisition times which lead to patient discomfort and claustrophobia^{47, 49, 56, 62-63}.

Positron Emission Tomography

PET imaging utilizes glucose metabolism to assess myocardial viability. High sensitivity and contrast resolution accurately detect ischemia and confer a high predictive value for future cardiac events⁶⁴. PET scans also have improved sensitivity in detecting multi-vessel disease⁶⁵, preventing balanced ischemia from going undetected. New radiotracers are being developed which target inflammation identifying sites of active atherosclerotic plaques⁶⁵,

which are more likely to rupture or progress. In theory, a high accuracy can eliminate unnecessary and costly interventions, and balance the high cost of the imaging test itself⁶⁴. Unfortunately, no randomized controlled trials (RCT) have been performed for PET imaging compared to traditional diagnostic techniques and therefore no formal recommendation can be made.

Computed Tomography

Coronary artery calcification can be determined by computed tomography (CT). Newer multidetector CT scans can often visualize the coronary artery lumen and characterize plaque in many subjects. Meta analysis has shown that patients with an increased coronary calcium score (CCS) are at a higher risk for CAD⁶⁶. Calcium deposition increases with age and with progression of atherosclerotic lesions; however, the two are not directly correlated. Lesions with significant calcifications may not show signs of critical stenosis and vice versa⁶⁷. It has not been established whether treating an asymptomatic patient with a positive CCS confers any benefit, therefore, more research is needed before further recommendations are made^{47, 49}. CCTA can also be used to assess patency of coronary artery bypass grafts (CABG), coronary artery anomalies and coronary fistulas⁶⁸. It may have a role in evaluating chest pain in patients with an atypical presentation, equivocal ETT, and in premenopausal women⁶⁹.

Coronary Angiography

While non-invasive imaging and stress testing aid in the diagnosis and assessment of IHD, the gold standard for definitive diagnosis of CAD remains invasive coronary angiography (CA)⁴⁷. CA allows visualization of the site and severity of a coronary lesion. Routine use of CA without prior noninvasive testing is not recommended unless a patient has a high pre-test probability of CAD, absolute contraindications to stress testing, or medically refractory angina. High cost, associated morbidity and mortality due to the procedure, as well as the inability to identify which plaques are liable to future rupture make CA a poor initial test in the diagnosis of CSA⁵⁶.

Coronary Reactivity Testing

Coronary reactivity testing (CRT) can be used to diagnose MCD in patients with persistent chest symptoms, evidence of myocardial ischemia, and non-obstructive coronaries⁷⁰. The test involves passing a doppler flow wire into the coronary artery and injecting vasoactive agents (nitroglycerin, acetylcholine, and adenosine) and measuring the resultant change in the velocity of blood flow⁷¹. The test helps to differentiate between endothelial-dependent and -independent MCD.

Treatment

Management of CSA is geared toward symptom reduction and prevention of adverse events such as acute MI, cardiac death and revascularization procedures. Data from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial show that a non-invasive approach of optimizing medical therapy and aggressive risk factor management in patients with CSA is as beneficial as percutaneous coronary intervention (PCI)⁷²⁻⁷³ and is recommended by the American College of Cardiology (ACC) and the American Heart Association (AHA)^{47, 74}.

Medical Therapies to Reduce Adverse Cardiovascular Events

Anti-platelet medications act to prevent coronary thrombosis. Low dose aspirin (75–150mg/day) has a favorable risk to benefit ratio and is cost-effective, making it an ideal agent⁷⁴. Higher doses of aspirin do not appear to confer any additional anti-thrombotic benefits⁷⁵. Instead,

higher doses increase the risk of gastrointestinal (GI) side effects. For patients who are intolerant to aspirin, clopidogrel is an equally to slightly more efficacious anti-thrombotic medication⁵. Combination of aspirin and clopidogrel is a mainstay of therapy in patients after PCI; however, combination therapy is not warranted in CSA⁷⁴.

Statin medications lower cholesterol and have anti-inflammatory effects that help reduce the risk of adverse cardiovascular events. Therapeutic goals are determined by assessing a patient's risk factors and the presence of CHD, or a CHD equivalent⁷⁶. CSA is a CHD subtype; therefore, current recommendations are to maintain LDL levels less than 100mg/dL. If a patient is considered to be very high risk or if a patient has a baseline LDL <100mg/dL and is high risk, an LDL goal of <70mg/dL can be considered as well⁷⁶.

Angiotensin converting enzyme (ACE)-inhibitors improve prognosis in the treatment of hypertension, heart failure or LV dysfunction, and in diabetic patients. Based on these findings, ACEinhibitors are recommended for treatment of CSA only if these co-morbidities exist⁷⁴.

Anti-Anginal and Anti-Ischemic Therapies

Beta-blockers decrease oxygen demand and increase diastolic filling time. This results in increased myocardial perfusion and decreased oxygen needs, which reduces angina symptoms and ischemia⁴⁷. Currently, studies confirm the anti-anginal benefit of beta blockade⁷⁷, however, clinical trials have not evaluated the effect on mortality in patients with CSA⁷⁴. Instead, studies have confirmed an improvement in mortality of post-MI and heart failure patients after receiving beta-blockers⁷⁸. Therefore, the ACC/AHA recommend beta blockade for anti-anginal symptom control in post-MI and heart failure patients to improve prognosis⁴⁷. If a patient is unable to tolerate a beta blocker, a non-dihydropyridine calcium channel blocker (CCB), such as diltiazem, may be used⁷⁴.

In contrast to non-dihydropyridine CCBs, clinical trials show that dihydropyridine CCBs (amlodipine), decrease adverse cardiovascular events at two years⁷⁹, although this was not statistically significant. These agents did, however, effectively reduce angina symptoms. This occurs primarily from systemic vasodilation which decreases cardiac work. In addition, dihydropyridine CCBs also dilate coronary vessels and counteract vasospasm, making them ideal anti-anginals in vasospastic coronary angina⁴⁷. To enhance the anti-anginal effect, dihydropyridine CCBs may be combined with beta-blockade. This union counteracts reflex sympathetic activation of the heart by dihydropyridine CCBs.

Beta blockers also improve mortality in patients post MI. Based on these findings, the ACC/AHA recommends selection of either agent as an anti-anginal be based on individual tolerance and coexistent disease; except if the patient has a history of MI, beta blockade is preferred. If all disease factors are equally weighted than beta-blockade is recommended as first line over a CCB^{47, 74}.

When beta blockers and CCBs are ineffective in controlling angina, long acting nitrates may be used. These agents reduce the frequency and severity of anginal attacks; however, they have not been tested regarding their impact on mortality⁷⁴. Nitrates cause venodilation, which reduces end diastolic volume and pressure leading to increased subendocardial perfusion. Patients may become tolerant to the effects of nitrates; therefore, appropriate dosing should consider a daily nitrate-free interval of 12 hours⁷⁴.

Short-acting nitrates carry a similar risk of tolerance. Rapidly acting, these agents provide 'situational prophylaxis' and can abort an acute angina attack⁷⁴. Because of this immediate relief, short acting nitrates can be prescribed for a wide variety of patients with angina⁷⁴.

Excessive usage may result in dose-dependent headache, flushing, and postural hypotension. Most importantly, excessive usage should warn patients to seek further medical attention.

Ranolazine

In 2006, the FDA approved the first sodium ion channel (I_{Na}) inhibitor, ranolazine, for the symptomatic control of CSA. It exerts its anti-anginal effect without affecting heart rate and blood pressure⁸⁰, making it an ideal drug of choice in bradycardic and hypotensive patients. Both the Combination Assessment of Ranolazine in Stable Angina (CARISA) and the Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) trials showed that ranolazine increased symptom related exercise duration^{81–82}. The Efficacy of Ranolazine in Chronic Angina (ERICA) and CARISA trials showed a decreased frequency of anginal symptoms and decreased use of short-acting nitrates^{81–83}. Unlike nitrates, ranolazine shows no evidence of tolerance at 12 weeks of therapy⁸¹. The recently published Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes (MERLIN)-TIMI 36 trial confirms the above findings, but concludes that ranolazine did not affect the incidence of cardiovascular mortality or MI^{84–86}. Subgroup analyses did demonstrate a significant beneficial effect in women, possibly due to a higher prevalence of MCD⁸⁵. Hence, for symptom control and improved prognosis, the medication should be used in conjunction with beta blockers and CCBs⁷⁴.

Revascularization Therapies

If a patient continues to have persistent angina after using multiple medications, or if imaging shows a large area of myocardium at risk, revascularization should be considered⁷⁴. In addition, if the benefit of revascularization outweighs the risk, and/or the patient prefers an interventional approach after a discussion of risks and benefits, revascularization may also be considered. PCI and CABG are two well-established treatment options. The goal of these interventions once again is to decrease occurrence of symptoms and to improve survival.

PCI may be considered an alternative to CABG in improving quality of life; however, clinical trial summaries demonstrate that there is no benefit in mortality⁷⁴. Balloon angioplasty is now infrequently used as a standalone therapy due to high rates of re-stenosis; it is usually combined with either a bare metal (BMS) or a drug eluting stent (DES), depending on lesion and patient characteristics. For stable angina, PCI should be mainly reserved for single vessel disease in moderate to severely symptomatic patients that have failed medical therapy. Due to advanced equipment and increasing physician experience, multi-vessel disease can also be treated with PCI given coronary anatomy is not high risk and therefore more suitable for CABG⁷⁴. Once again, risk of the procedure must be weighed against benefit of angina relief.

CABG can reduce mortality in medium to high-risk patients and in the presence of specific multi-vessel disease anatomy greater than 50% left main artery (LMA) stenosis, greater than 70% proximal stenosis of three major coronary arteries, or greater than 70% proximal left anterior descending (LAD) artery stenosis and any two other major coronary arteries^{74, 87}. CABG is beneficial in reducing symptoms, however, the incidence of MI is not affected⁸⁸. These are important considerations due to the operative morbidity and mortality associated with this intervention.

Summary

Cardiac risk factors and inflammation leads to the development of obstructive CAD and MCD which are common causes of CSA chest pain. AS, LVH, CAS, congenital coronary anomalies, and abnormal cardiac nociception are less likely causes of CSA. ETT is typically the first step in the diagnosis of CAD in intermediate risk subjects who are able to exercise and have a normal

baseline ECG. However, ETT has a modest sensitivity and specificity in women, who are more likely to have angina due to MCD in the absence of obstructive CAD. There are many other stress imaging modalities available for detection of ischemia, including SPECT, PET, SE, MPS, and stress CMRI. The test of choice depends on the patient characteristics and local testing center expertise. CCS and CCTA may allow for noninvasive visualization of obstructive CAD, but invasive CA remains the gold-standard for detection and treatment of obstructive lesions. CRT should be considered in patients with CSA, objective evidence of myocardial ischemia and non-obstructive coronary arteries, to evaluate for MCD. Management for CSA includes aggressive life-style and risk factor modification to control cardiac risk factors; pharmacologic interventions such as beta-blockers, nitrates, CCBs, anti-platelet agents, and statins remain the standard of care. Ranolazine is the most recent anti-anginal medication available and may be appropriate for some patients, especially women. If however, maximal medication therapy fails to resolve symptoms, interventional therapy in the form of PCI or CABG can reduce frequency of symptoms. While there are many therapies available, the optimal management of CSA, especially in patients with angiographically normal coronaries, remains to be delineated. Mechanistic understanding studies that lead to new interventions are needed to reduce the burden of angina in our society.

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Figure 1. Practical Algorithm for Management of Patients With Anginal Chest Pain Symptoms and No Obstructive Coronary Artery Disease

MRI indicates magnetic resonance imaging; PET, positron emission tomography; CAD, coronary artery disease. Vascular function studies include coronary flow reserve and coronary acetylcholine testing.

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Figure 2. Stress Cardiac MRI

(R) Cardiac MRI depicting normal myocardial perfusion at rest. (L) Under stress, arrows identify radiolucent region of subendocardial hypoperfusion of the left ventricle, suggestive of microvascular coronary disease.

Table 1
Pretest Likelihood of Obstructive CAD in Symptomatic Patients According to Age and Sex

Age	Nonanginal Chest Pain		Atypical Angina		Typical Angina	
	Men	Women	Men	Women	Men	Women
y						
30-39	4	2	34	12	76	26
40-49	13	3	51	22	87	55
50-59	20	7	65	31	93	73
60-69	27	14	72	51	94	86

Each value represents the percentage of patients with obstructive coronary artery disease on catheterization.

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Snow V, Barry P, Fihn SD, et al. Evaluation of primary care patients with chronic stable angina: guidelines from the American College of Physicians. *Ann Intern Med.* Jul 6 2004;141(1):57-64.