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Stable Angina Pectoris

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INTRODUCTION

The life time risk for the development of symptomatic coronary artery disease **(CAD)** after 40 years of age is 49% for men and 32% for women accounting 48 % of all cardiovascular deaths. Nearly half of the patients with CAD, present with angina pectoris **(AP)**. Angina pectoris results from myocardial ischemia, which is caused by an imbalance between myocardial O_2 requirements and myocardial O_2 supply. Exercise ECG, stress echocardiography, myocardial perfusion imaging and coronary angiography are the widely used diagnostic tests. Patients with AP should be treated with guideline-directed medical therapy: beta-blockers, long-acting nitrates and calcium channel blockers. Newer antianginal therapies are also available for patients with refractory angina. Symptomatic patients with high ischemic burden or extensive coronary artery disease and reduced left ventricular ejection fraction are best treated with revascularization modalities.

STABLE ANGINA PECTORIS

Coronary artery disease **(CAD)** remains a major cause of morbidity and mortality worlwide. Angina pectoris **(AP)** is one of the classic symptoms of CAD, originally described in 1772 by William Heberden [1]. Traditionally defined as substernal chest pain of less than 10 minutes' duration. It is usually precipitated by exertion and relieved by rest [2]. Not only critical coronary stenosis but endothelial dysfunction, micro vascular disease, inflammation, and vasospasm can be the major or contributing mechanism of myocardial ischemia. The pain can be constricting, suffocating, crushing, heavy, and squeezing in character. Typical angina pectoris is relieved within minutes by rest or the use of short-acting nitroglycerin. Response to the latter is often a useful diagnostic tool, although it should be remembered that esophageal pain and other syndromes may also respond to nitroglycerin. A delay of more than 5 to 10 minutes before relief is obtained with rest and nitroglycerin suggests that the symptoms are either not caused by ischemia or are caused by severe ischemia, as with acute myocardial infarction or unstable angina.

The prevalence of angina pectoris differs dramatically worlwide. According to World Health Organization Survey across 52 countries with 210787 participants, the prevalence ranges from 2.4 % to 23.9% [3]. The life time risk for the development of symptomatic CAD after 40 years of age is 49% for men and 32% for women accounting 48 % of all cardiovascular deaths [4].

GRADING ANGINA PECTORIS SEVERITY

Canadian Cardiovascular Society **(CCS)** classification has gained widespread acceptance for quantifying physical activity thresholds at which angina occurs (Table 1). No limitation, slight and marked limitation of ordinary activities due to AP is classified as CCS I, II and III, respectively whereas AP at rest is CCS IV in severity [5]. CCS class is a significant predictor of long-term mortality [6].

Table 1: Grading of Angina Pectoris Severity.

Grade	Description
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
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
III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace
IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest

Mechanism

Angina pectoris results from myocardial ischemia, which is caused by an imbalance between myocardial O_2 requirements and myocardial O_2 supply (Fig 1). Increased heart rate, contractility and wall tension increase myocardial oxygen demand. Myocardial oxygen supply is determined by coronary blood flow and hemoglobin concentration. Coronary blood flow is maintained by the pressure difference between diastolic blood pressure and left ventricular end-diastolic pressure. So occlusive coronary artery disease, vasospasm, anemia and any condition that decreases coronary perfusion gradient will produce ischemia [7] . The pathophysiologic mechanism underlying myocardial ischemia is utmost importance for the prompt management of the patient. For example a symptomatic patient with 70 % of stenosis in one coronary artery with hemoglobin concentration of 7 mg/dl maybe first treated by correction of the anemia rather than antianginal therapy or coronary revascularization.

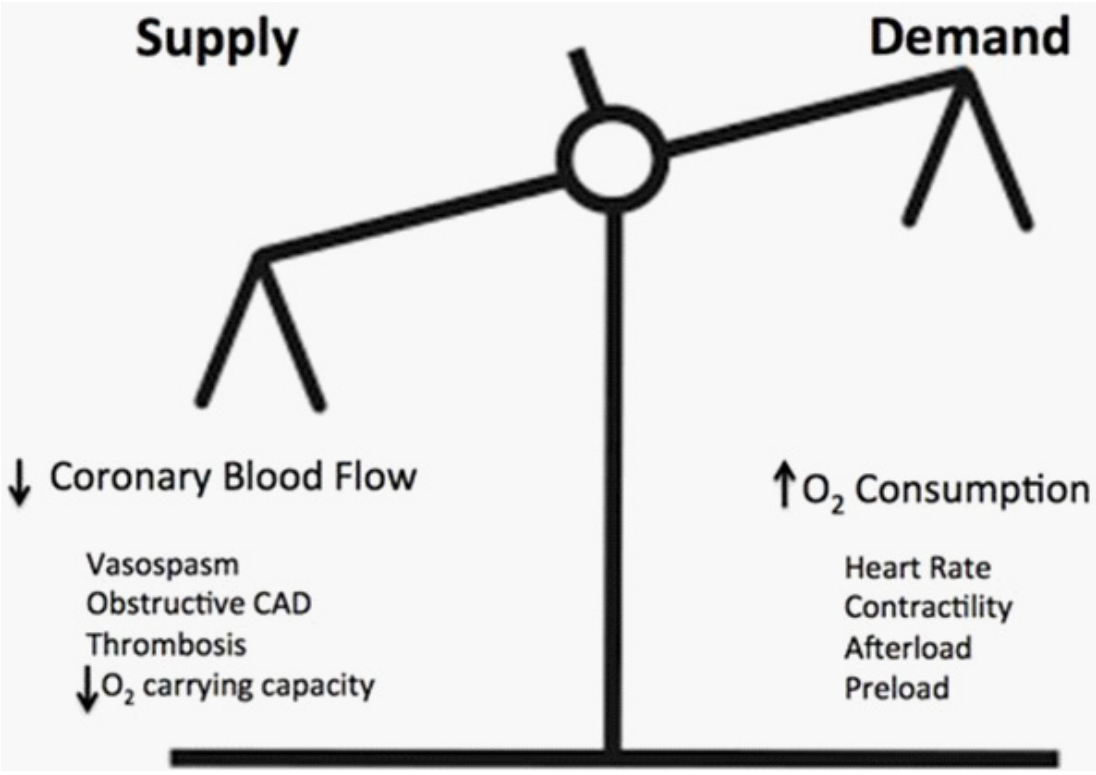

Figure 1: Mechanism of myocardial ischemia.

Evaluation

The first step in the evaluation of angina is to assess the likelihood of significant coronary artery disease on the basis of the following parameters: character of chest pain (typical, atypical, nonanginal), traditional cardiovascular risk factors and ECG changes [8]. Patients with more

cardiovascular risk factors with typical angina pectoris are more likely to suffer from coronary artery disease rather than non ischemic chest pain. So a careful history and physical examination of a patient with AP may give clue to the presence of anemia, hypertension, valvular heart disease, hypertrophic obstructive cardiomyopathy or arrhythmias. Laboratory tests are used to investigate the presence of any of the following conditions associated with angina pectoris: anemia, thyroid disease, renal dysfunction, diabetes mellitus or impaired glucose metabolism and hyperlipidemia. Resting ECG is also recommended in every patient being evaluated. Transthoracic echocardiography will give many clinical clues for diagnosis and risk stratification such as: wall motion abnormalities, left ventricular ejection fraction, diastolic dysfunction, associated valvular disease or cardiomyopathies [9,10].

Diagnostic tests are recommended for patients with intermediate pre-test probability **(PTP)**. Patients with low PTP < % 15 need no for testing whereas patients with high PTP > 85% assumed to have CAD and need further testing only for risk stratification. So accurate risk estimation will guide the appropriate diagnostic strategy [9].

Table 2, summarizes the major diagnostic tests used in the diagnosis of CAD [9,10]. Which test to be chosen depends on local expertise and resources as well as the patient characteristics. Because of simplicity and widespread availability, exercise ECG is the first preferred diagnostic test in patients with normal resting ECG. Patients with low exercise capacity and/or uninterruptable ECG are best evaluated with imaging modalities such as nuclear testing or exercise echocardiography. CT angiography has very high negative predictive value so it is wise to use CTA to exclude CAD. CTA will overestimate stenosis severity in patients with severe coronary calcifications [11].

A patient with new onset typical angina pectoris and wall motion abnormality on echocardiography with left ventricle ejection fraction **(LVEF)** < 50% is best evaluated with direct coronary angiography rather than non-invasive tests whereas a young patient with atypical angina pectoris with good exercise capacity but a strong family history of early CAD can be evaluated with CTA to see the anatomy as well as Agatson score for future risk stratification.

Table 2: Non-invasive diagnostic tests for coronary artery disease.

	Sensitivity %	Specificity %	Advantages-Disadvantages
Exercise ECG	45-50	85-90	Easy, safe
Exercise Echocardiography	80-85	85-90	Operator dependent Additional information
Nuclear MPI	75-90	65-85	Radiation, limited in 3-vessel disease/left main
Cardiac CTA	90-95	65-83	High negative predictive value
CMR	79-88	80-90	High cost , no radiation, additional information

MPI: Myocardial perfusion imaging, **CTA:** Computed tomographic angiography, **CMR**: cardiac magnetic resonance.

Risk Assessment

The prognosis of patients with stable CAD varies considerably. Patients with high risk factors have annual mortality as high as 3.8 % six times higher than with low risk patients [12]. Patients with more ischemic burden such as inducible wall motion abnormalities more than 3 segments detected by stress echocardiography have annual mortality > 3% [13]. Also stable CAD patients with reversible perfusion defect assessed by SPECT, or cardiac MRI > 10 % of LV myocardium represent a high risk subset. Table 3 summarizes high risk parameters of widely used diagnostic tests [14].

Table 3: Major prognostic high risk parameters in patients with stable coronary artery disease.

Risk Assessment of Stable CAD	
1. Clinical Features Age Diabetes Mellitus Hypertension Current smoking Prior MI,PVD Angina severity	4. Echocardiography LVEF < 50% Inducible wall motion abnormality >3
2. Laboratory Markers Total Cholesterol hs CRP hs Troponin	5. Stress Perfusion Scintigraphy Reversible perfusion defect > 10% LV
3. Exercise ECG Exercise duration Duke treadmill score	6. Coronary anatomy Left main disease 3- vessel disease especially proximal LAD Syntax Score > 32

MI: Myocardiial infarction **LV**: Left ventricle, **PVD:** Peripheral vascular disease **HS:** High sensitivity **LVEF:** Left ventricle ejection fraction **LAD**: Left anterior descending artery.

Anatomic *vs* Functional Severity of a Coronary Stenosis

Obstructive coronary artery disease is traditionally defined as > 50% luminal diameter stenosis in at least one major coronary artery diagnosed by coronary angiography. All of the non-invasive diagnostic tests are compared to coronary angiography findings considered as the gold standard. However with the advance of physiological assessment of coronary stenosis we understand that functional severity of a stenosis is not synonymous with anatomic severity. A long 60% stenosis in proximal left anterior descending artery can cause severe ischemia whereas a discrete 90 % stenosis in the same artery with a prior myocardial infarction in the territory will only cause little ischemia. The presence and the extent of ischemia is the most important parameter for prognosis [15]. Nowadays, intracoronary artery pressure recording or fractional flow reserve **(FFR)** is considered as the gold standard in invasive physiological assessment of coronary stenosis [16]. A value more than 80 % rarely signifies ischemia and hard cardiovascular events [17]. Functional assessment of ischemia is highly recommended in multivessel disease revascularization decision making [9].

Management

The goal of management of patients with stable CAD are as follows:

1) Prevent future cardiovascular events such as cardiovascular death, myocardial infarction and stroke

2) Reduce exercise-induced ischemia

3) Improve quality of life

Guideline Directed Medical Therapy

In patients with suspected CAD, there is conclusive evidence that preventive therapies reduce future adverse cardiovascular and cerebrovascular events. So these measures should be promptly initiated. According to studies aspirin reduces cardiovascular events 18% with respect to controls mainly driven by the reduction of myocardial infarction [18]. Clopidogrel is an option in patients intolerant to aspirin [19]. Mono antiplatelet therapy is sufficient for patients with stable CAD.

Blood pressure should be reduced to target blood pressure < 140/90 mmHg, LDL level reduced 30-50% with respect to pre-treatment levels and hemoglobin A1C levels < 7 % in diabetic patients. Regular exercise increases exercise capacity and lowers ischemic episodes as well as maintaining ideal body weight. Smoking cessation is also mandatory [9,10].

CLASSICAL ANTIANGINAL DRUGS

Beta-blockers, calcium-channel blockers, and long-acting nitrates reduce angina pectoris similarly with a similar safety profile. Beta blockers by decreasing heart rate, contractility and blood pressure decreases myocardial oxygen consumption while calcium channel blockers and nitrates mainly increase coronary flow by vasodilatation [8]. Which drug first or which combination depend on patient's baseline characteristics. Beta blocker therapy is the first choice in patients with prior recent myocardial infarction or heart failure patients with reduced ejection fraction. Beta blocker is also a good first option for patients with higher resting heart rates mainly > 80 beats/min.

Combination of two antianginal therapies in different classes act synergistically minimizing side-effects. Doses of antianginal drugs should be increased as needed to achieve symptom control and improvements in heart rate and blood-pressure levels.

NOVEL ANTIANGINAL THERAPIES

Ranolazine reduces myocardial ischemia by reducing calcium overload caused by inhibition of the late sodium current. It does not have adverse hemodynamic effect thus may be considered as a first-line agent for patients with slow heart rate or low blood pressure. Exercise duration was longer with fewer angina episodes among patients who received ranolazine therapy compared to controls [20,21]. It must be used cautiously with drugs known to prolong QT interval.

Trimetazidine: Inhibition of fatty acid oxidation increases cardiac metabolic efficiency. Addition of timetazidine to metoprolol decreases anginal episodes and time to ECG changes in patients with stable coronary artery disease [22].

Nicorandil: A potassium channel activator acts as an arterial and venous dilator On top of standard medical therapy, nicorandil reduces coronary death, non fatal myocardial infarction and hospitalization for angina pectoris by 17 %. Flushing, headache are frequent side effects [23].

Allopurinol: A xanthine oxidase inhibitor classically used in gout has been shown to increase exercise time and improve vasodilation by abolishing oxidative stress [24].

REVASCULARIZATION STRATEGY

Patients with high risk features and those whose symptoms are not relieved within 2 weeks after the initiation of at least two antianginal drug therapies should be considered for revascularization [25]. The Bypass Angioplasty Revascularization Investigation **(BARI 2D)** trial [26] and Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation **(COURAGE)** trial [27], compared optimal medical therapy plus revascularization versus optimal medical therapy alone to reduce mortality or major cardiovascular events in stable CAD patients. These two trials have not shown survival benefit from revascularization compared with drug treatment. However in the nuclear sub study of COURAGE, PCI was shown to be more effective in treating is chaemia and associated with greater event-free survival.

In mildly symptomatic patients with less than 10% of provocable ischemia, can be managed with guideline directed medical therapy alone. Symptomatic patients with high ischemic burden should be considered for revascularization. Analysis of the comparative efficacy of percutaneous coronary intervention **(PCI)** vs CABG for patients with stable angina is difficult because of the advances in revascularization strategies over several decades. SYNTAX score is used to stratify coronary anatomy into low, intermediate and high risk groups [28]. For high SYNTAX scores CABG is better than PCI mainly driven by lesser revascularization rates. Whatever the mode of revascularization, complete revascularization success will predict the future events like angina pectoris and revascularization rates. So a patient with only an osteal or shaft left main artery disease can be successfully treated with PCI whereas a diabetic patient with multiple and diffuse stenosis best treated with CABG. The patient preference is also important in choosing the type of revascularization modality in patients with stable CAD.

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