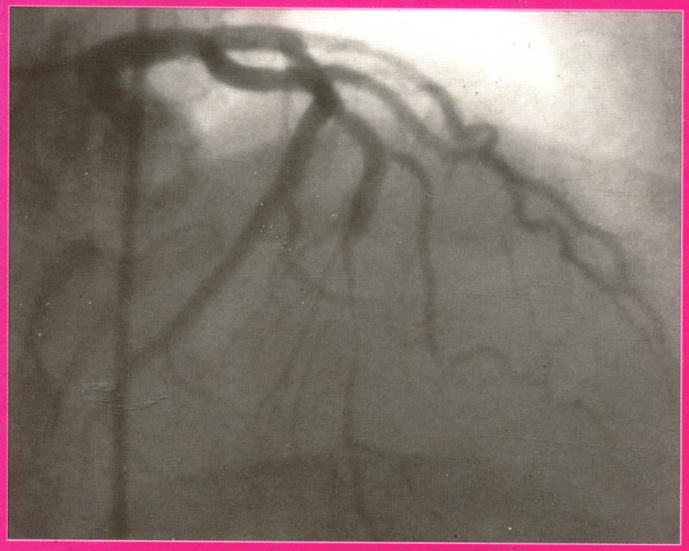
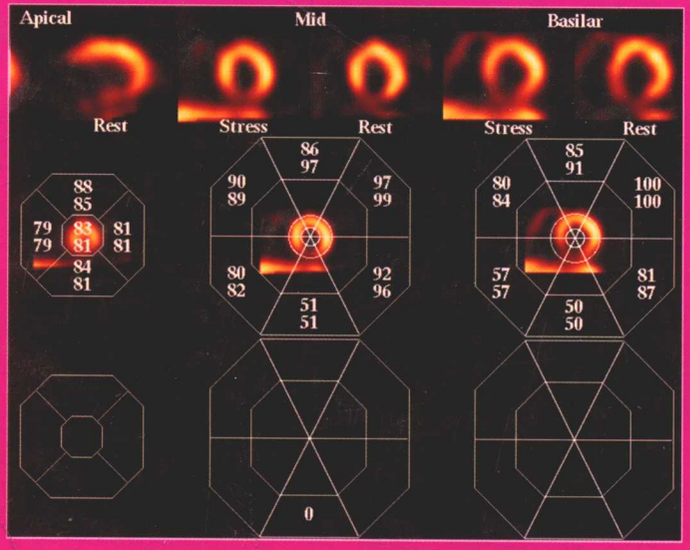
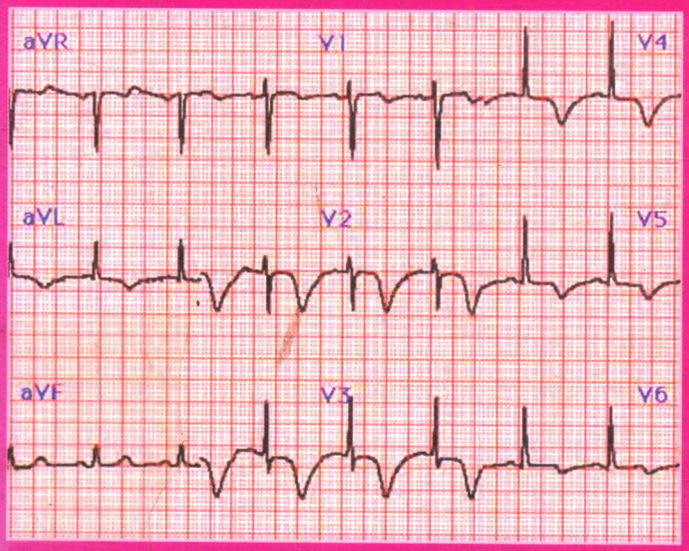
An Atlas of Investigation and Management

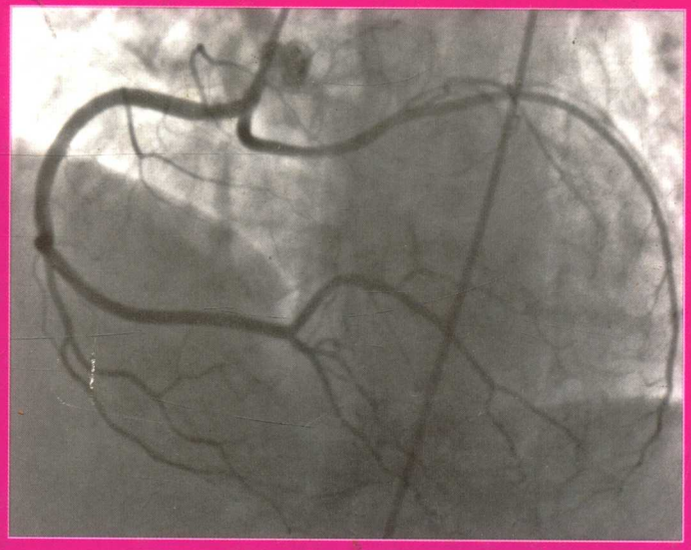
ANGINA

Ian J Sarembock









CLINICAL PUBLISHING

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ANGINA

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An Atlas of Investigation and Management

ANGINA

Preface

The purpose of this book, *Angina: An Atlas of Investigation and Management*, is to share with the readers an outline of the most important aspects of the epidemiology, natural history, pathophysiology, clinical evaluation, non-invasive detection and invasive assessment of angina pectoris, a common manifestation of ischemic heart disease. In addition, we review the important non-atherosclerotic causes of chest pain and articulate an overall approach to the management of chronic angina with respect to goals of therapy including strategies to control symptoms and the role of coronary artery revascularization.

Over the last century, cardiovascular disease (CVD) has burgeoned from a relatively minor disease worldwide to a leading cause of morbidity and mortality. By 2020 it is projected that CVD will surpass infectious disease as the world's leading cause of death and disability. The major factors impacting this include the projected 60% increase in population between 1990 and 2020, the increasing life expectancy as a result of improvements in public health and medical care that are reducing rates of communicable disease, malnutrition, and maternal and infant deaths and the economic, social, and cultural changes that have led to increases in risk factors for CVD. Chronic angina is traditionally recognized as the cardinal symptom or manifestation of coronary artery disease (CAD), and worsening angina symptoms signal progression of the underlying pathology. Angina is a clear warning sign of a potential myocardial infarction; approximately 50% of myocardial infarction patients have had preceding angina. Overall, angina presents a tremendous economic burden on the health care system, society, employers, patients, and their families.

According to the American College of Cardiology/American Heart Association (ACC/AHA) 2002 Guideline Update for the Management of Patients with Chronic Stable Angina, the goals of chronic angina management are two-fold: to reduce morbidity and mortality; and to reduce symptoms. Medical therapy and revascularization procedures, either coronary bypass grafting (CABG) or percutaneous coronary interventions (PCI), play important roles in achieving these goals. However, these treatment options have limitations and significant expense and many patients have anatomical features or co-morbid conditions that prevent their optimal implementation. Newer drugs and procedures, such as transmyocardial revascularization, enhanced external counterpulsation, and gene therapy, are all under investigation.

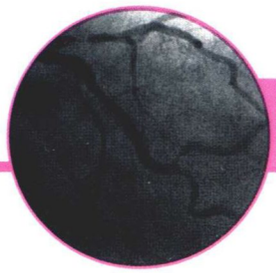
An undertaking of this magnitude needs the combined efforts of numerous individuals, and as editor of this atlas, I want to express my sincere gratitude to my contributing authors, each of whom made critically important contributions. They have worked diligently to meet the format requirements of this atlas, the concept of which entails a brief and highly structured text, supported by extensive graphics, flowcharts and tables and numerous photographs of both the clinical signs of disease and of corresponding underlying pathology. Flowcharts, checklists and algorithms have been used to summarize key facts, and present the reader with a rapid reference to the diagnostic process. Tables include all key data of diagnostic value. In addition, it has been a true pleasure working with the publishing team of this atlas. Their advice, enthusiasm and commitment to the project were critical to its success and are sincerely appreciated.

Ian J Sarembock

Abbreviations

ACC American College of Cardiology
ACE angiotensin-converting enzyme
ACS acute coronary syndrome
ADR adverse drug reactions
AHA American Heart Association
BMI body mass index
BNP brain natriuretic peptide
BP blood pressure
CABG coronary artery bypass grafting
CAD coronary artery disease
CCB calcium channel blocker
COPD chronic obstructive pulmonary disease
CRP C-reactive protein
CSA chronic stable angina
CT computed tomography
DENSE displacement encoding with stimulated echo
DES drug-eluting stent
DSE dobutamine stress ECHO
EBCT electron beam computed tomography
ECHO echocardiography
ED Emergency Department
EECP enhanced external counterpulsation
ETT exercise tolerance test
EKG electrocardiogram
FFR fractional flow reserve
GERD gastroesophageal reflux disease
GI gastrointestinal
HDL high-density lipoprotein
IHD ischemic heart disease
ISD ischemic sudden death
LAD left anterior descending (artery)
LAO left anterior oblique
LBBB left bundle branch block
LCA left coronary artery
LDL low-density lipoprotein
Lp(a) lipoprotein-a
LV left ventricle
LVEF left ventricular ejection fraction
MDCT multi-detector computed tomography
METS metabolic equivalent tasks
MI myocardial infarction
MRFP magnetic resonance first pass perfusion
MRI magnetic resonance imaging
MSCT multi-slice CT
PCI percutaneous coronary intervention
PET positron emission tomography
PPI proton pump inhibitor
PTCA percutaneous transluminal coronary angioplasty
QOL quality of life
RAO right anterior oblique
RCA right coronary artery
RV right ventricle
SCS spinal cord stimulation
SECP sequential external counterpulsation
SPECT single photon emission computed tomography
SSFP steady state free precision
STEMI ST segment elevation myocardial infarction
TENS transcutaneous electrical nerve stimulation
TIC time–intensity curves
TIMI Thrombolysis In Myocardial Infarction (risk score)
TMR transmyocardial laser revascularization
TTE trans-thoracic echocardiography
UA unstable angina
WHO World Health Organization

Contents



Angina pectoris: epidemiology, natural history, and pathophysiology

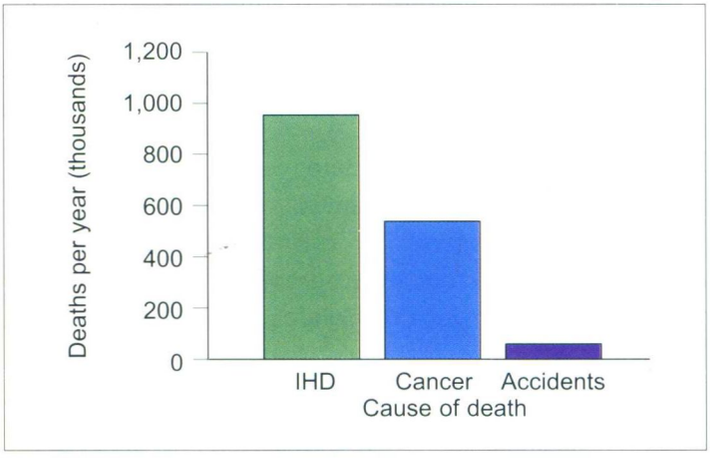
Fadi El-Ahdab, MD, and Michael Ragosta, MD

Introduction

The term 'angina' is from the Latin 'angere' meaning to strangle, and was first described by the English physician William Heberden in 1768. Angina pectoris refers to the predictable occurrence of pain or pressure in the chest or adjacent areas (jaw, shoulder, arm, back) caused by myocardial ischemia. Typically, angina occurs in association with physical or emotional stress and is relieved by rest or sublingual nitroglycerin. Chronic stable angina refers to an anginal condition that has been observed over time and has not changed in terms of the level of exertion leading to angina, its severity, or frequency. It is important to distinguish stable angina from the acute ischemic syndromes which also cause anginal chest pain.

Epidemiology

Angina pectoris is due predominantly to ischemic heart disease (IHD) from coronary atherosclerosis. IHD represents the leading cause of death in the United States (**1.1**), from several mechanisms including acute myocardial infarction (MI), fatal arrhythmia, and heart failure. Although IHD is a major cause of death, its most common manifestation is chronic stable angina. In several studies performed in Western countries, the prevalence of angina pectoris in middle-aged individuals is estimated to be between 4 and 12%[1–3]. The American Heart Association estimates that there are 16,500,000 patients with stable angina in the United States, and the reported annual incidence of angina among individuals more than 30 years



1.1 Causes of death in the United States per year (in thousands). Ischemic heart disease is the leading cause of death followed by cancer, cerebrovascular disease, and trauma.

old is 213 per 100,000 population. Angina pectoris is more often the presenting symptom of coronary artery disease (CAD) in women than in men, with a female-to-male ratio of 1.7:1. The frequency of atypical presentation is also more common among women compared with men. Women have a slightly higher mortality rate from CAD compared with men, in part because of an older age at presentation and a frequent lack of classic anginal symptoms, thus delaying the diagnosis and treatment of CAD.

Natural history

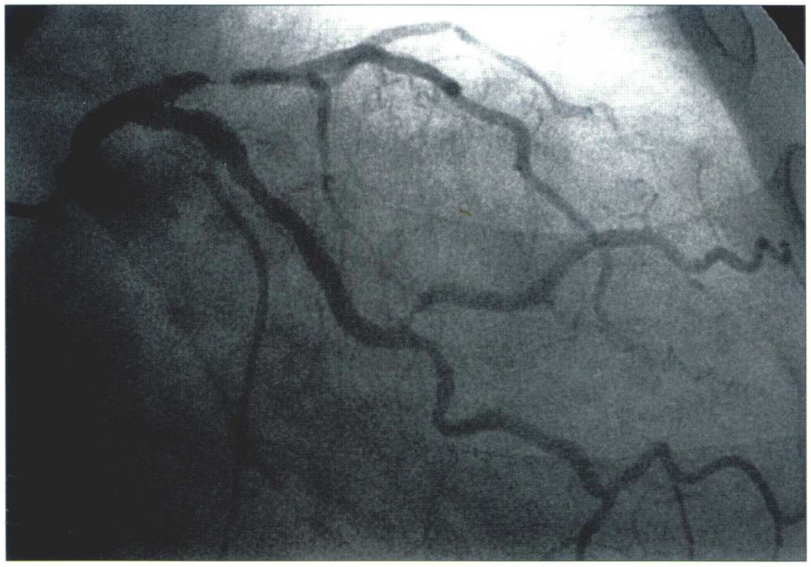
The majority of patients with chronic stable angina have underlying coronary atherosclerosis. The natural history of this condition is based on the extent, severity, and nature of the underlying atherosclerosis (*Table 1.1*). The majority of patients with angina remain stable, with predictable angina controlled with medical therapy or by limitation of activity. In some patients, the condition actually attenuates with reduction of angina over time (likely due to the development of collaterals) or even development of an asymptomatic state. The condition may exacerbate, however, with worsening of symptoms despite medical therapy and lead to substantial impairment in the quality of life from debilitating chest pain with minimal exertion. This may necessitate revascularization procedures such as percutaneous coronary intervention (PCI) or coronary bypass surgery. More importantly, the patient may develop an acute syndrome such as MI or unstable angina. The transformation of a stable to an unstable atherosclerotic lesion is poorly understood but is an important cause of death and morbidity in patients with coronary disease. It is interesting to note that while 50% of patients with acute MI have antecedent angina, few patients with angina progress to acute infarction. Two population-based studies from Olmsted County, Minnesota and Framingham, Massachusetts found 3–3.5% annual rates of MI in patients with angina[4,5]. Overall, survival in patients with chronic stable angina is good. The 5-year survival for patients with 'typical stable angina' was 83% in one study from Italy involving 519 patients with angina pectoris. Age, long-standing angina, the presence of previous infarction, heart failure, and an ischemic resting electrocardiogram (EKG) were among factors associated with a poor prognosis[6].

Table 1.1 Outcome of patients with coronary disease

- Chronic stable anginal pattern
- Exacerbation:
  - need for revascularization procedure:
    - percutaneous coronary intervention
    - coronary bypass surgery
  - development of acute coronary syndrome:
    - acute ST segment myocardial infarction
    - non-ST segment myocardial infarction
    - unstable angina
- Improvement:
  - reduction in angina
  - development of asymptomatic state

Pathophysiology

The causes of angina pectoris are shown in *Table 1.2*. The most common cause of angina pectoris is coronary atherosclerosis, with a severe stenosis obstructing blood flow leading to myocardial ischemia (**1.2**)[7,8]. Other causes of angina due to obstruction are rare and include vasospasm, microvascular disease, coronary embolism, and anomalous coronary arteries. Angina can also be observed in the absence of coronary obstruction from decreased oxygen supply (anemia, hypoxemia, or profound hypotension) or from conditions causing increased oxygen demand (left ventricular hypertrophy, hypertensive crisis, or marked tachycardia).

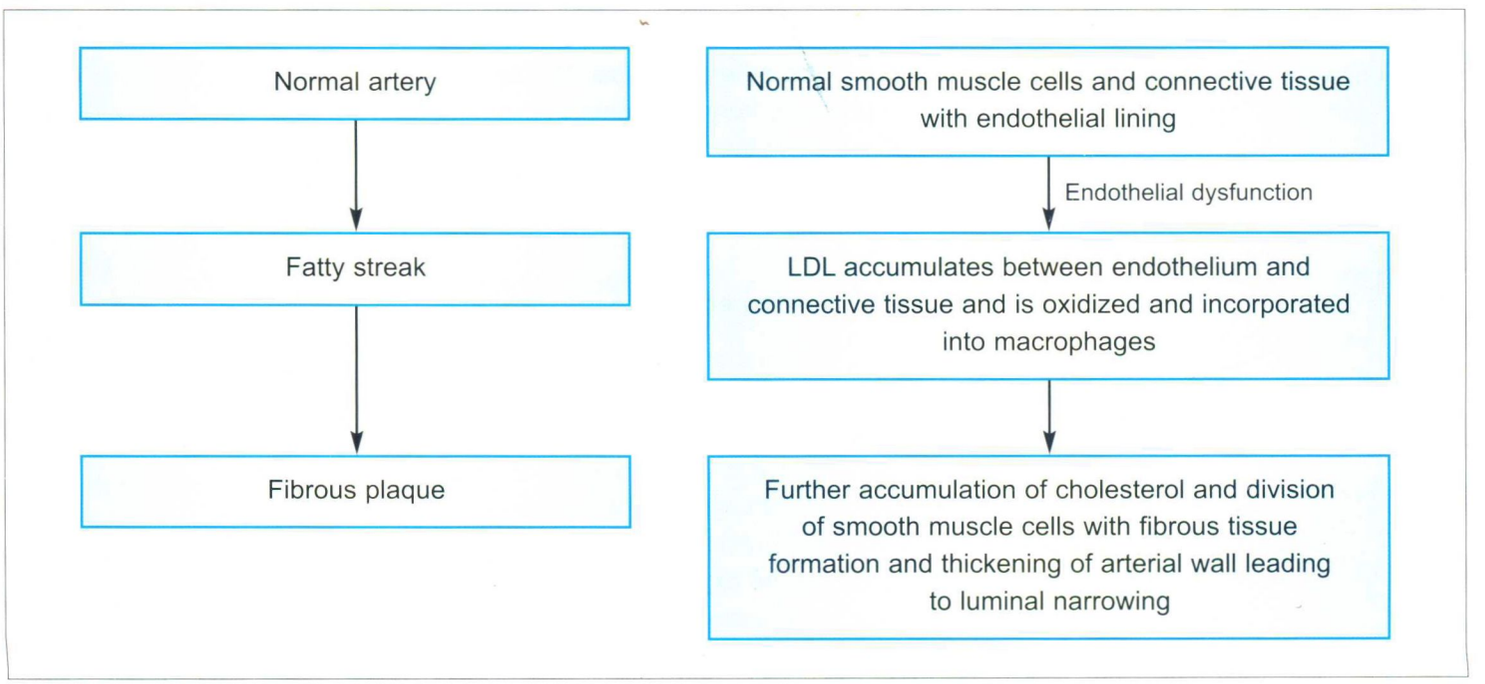


1.2 Angiogram of a patient with worsening chronic stable angina. It shows severe narrowing of the proximal left descending coronary artery secondary to atherosclerosis. This results in decreased perfusion pressure from the stenosis, mismatch in the oxygen demand–supply to the myocardium supplied by that artery, and consequently angina.

Table 1.2 Causes of angina pectoris

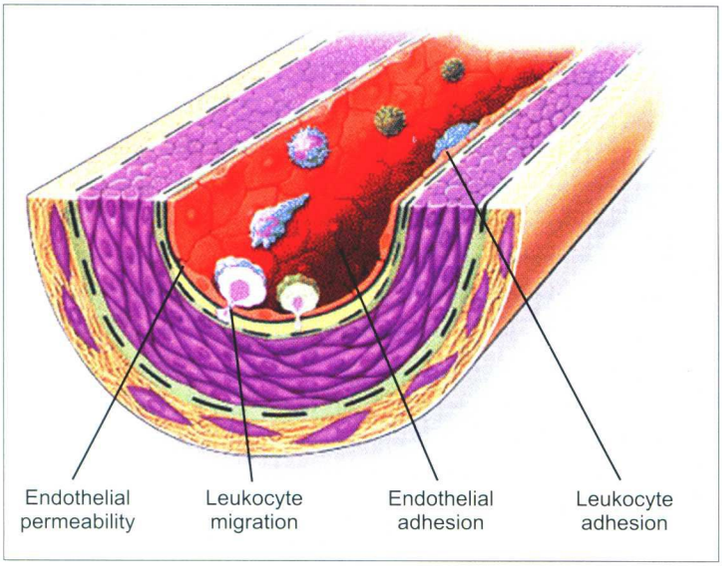
- Ischemia due to obstruction:
  - coronary atherosclerosis
  - coronary vasospasm
  - coronary emboli
  - anomalous coronaries
- Ischemia due to decreased oxygen supply:
  - anemia, hypoxia, hypotension
- Ischemia due to increased oxygen demand:
  - left ventricular hypertrophy, hypertension, tachycardia

The atherosclerotic coronary lesion is a lipid-containing plaque (also known as an atheroma) in the intima of the artery[7–11]. Atheroma formation is secondary to a complex set of mechanisms only partially understood, involving endothelial dysfunction, lipoprotein deposition and oxidation in the arterial wall, infiltration by inflammatory cells, cellular proliferation, especially smooth muscle cells, and matrix deposition (**1.3**). This mechanism may start at an early age. Endothelial dysfunction is thought to be the initial step in atherosclerosis (**1.4**). Endothelial dysfunction may result from the injurious effects of free radicals caused by tobacco smoking or from the effects of low-density lipoprotein (LDL) cholesterol, hypertension, diabetes, infectious agents, genetic factors, or a combination of these. Endothelial dysfunction results in increased endothelial permeability to lipoproteins, increased expression of adhesion molecules, and release of chemotactic factors that attract inflammatory cells (monocytes, macrophages, lymphocytes) and smooth muscle cells and facilitate their migration into the arterial wall. The fatty streak (**1.5**) results from the deposition of macrophages, lymphocytes, and smooth muscle cells into the arterial wall. In the arterial wall, macrophages containing LDL form 'foamy cells' and release cytokines and free radicals, causing more local damage and attracting more cells. As more foamy cells, inflammatory cells, and smooth muscle cells accumulate in the arterial wall, the fatty streak will grow in size and will tend to form a fibrous cap surrounding a lipid core (fibrofatty plaque or atheroma) (**1.6**). The cap consists of connective tissue and the lipid core includes foamy cells, leukocytes, and debris. As the plaque grows in size, it will push its way towards the lumen of the artery. When it is large enough to interfere with blood flow, ischemia and angina will result. Stable atheromas have a collagen-rich, thick fibrous cap, abundant smooth muscle cells, and fewer macrophages and usually result in chronic stable angina. Atheromas with thin caps, a large necrotic core and abundant macrophages tend to be less stable (vulnerable plaque) with a tendency to rupture, resulting in acute coronary syndromes, including MI.

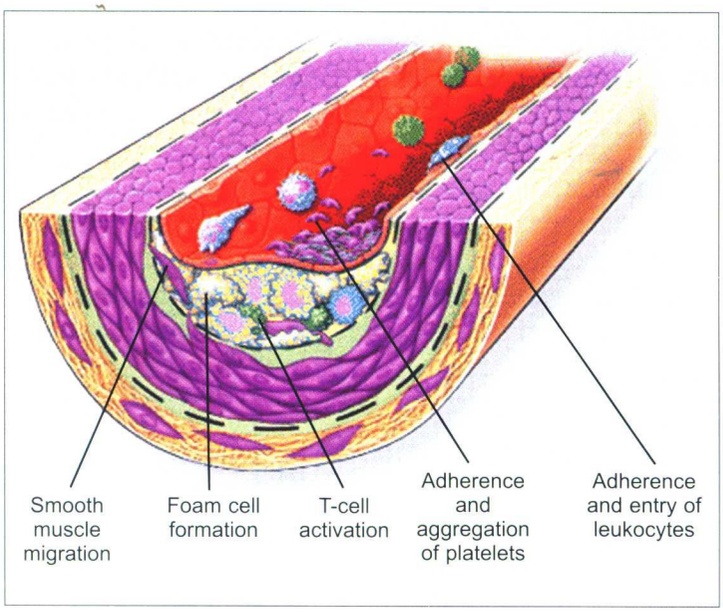


1.3 Steps in the development of atheroma. Atheroma formation is secondary to a complex set of mechanisms involving endothelial dysfunction, lipoprotein deposition and oxidation in the arterial wall, infiltration by inflammatory cells, cellular proliferation, especially smooth muscle cells, and matrix deposition.

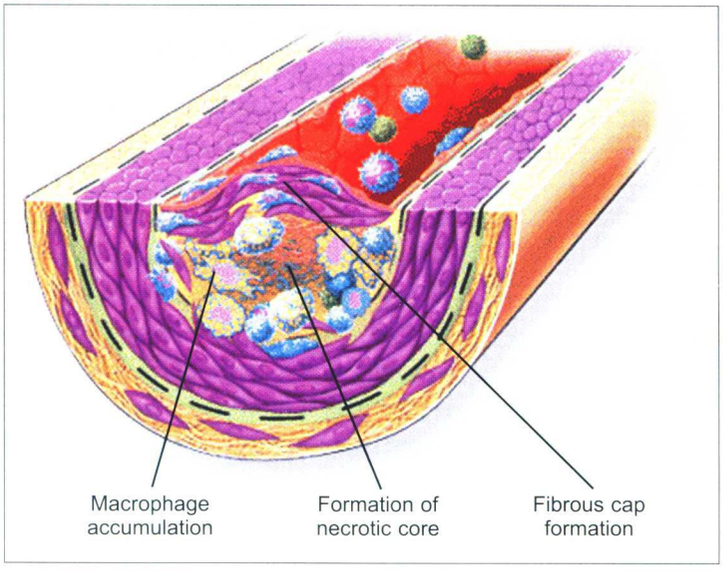
1.4 Endothelial dysfunction leading to atherosclerosis. Endothelial dysfunction is thought to be one of the initial steps in atheroma formation. Endothelial injury from multiple causes (including elevated lipids, hypertension, and smoking) leads to increased permeability allowing the passage of lipoproteins and inflammatory cells into the artery wall. (From Ross, R. Atherosclerosis: an inflammatory disease. *NEJM*, 1999,**340**:115–126, with permission.)



1.5 Development of a fatty streak. The fatty streak is formed when macrophages infiltrate the arterial wall and ingest oxidized lipids, predominantly LDL, to form 'foamy cells'. This is the earliest lesion in atherosclerosis and also contains scanty smooth muscle cells and other inflammatory cells such as lymphocytes. (From Ross, R. Atherosclerosis: an inflammatory disease. *NEJM*, 1999,**340**:115–126, with permission.)

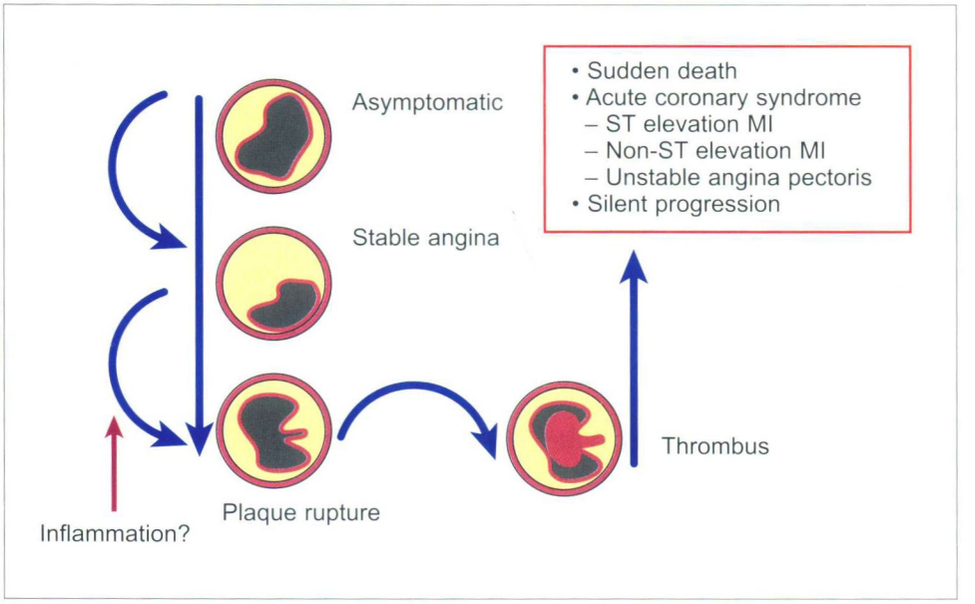


1.6 Development of an atheroma. This results from the accumulation of 'foamy cells', cellular debris, inflammatory cells including macrophages and mast cells, smooth muscle cells, and matrix, including collagen. Complex atheromas are usually organized into a necrotic core consisting mainly of lipid-rich 'foamy cells' and a fibrous cap containing smooth muscle cells and connective tissue. The morphology of the atheroma plays a major role in its stability. (From Ross, R. Atherosclerosis: an inflammatory disease. *NEJM*, 1999,**340**:115–126, with permission.)

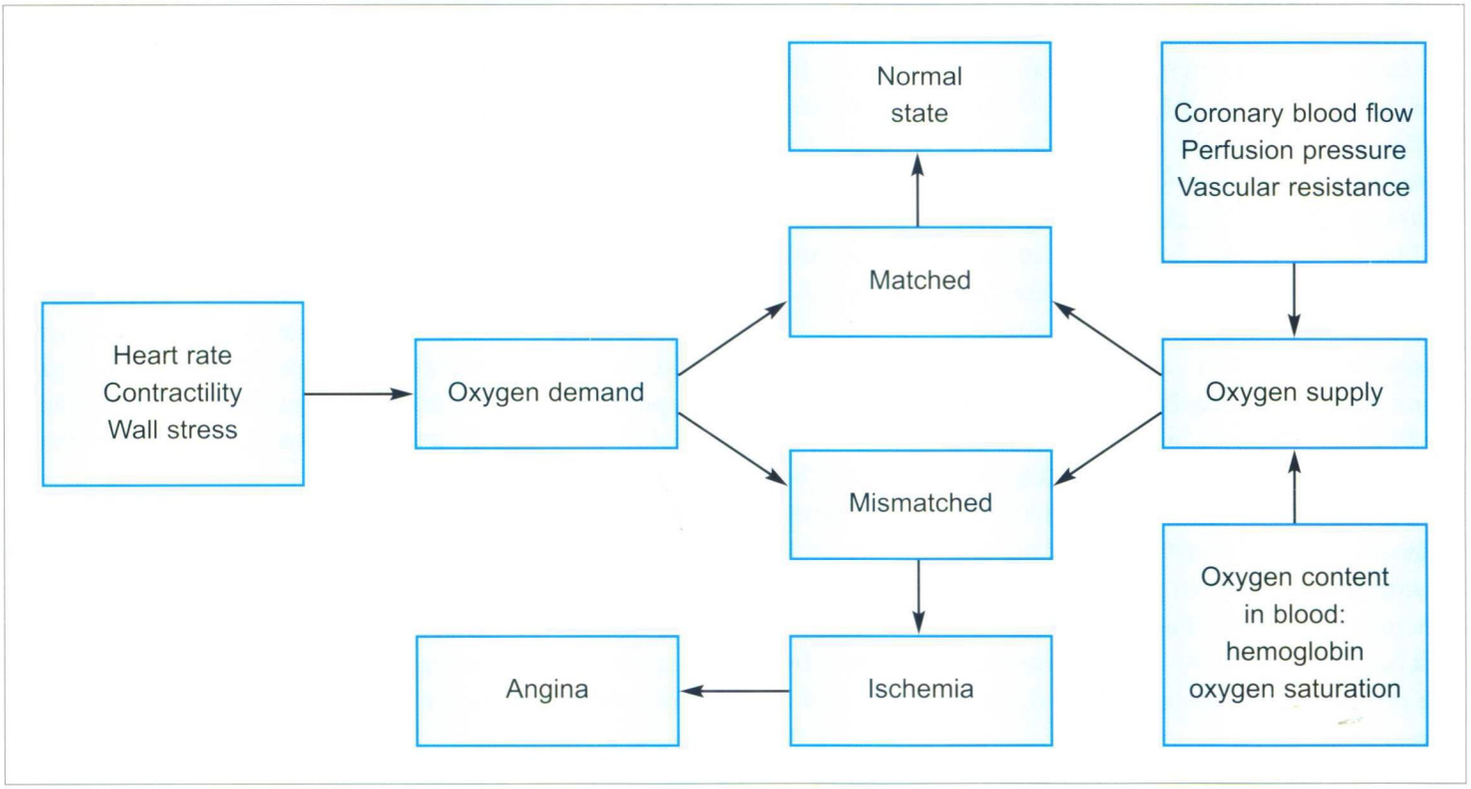


In patients with stable angina, the plaque tends to be slow growing and relatively stable. However, the plaque may undergo rapid and dynamic changes (**1.7**). Plaque rupture due to inflammation and other poorly understood mechanisms may result in platelet aggregation and thrombus formation. There are several consequences of this event. The event may be silent and lead to progression of luminal narrowing. More importantly, the thrombus may be occlusive and lead to sudden death from ventricular fibrillation or a nonfatal ST segment elevation MI. Nonocclusive thrombus may lead to significant flow limitation at rest and cause the acute ischemic syndromes of non-ST segment elevation MI or unstable angina. Unlike chronic stable angina, these conditions are potentially life-threatening and lead to substantial morbidity and mortality.

The mechanisms involved in the development of ischemia are complex and not solely related to the presence of a coronary stenosis. The amount of oxygen available in the myocardium is a function of the oxygen demand by the heart and of oxygen supply. Ischemia and subsequently angina result from mismatch between the amount of oxygen needed by the myocardium (oxygen demand) (*Table 1.3*) and the amount supplied to the myocardium (oxygen supply) (**1.8**). Myocardial oxygen demand is the major determinant of coronary blood flow. It is important to note that exercise may increase myocardial oxygen demand as much as 4–5-fold over baseline. Oxygen supply to the myocardium depends on coronary blood flow, the oxygen content of the blood (which depends on the blood oxygenation from the lungs and the amount of hemoglobin that carries oxygen), and the amount of oxygen extracted by the myocardium. Since the oxygen content is fixed and the myocardium already extracts most of the oxygen delivered to it, there is little or no oxygen extraction reserve. Thus, any increase in oxygen consumption requires an increase in coronary blood flow.



1.7 Pathogenesis of acute coronary syndromes. Atherosclerotic plaque may have a thick fibrous cap and be stable, causing chronic stable angina when flow-limiting. In contrast, it might have a thin fibrous cap, large necrotic core and abundant inflammatory cells, resulting in a vulnerable plaque that is prone to rupture, and thrombosis which might be occlusive (resulting in ST-elevation myocardial infarction or sudden cardiac death) or nonocclusive (resulting in an acute coronary syndrome). Causes of plaque rupture include inflammation and other unknown mechanisms.



1.8 Determinants of myocardial oxygen supply and demand. Ischemia and subsequently angina result from mismatch between the amount of oxygen needed by the myocardium (oxygen demand) and the amount supplied to the myocardium (oxygen supply).

Table 1.3 Determinants of myocardial oxygen demand

- Wall stress (T = wall stress):
  LaPlace's Law: $T \propto \frac{\text{pressure x radius}}{\text{wall thickness}}$
- Heart rate
- Contractility

Coronary blood flow is determined primarily by the coronary resistance vessels (*Table 1.4*). These vessels in turn are influenced by endothelial-mediated factors, metabolites, and neurohormonal mechanisms. A complex balance of these factors maintains basal flow at fairly constant levels despite changing perfusion pressure, by a process known as 'autoregulation' (**1.9**). Autoregulation plays a major role in stabilizing myocardial blood flow under varying perfusion pressures and is stable over a large range of perfusion pressure. However, autoregulatory mechanisms are overwhelmed when the perfusion pressure drops significantly, resulting in a decrease in blood flow. Thus, myocardial ischemia represents an exhaustion of the compensatory mechanisms regulating blood flow.

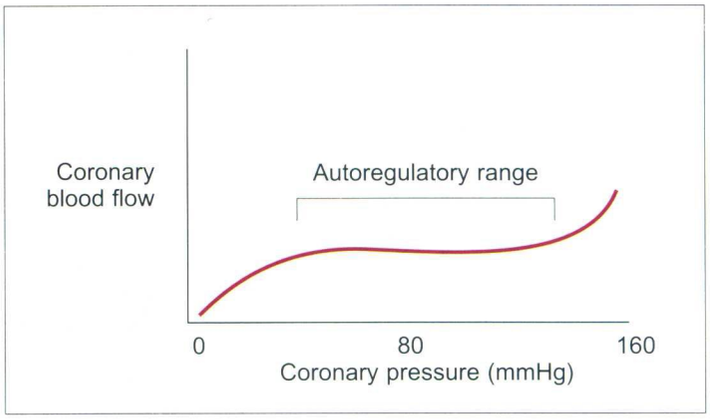
Coronary flow reserve is an important mechanism that protects the heart from ischemia with progressive coronary obstruction (**1.10**). With progressive luminal narrowing from atherosclerosis, blood flow remains essentially unchanged at rest because of arteriolar vasodilatation and recruitment from the process of autoregulation until the stenosis becomes too severe (>80%). However, under hyperemic stress, the flow reserve is exhausted, and flow begins to decline when the diameter of the stenosis exceeds 50%.

Other factors may play a role in causing demand–supply mismatch and ischemia in patients with CAD. One suggested mechanism is paradoxical vasoconstriction of the diseased coronary vessels due to dysfunction of the coronary endothelium, which normally releases vasodilators such as nitric oxide. In atherosclerotic arteries, the dysfunctional endothelium fails to release vasodilators in response to hyperemia, resulting in vasoconstriction and ischemia. Another mechanism involves de-recruitment of myocardial capillary beds in diseased coronary vessels during hyperemic states, causing decreased blood flow to the affected myocardium.

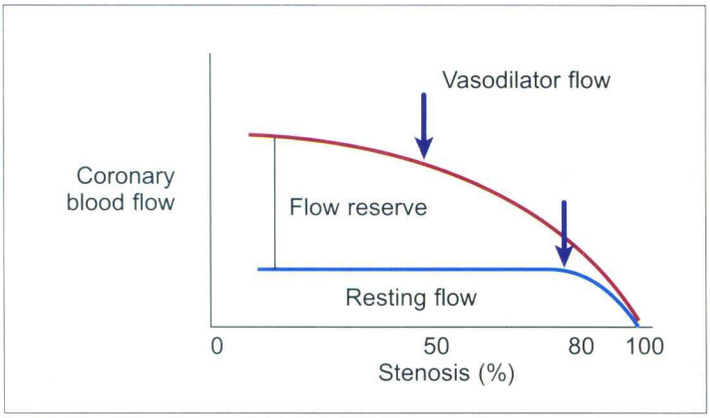
Patients with chronic stable angina may have worsening of their symptoms due to progressive disease or transformation into an acute coronary syndrome. However, based on the complex mechanisms involved in the development of ischemia, factors other than progressive obstruction may be involved. These factors are summarized in *Table 1.5*.

Table 1.4 Determinants of coronary blood flow

- Driving pressure through the coronary vessel
- Extravascular compression
- Coronary resistance vessels:
  - endothelial factors – nitric oxide, prostaglandins, endothelin
  - metabolites – adenosine, hypoxia, hypercapnea
  - neurohormonal mechanisms



1.9 Autoregulation of coronary blood flow. The role of coronary autoregulation in stabilizing myocardial blood flow under varying perfusion pressures is important, and is stable over a large range of perfusion pressure. But when the perfusion pressure drops significantly, autoregulatory mechanisms become overwhelmed. This results in decrease in blood flow and subsequently ischemia.



1.10 Relation of stenosis severity to coronary blood flow. Coronary flow reserve is an important mechanism that protects the heart from ischemia and generally increases from 2–5-fold with maximal coronary vasodilatation. Coronary flow reserve becomes diminished when lesions are >50% and is essentially overwhelmed for lesions >80%.

Table 1.5 Causes of myocardial ischemia other than coronary atherosclerosis

Increased oxygen demand

Noncardiac:
- Hyperthermia
- Hyperthyroidism
- Sympathomimetic toxicity (cocaine use)
- Hypertension
- Anxiety
- Arteriovenous fistula

Cardiac:
- Hypertrophic cardiomyopathy
- Aortic stenosis
- Dilated cardiomyopathy
- Tachycardia:
  - ventricular
  - supraventricular

Decreased oxygen supply

Noncardiac:
- Anemia
- Hypoxemia:
  - pneumonia, asthma, COPD, pulmonary hypertension, interstitial pulmonary fibrosis, obstructive sleep apnea
- Sickle-cell disease
- Sympathomimetic toxicity (cocaine use)
- Hyperviscosity:
  - polycythemia, leukemia, thrombocytosis, hypergammaglobulinemia

Cardiac:
- Aortic stenosis
- Hypertrophic cardiomyopathy