

Myocardial infarction and angina

pathophysiology, risk factors and features

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Coronary heart disease is the commonest cause of premature death in the United Kingdom. This month's special feature focuses on myocardial infarction and angina. In the first of three articles, the pathophysiology, risk factors and features are discussed

Coronary heart disease is one of the major causes of death in the UK. Every year 300,000 people have a heart attack and there are 110,000 deaths from heart problems. Angina affects 1.4 million people. In March, 2000, the Government launched the National Service Framework for Coronary Heart Disease which set out a plan to tackle the problem and reduce these figures. This article discusses the pathophysiology, risk factors and features of myocardial infarction and angina pectoris.

■ PATHOPHYSIOLOGY

Pathophysiology is defined as the derangement or alteration of function seen in a disease. In the case of myocardial ischaemia the altered function is the result of an imbalance between oxygen demand and supply (Figure 1, p124). The oxygen demand depends principally on heart rate, contractility and systolic wall tension, whereas the oxygen supply depends mainly on the coronary blood flow and the oxygen carrying capacity of the blood.

Chronic stable angina pectoris is caused by a condition termed "demand ischaemia" or "high flow ischaemia". This form of ischaemia reflects the pathological insufficiency of chronically obstructed coronary arteries to meet the increased myocardial oxygen demand, particularly with exercise but also with other conditions leading to tachycardia. Myocardial infarction and unstable angina pectoris (together often referred to as acute coronary syndromes) are caused by a condition termed "supply ischaemia" or "low flow ischaemia". This form of ischaemia results from a significant reduction in coronary blood flow and oxygen supply which is secondary to increased vasculature tone, intracoronary platelet aggregation, or thrombus formation. It has to be borne in mind that coronary autoregulation means that an increased oxygen demand of the myocardium is met mainly by a rise in coronary blood flow and only to a very small extent by an increased oxygen extraction from coronary blood.

The myocardial oxygen consumption is determined by the myocardial wall tension, heart rate and myocardial contractility.

The regulation of coronary blood flow is mainly dependent on the vascular resistance which, in turn, appears to be regulated by several control mechanisms. These factors can be described as either intrinsic or extrinsic to the vascular bed.

The intrinsic factors are:

- metabolic control by adenosine, nitric oxide (NO), prostaglandins
- endothelial control by endothelium-derived relaxing factor, prostacyclin, endothelin-1
- autoregulation via myogenic control and nitric oxide

The extrinsic factors are:

- extra vascular compressive factors such as left ventricular systolic compression and the bending of arterioles through the ventricular wall which are greater in the subendocardium than in the subepicardial layer

The effects of coronary atherosclerosis are related to the severity and length of the stenosis, the degree of calcification of the atherosclerotic plaque and "vessel compliance", the presence of superimposed platelet activation, and aggregation and thrombosis. However, there seems to be little doubt that the severity of an atherosclerotic stenosis does not correlate with the likelihood of suffering unstable angina pectoris, myocardial infarction or, at worst, sudden coronary death. The identified pathophysiological culprit in most cases is a ruptured atherosclerotic plaque, leading to activation and aggregation of platelets, and to the formation of an occlusive thrombus. Atherosclerotic plaques are predominantly composed of fibrous tissue, calcium and lipid-laden foam cells, and necrotic debris.

The conversion from chronic stable angina pectoris to acute coronary syndromes (unstable angina pectoris, myocardial infarction) seems to be the sequel to an initial endothelial injury which, usually at the sites of atherosclerotic plaques and commonly at the site of plaque ulceration and fissure, leads to platelet activation, adhesion

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and aggravation via mediators such as thromboxane A₂, serotonin, adenosine diphosphate, platelet activating factors, thrombin and tissue factor which exhibit a vasoconstrictive effect as well. This establishes a vicious circle of thrombosis, vasoconstriction and, eventually, so-called neointimal proliferation. This term describes a very complex interaction between activated macrophages, fibroblasts and intimal smooth muscle cells which, via certain growth factors, appear to stimulate the formation of new connective tissue. This consequently leads to a dynamic narrowing of the coronary artery lumen and thereby a significant reduction in its blood flow.

The dynamic process of plaque rupture may evolve to a completely occlusive thrombus, typically leading to a large zone of myocardial necrosis involving the full or nearly full thickness of the ventricular wall in the myocardial bed supplied by the affected coronary artery. This is the pathophysiological substrate of a transmural myocardial infarction.

Unstable angina pectoris or a subendocardial infarction are considered to be caused by less obstructive thrombi. Furthermore, other compensatory mechanisms, including relief of transient vasospasm, spontaneous lysis and restoration of blood flow in the culprit coronary vessel may prevent the plaque rupture from necessarily terminating in myocardial necrosis.

It is noteworthy that there is a long list of causes of myocardial infarction without coronary atherosclerosis, a few of which are:

- arteritis, for example, in connective tissue diseases, polyarteritis nodosa, Takayasu's disease, syphilis, ankylosing spondylitis
- trauma to coronary arteries, for example, radiation, myocardial contusion
- spasms, for example, in Prinzmetal angina or after nitrate withdrawal
- emboli, for example, from bacterial or non-bacterial endocarditis, valve prosthesis, myxoma, intracardiac catheters or guidewires
- congenital, for example, anomalous origin of coronaries, coronary aneurysms, fistulas
- haematological, for example, polycythaemia vera, disseminated intra-vascular coagulation, hypercoagulability
- myocardial oxygen demand-supply disproportion, for example, aortic stenosis or insufficiency, thyrotoxicosis, carbon monoxide poisoning, prolonged hypotension
- miscellaneous, for example, cocaine abuse

A myocardial infarction affects the ventricular structure and function, and leads ultimately to ventricular remodelling, a term which describes the changes in size, shape and thickness involving both the infarcted and the non-infarcted segments of the ventricle. This complex process does not only determine the ventricular function but also the prognosis post-infarction, and is dependent on factors such as the infarct size, ventricular loading conditions and infarct artery patency.

Ventricular enlargement and subsequent remodelling can be significantly attenuated with measures, that aim for an early opening of the occluded infarct artery. Furthermore, current evidence suggests that the myocardium can be protected with drugs that exhibit a so-called plaque stabilising, possibly antioxidative effect and are thought to reverse endothelial dysfunction. The timing of reperfusion here appears to be the single most important variable to reduce both ventricular dilatation and remodelling and, as a direct or indirect consequence of this, pump failure and/or death.

— CLINICAL FEATURES

Clinically, angina pectoris commonly presents as a central, crushing chest pain, which can radiate to the jaw, neck, back, one or both arms. Although the discomfort is typically described as constricting, choking and "like a heavy weight", it may also be characterised as stabbing, burning or "like a knife". The pain is usual-

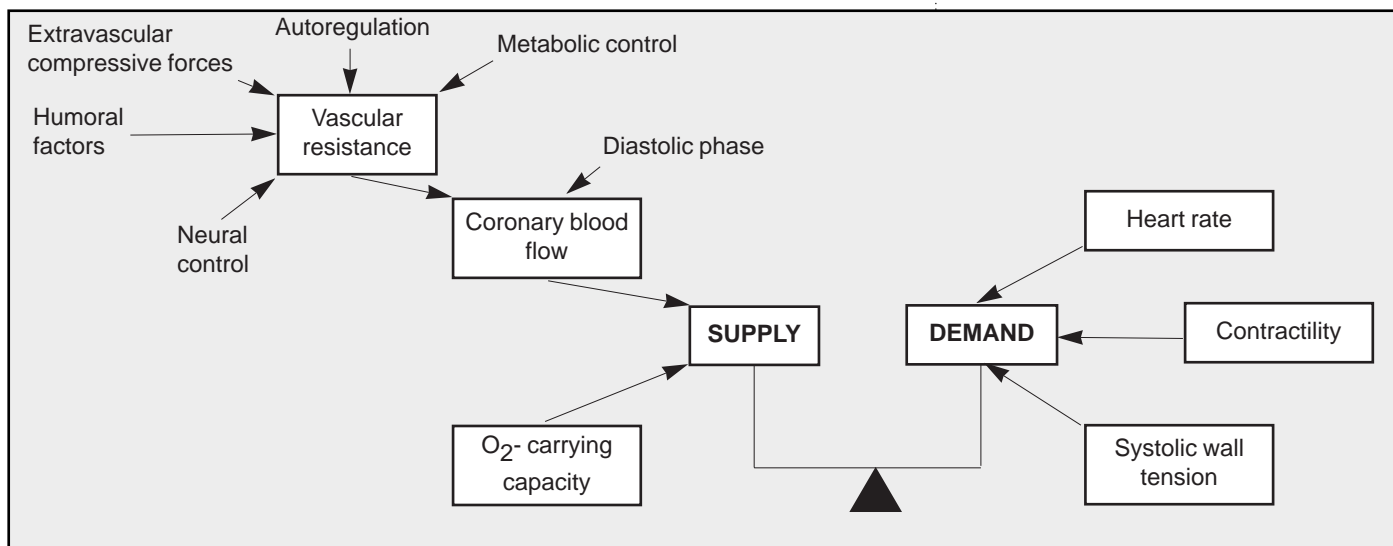


Figure 1: Factors influencing myocardial oxygen supply and demand. Credit: Ardehali A, Ports TA. Myocardial oxygen supply and demand. *Chest* 1990;98:699.

ly retrosternal, but it may present in a more unusual location such as the epigastrium or the back. Angina is often self-limiting and relieved by rest and/or nitrates. Angina is not only brought on by exercise but also by emotions, cold weather or heavy meals. It can be associated with other complaints such as breathlessness, palpitations, sweating, nausea or faintness. The duration of the chest pain is usually well below 30 minutes.

The pain of myocardial infarction usually resembles that of angina with respect to character and location. However, it is generally much more severe, lasts considerably longer than 30 minutes, is not relieved by rest or nitrates and is associated with systemic features such as diaphoresis, nausea and vomiting, breathlessness, palpitations and great anxiety. Diagnostic difficulties can occur for the following:

- the elderly who are either unable to provide a “classical history” or tend to present late with other predominant symptoms such as breathlessness due to left ventricular failure, syncope due to cardiac arrhythmias or solely by generalised weakness
- diabetic patients who sometimes suffer with an autonomous neuropathy which “desensitises” them to the cardiac pain (which is thought to arise from nerve endings in the ischaemic myocardium)
- young patients who frequently discount symptoms because they consider the possibility of cardiac pain highly unlikely (as occasionally do their treating doctors)
- patients without antecedent angina pectoris who therefore lack the experience of symptoms of coronary artery disease
- patients with atypical symptoms

The differential diagnosis of angina pectoris can be difficult and requires considerable clinical skills. The list below features a few commonly encountered differential diagnoses:

- musculoskeletal pain
- dyspepsia/gastric or duodenal ulcer
- pleurisy
- pulmonary embolus
- aortic dissection
- cholelithiasis
- renal colic

RISK FACTORS

The most important risk factors are those that are clearly associated with an increase in coronary heart disease, for which interventions have been shown to reduce the incidence of events.

Such risk factors must be identified and, when present, treated as part of an optimal secondary prevention strategy in patients with angina pectoris. They are common in this patient group, readily amenable to modification and their treatment can affect clinical outcome favourably. They comprise:

- cigarette smoking;
- hypertension
- diabetes mellitus
- hyperlipidaemia
- increased body mass index

Other proven risk factors for atherosclerosis are:

- familial history
- male gender — men are more prone than women
- age — the older the patient, the greater the risk

The hypothesised risk factor of a “positive family history” (that is, a first degree relative with coronary heart disease, aged 55 years or less for a male, and 65 years or less for a female) has led to extensive research as to whether one particular culprit is responsible. The list includes elevated homocysteine, fibrinogen and lipoprotein. It seems more likely that these are surrogate markers and that the underlying pathophysiology of an inherited susceptibility to premature atherosclerosis is a complex genetic defect that can be modified by environmental factors. It has to be stressed that the presence of a risk factor does not imply a causal relationship to coronary heart disease; a risk factor can be causative but not necessarily so.

Vigorous treatment of diabetes mellitus, hyperlipidaemia and hypertension, and smoking cessation are of paramount importance to prevent atherosclerosis from developing (primary prevention) or progressing (secondary prevention). There are also a number of hypothesised atherosclerosis-protective factors:

- increased aerobic exercise
- mono- and polyunsaturated fat fish oil (omega-3 fatty acids)
- iron and antioxidants
- rural life
- oestrogen replacement
- dietary fibre

Evidence suggests that an active lifestyle and a healthy, preferably Mediterranean diet including fresh fruit, vegetables, fish and olive oil, significantly reduces the risk of morbidity and mortality related to coronary heart disease.