The pathophysiology of myocardial ischaemia

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In this review paper on the pathophysiology of myocardial ischaemia, the recent concepts of the ischaemic cascade, as well as the concepts of stunning and hibernating myocardium, are discussed. It is clear that painful ischaemia is the final phenomenon in the ischaemic cascade and that it is preceded by biochemical disturbances, diastolic and systolic dysfunction and electrocardiographic abnormalities. Silent ischaemia remains a difficult research field.

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Introduction

Myocardial ischaemia is present when the demand for oxygen of any significant myocardial zone is no longer met by the coronary blood flow. In this review, the discussion of this broad topic will consider successively the mechanisms regulating normal coronary blood flow, some experimental data and myocardial ischaemia in the clinical setting.

Regulation of coronary blood flow and of coronary arterial tone

In the normal state the myocardial oxygen demand is almost always met by the coronary blood flow. The easiest way to maximize the myocardial oxygen demand is through maximal exercise testing and, in this setting, the normal myocardium does not become ischaemic (Fig. 1). Other invasive ways to test the coronary circulation include the coronary injection of papaverine, for the measurement of the coronary reserve (normal values are usually 3.5-5 times greater than the resting coronary blood flow), or the i.v. injection of increasing doses of vasodilators, such as dipyridamole, or positive inotropic agents, such as dobutamine, with analysis for signs of ischaemia on the ECG and left ventricular function by echocardiography or radionuclide markers.

The major determinants of myocardial oxygen demand and coronary blood flow are listed in Table 1. Among these the heart rate and the systolic blood pressure and, thus, the double product, are the most important and are easily measured during exercise testing and, in fact, the majority of the changes in myocardial contractility are directly related to the changes in heart rate.[3-3].

The regulation of coronary blood flow and tone is normally an auto-regulated mechanism involving adenosine released by the working myocardium (Hypothesis of Berne)[6]. Other mechanisms also play a role, including the production of relaxing or constricting factors by the platelets and endothelium-derived relaxing factor by the vascular endothelium[5]. These effective regulatory mechanisms become totally inadequate when the endothelium of the coronary arteries is abnormal due to coronary artery disease and the subendothelial layers are exposed to the circulatory blood. In this situation platelets produce potent vasoconstrictor substances, such as thromboxane or serotonin, and acetylcholine acts as a vasoconstrictor. In addition, the normal regulatory mechanisms become ineffective and coronary spasm is likely to occur if there is a plaque rupture (see below).

Experimental data

Early experimental data from Gould and Lipscomb[6] showed that the resting coronary blood flow was not decreased until a very tight coronary stenosis (above 90%) developed (Fig. 2). In contrast, the maximal coronary blood flow and the coronary reserve were reduced during stress or exercise when the coronary stenosis exceeded 50%. This observation is consistent with the view in clinical cardiology that a 50% reduction in coronary artery diameter is considered to be a significant lesion.

It is also known that for any given percentage stenosis, the length of the stenosis plays a major role in the reduction of coronary blood flow and coronary reserve which should also explain the damaging effect of several successive stenoses in the same coronary artery.

A transient interruption of the coronary blood flow in a significant portion of the myocardium in animals (due to coronary ligation), or in patients (as
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Myocardial oxygen demand (HR x BP)

Figure 1 Myocardial oxygen demand vs supply in the normal (solid line) and ischaemic myocardium (dotted lines). As shown by the two dotted lines, ischaemia may occur at different levels of myocardial oxygen demand in different patients. BP = blood pressure; CBF = coronary blood flow; HR = heart rate.

Table 1 Pathophysiology of myocardial ischaemia

1. Determinants of myocardial oxygen consumption
   - Left ventricular wall tension
   - Intraventricular pressure
   - Intracavitary radius
   - Ventricular wall thickness
   - Inotropic state
   - Heart rate
   - Systolic blood pressure
   - Diastolic relaxation
   - Basal metabolism = calcium handling
   - Myocardial substrates

2. Determinants of coronary blood flow
   - Driving pressure
     - Aortic diastolic pressure
     - Right atrial or left ventricular end-diastolic pressure
   - Coronary vascular resistance
   - Diastolic time

3. Myocardial metabolism itself

4. Blood coagulation

Table 2 The ischaemic cascade

<table>
<thead>
<tr>
<th>Local ischaemia</th>
<th>Metabolic abnormalities</th>
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<tbody>
<tr>
<td>Abnormal diastolic performance</td>
<td>Abnormal systolic function</td>
</tr>
<tr>
<td>ECG abnormalities</td>
<td>Chest pain</td>
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</tbody>
</table>

(5) angina pectoris, the clinical manifestation of myocardial ischaemia, is usually the last phenomenon, indicating severe ischaemia in a given region of the myocardium.

When the coronary blood flow is restored after a brief interruption, all these abnormalities disappear progressively but, if the blood flow is not restored within approximately 1 h, myocardial necrosis will start to occur to an extent dependent on the duration of the flow interruption, on the size of the myocardium at risk and/or the presence or absence of collateral blood flow. When the coronary blood flow is restored after a shorter period of time (15 min), myocardial infarction (MI) will be unlikely to occur but myocardial function will take at least 24 h to recover completely (Fig. 3). This phenomenon, first observed by Heyndrickx and coworkers, was later named myocardial stunning.

This cascade of ischaemic events is one of the reasons for the development of new diagnostic tests such as adenosine, dipyridamole or dobutamine stress echocardiography which are able to detect the early phases of myocardial ischaemia. The exact diagnostic and prognostic significance of these new tests has still to be defined but they are already important in patients unable to perform a maximal exercise test.

Myocardial ischaemia in the clinical situation

The major clinical problems are those of: (1) diagnosing and adequately treating symptomatic myocardial ischaemia, i.e. angina pectoris; (2) detecting and possibly treating asymptomatic myocardial ischaemia in symptomatic or high-risk asymptomatic persons (with several risk factors, such as male sex, age, family history, arterial hypertension, smoking and high cholesterol levels); (3) treating adequately the major complications of myocardial ischaemia, which are unstable angina pectoris or acute MI with the very frequent late consequence of congestive heart failure; (4) the detection of myocardial viability after one or several episodes of MI.

Angina pectoris

Angina pectoris is most often evident from a simple questionnaire and examination of the patient. Symptom-limited maximal exercise testing, adequately analyzed by a multivariate analysis, allows the diagnosis to be made on the basis of an abnormal ECG response, a low maximal workload with a low maximal heart rate. Once the diagnosis has been confirmed, many centres perform coronary angiography in order to select the best therapeutic option (drugs, percutaneous transluminal coronary angioplasty or surgery), after taking into account all the characteristics of the patient (age, social, psychological, professional).

In a patient with a history of stable angina pectoris, the symptoms of angina pectoris most often occur at a reproducible level of exercise and myocardial oxygen demand (double product) (Fig. 4). However, a variable exertional anginal threshold is possible since exercise by itself can induce a coronary vasospasm.

The pathophysiology of unstable angina pectoris is illustrated in Fig. 4, panel III.

Asymptomatic myocardial ischaemia

Asymptomatic myocardial ischaemia, detected either by exercise testing or by continuous ambulatory ECG (Holter) monitoring, raises more difficult questions since the prognosis of silent ischaemia remains disputed. We have shown that painful or silent myocardial ischaemia have the same poor prognosis, but this problem remains unresolved since other groups have shown that patients with stable angina pectoris and silent myocardial ischaemia have a good prognosis. However,
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Figure 4  Schematic illustration of the relation between physical activity (during 24 h) expressed as METS (multiple of basal metabolic oxygen consumption) and coronary flow reserve. A=exercise below level of maximal coronary flow reserve without experiencing ischaemia; B=exercise above level of maximal coronary flow reserve; C=coronary flow reserve is impaired; D=coronary flow reserve decreases so that resting flow is impaired and ischaemia occurs at rest. (Modified with permission from Maseri et al.)

Unstable angina pectoris and/or acute myocardial infarction

Both of these phenomena probably have the same cause, i.e. rupture of an atherosclerotic coronary plaque (Fig. 5) that leads to coronary spasm and intracoronary coagulation. The problem is either transient or leads to the occurrence of a fresh MI whose size may be limited by early i.v. thrombolysis or, if available, by early mechanical reperfusion.

The problem of myocardial viability

The problem of myocardial viability after acute MI is clinically very important. After an MI with documented coronary stenosis or obstruction, there is usually an akinetic or dyskinetic myocardial zone. This area may become either totally or partially necrotic and so partially or largely viable mostly in the presence of an important residual anterograde or collateral coronary blood flow. In order to try to define the concept of akinetic but viable myocardium, the term ‘hibernating’
myocardium has been introduced, i.e. a myocardium that defends itself from a low coronary flow by a decreased contractile function\[20-22\]. This clinically interesting concept has been questioned since it might simply result from repeated episodes of myocardial stunning, leading to a chronic stunning (with normal flow) rather than from chronic hibernation\[23,24\]. Whatever the final pathophysiological explanation might be, it is important to assess the viability of apparently necrotic myocardium since reperfusion may improve the prognosis and prevent further myocardial remodelling leading to irreversible myocardial failure.

References


