Coronary flow reserve

The concept of coronary flow reserve
The main resistance to coronary blood flow lies in the small intramural, coronary arteries. These vessels range in diameter from 10 nm to 140 nm, which is beyond the resolution of standard coronary angiographic methods. Because the myocardium is totally dependent on aerobic metabolism, an increase in myocardial oxygen consumption requires an increased coronary blood flow. This is achieved by dilatation, mainly in the microvascular coronary arterial bed. The concept of coronary flow reserve was first introduced by Gould et al in 1974—it is the ability of coronary blood flow to increase substantially when metabolic requirements demand it. Coronary autoregulation is complex, with a number of potential controlling factors. It is also affected by several pathological states, including myocardial hypertrophy, atherosclerosis, myocardial ischaemia, and infarction. The concept and measurement of coronary flow reserve is important to our understanding of the normal physiological control of coronary blood flow and the pathophysiology of these conditions. However, measurements of coronary flow reserve are hampered by major shortcomings in methodology. Coronary flow reserve assessments have attempted to identify the effect of epicardial coronary stenoses and to evaluate the results of revascularisation processes such as angioplasty and coronary artery bypass graft surgery. They have also been used in an attempt to identify the pathophysiological mechanisms of chest pain syndromes in patients with apparently normal epicardial coronary arteries, such as patients with syndrome X, microvascular angina, and dilated cardiomyopathy.

Mechanisms of coronary autoregulation
There are several theories and mechanisms to explain how flow is controlled in the coronary vascular bed. The coronary arterioles are innervated by sympathetic, parasympathetic, and non-adrenergic, non-cholinergic nerve fibres. When metabolic demands require an increase in coronary blood flow, various mediators may be involved in a hyperaemic response.

One of the main mediators of coronary hyperaemia is adenosine, which is produced by the breakdown of adenosine triphosphate. When metabolic requirements increase, adenosine is produced by the myocardial cells. Adenosine causes an increase in cyclic AMP concentrations within the vascular smooth muscle cells which results in their relaxation; blood flow then increases. Washout of adenosine quickly occurs during recovery and the hyperaemic response is thus limited.7

The importance of the vascular endothelium in the control of vascular tone is being increasingly recognised. The release of vasodilator substances such as endothelium derived nitric oxide,34 endothelium derived hyperpolarising factor4 and prostacyclin,9 may all be implicated in the vasodilatation that occurs because of increased metabolic demand. These endothelium dependent relaxing factors can be released by various stimuli including both pharmacological and mechanical factors. Pharmacological releasing agents include acetylcholine, substance P, and catecholamines. Physical stimuli include blood flow, pulsatile flow, and increased sheering stress.7

The endothelium can release vasoconstrictor factors as well as vasodilator factors. One of the most potent naturally occurring vasoconstrictor factors is endothelin, a 21-residue peptide, which has potent smooth muscle vasoconstrictor activity.9 The importance of the release of endothelin in the coronary circulation is, however, still not fully understood.9 Other vasoconstrictor agents include thromboxane A2 and angiotensin. Certain disease states may upset the balance between the production of vasodilator and vasoconstrictor substances from the endothelium—e.g. oxidised LDL has been shown to inhibit endothelium derived relaxing factor10 and this may be one of the factors involved in the hyper-responsiveness of atherosclerotic coronary arteries to acetylcholine.11 The vascular endothelium produces less prostacyclin with increasing age. Production of prostacyclin also decreases in disease states, such as diabetes mellitus and atherosclerosis.12

The coronary circulation is innervated by sympathetic and parasympathetic nerve fibres. The composite effect of neural innervation is complex because cholinergic and adrenergic mediators such as acetylcholine and noradrenaline can have various effects depending on the presence or absence of a normally functioning endothelium and the responsiveness of the vascular smooth muscle. It has been shown that vasoconstriction in response to these agents is potentiated by atherosclerosis.13 It is also well known that substances such as acetylcholine have a differential effect on blood flow, causing more vasodilatation in the endocardial than in the epicardial coronary vessels thus altering the distribution of coronary blood flow across the myocardium.14

Methods of measuring coronary flow reserve
Coronary flow reserve may be defined as the ratio of maximal coronary blood flow to resting coronary blood flow. The normal heart can increase its coronary blood flow up to four or five times above resting values during normal exercise. It is essential that during measurement of coronary blood flow, basal and maximal flow are stimulated and that these measurements are accurately assessed. Coronary blood flow can be increased more by pharmacological substances than by exercise.15 Methods that can achieve maximal coronary vasodilatation include transient coronary occlusion, intravenous dipyridamole,
intracoronary papaverine, intracoronary adenosine, intracoronary acetycholine, and substance P. A major criticism of many studies that attempt to measure coronary flow reserve is that one cannot be certain whether or not maximal coronary flow has been stimulated. All methods of measuring coronary flow have technical limitations.

One method used is that of taking timed collections of blood from the great cardiac vein which drains the myocardium supplied by the left anterior descending coronary artery.\(^\text{16}\) Coronary sinus thermodilution catheters have been used to measure coronary blood flow.\(^\text{17}\) The main problem with these techniques is the variability in venous drainage, which limits the accuracy of both thermodilution and timed venous collections. Recently developed small Doppler flowmeters can be placed directly into the coronary artery. These allow measurement of coronary blood flow velocity, which has been shown to be proportional to blood flow.\(^\text{18}\) Coronary flow reserve can then be computed as the ratio of resting to maximal blood flow velocity and when this is combined with quantitative coronary angiography it is possible to assess coronary flow. In some studies blood flow velocity alone has been measured. This, however, requires that the cross sectional area of the vessel at the site of the Doppler probe remains constant between measurements. Some workers have tried to reduce this diameter variability by infusing nitrates to produce maximal dilatation in the vessels.\(^\text{19}\) The Doppler probe method is used widely but among its limitations is the relative obstruction of the vessel by the catheter, though the catheters are small, and indeed a new Doppler guide wire for intravascular measurement of coronary artery flow velocity is now available.\(^\text{20}\) Obstruction to flow becomes much more important in diseased vessels.

Myocardial perfusion has been assessed by myocardial distribution of uptake of radioactive tracers such as thallium-201. This technique cannot distinguish between epicardial and endocardial blood flow and cannot measure acute changes in blood flow. It can only be used once or twice during an intervention.

Quantitative digital subtraction angiography compares the density of a contrast medium that is injected into the coronary artery with the contrast concentration, appearance time:density ratio, and myocardial washout time.\(^\text{21}\) However, absolute blood flow is not calculated. A measure of coronary flow reserve can be obtained by calculating the ratio of the initial two hyperaemic measurements. Contrast medium induces coronary vasodilatation but this is by no means maximal possible dilatation.

Positron emission tomography can measure most of the essential components of cardiac blood flow including perfusion, myocardial function, and viability.\(^\text{22,24}\) This technique represents the reference standard for the measurement of coronary flow reserve; however, one drawback with this method is its inability to distinguish between endocardial and epicardial perfusion.

Radioactive labelled microspheres have been used to measure the transmural difference in myocardial perfusion in animals.\(^\text{25}\) Diffusible indicators and inert gas clearance techniques with nitrous oxide, hydrogen, helium, xenon\(^\text{13,26}\) and krypton\(^\text{49}\) have also been widely used.\(^\text{26}\) These methods compare the initial concentration of the tracer with the arterial and coronary sinus concentrations to determine coronary blood flow by clearance equations.

Many of the techniques mentioned measure relative changes in perfusion and not absolute coronary blood flow. The methods currently available for measuring coronary blood flow are subject to data scatter, wide confidence intervals, and methodological issues that limit their accuracy.\(^\text{14}\) Other variables affecting coronary blood flow must be taken into account, particularly changes in heart rate, left ventricular preload, and pharmacological interventions.\(^\text{27}\) Advances in the technology of coronary blood flow measurement will make the concept of clinical measurement of coronary flow reserve more feasible in the future.

**Disease states and the measurement of coronary flow reserve**

Several disease states have been investigated by these various methods of measuring coronary flow. These include coronary atheromatous disease\(^\text{28,29}\) and left ventricular hypertrophy.\(^\text{30}\)

The effect of angioplasty on coronary flow reserve has been assessed by coronary sinus thermodilution and xenon scintigraphy. Both techniques have shown that there is an improvement in both resting and hyperaemic coronary blood flow after successful coronary angioplasty.\(^\text{31}\)

There are, however, conflicting reports of the effect of coronary angioplasty on coronary flow. Improvement in myocardial perfusion has been demonstrated by positron emission tomography and oxygen-15 labelled water during single vessel angioplasty.\(^\text{32}\) Papaverine has been used to induce an increase in coronary flow velocity and improvements after angioplasty have been demonstrated with papaverine and Doppler flow probes.\(^\text{33,34}\) Such technology has been useful because it has been shown that immediately after coronary angioplasty, coronary flow reserve correlates poorly with residual coronary stenosis, minimum cross sectional area of the stenosis, and the translesional pressure gradient. At follow up, on average seven months afterwards, however, coronary flow reserve had returned to normal in all but those vessels that had developed restenosis.\(^\text{35}\)

As pointed out by Ishihara et al\(^\text{36}\) on pages 288–92, the measurement of coronary flow reserve immediately after coronary angioplasty is limited by several difficulties. It can be difficult to assess stenosis severity by quantitative angiography and reciprocal lumen diameter because fracture of the atherosclerotic plaque can make the vessel borders indistinct.\(^\text{36}\) Vasoactive substances may be released from the vascular endothelium and vascular smooth muscle after injury of the site. These substances may have variable effects on the distal vascular bed.\(^\text{37,38}\) During angioplasty, routinely administered medications can affect coronary blood flow. These substances include glyceryl trinitrate, calcium antagonists, and β blockers. There may be a temporary increase in resting coronary blood flow, causing an apparent impairment of coronary flow reserve after angioplasty.\(^\text{39}\) This study used measurements of flow in the great cardiac vein at rest and during rapid atrial pacing before and immediately after angioplasty in 22 patients with stenosis of the left anterior descending coronary artery. It compared these with 12 control patients who had minimal narrowing of the left anterior descending coronary artery. Immediately after angioplasty, coronary flow reserve was not fully restored. At this time it was shown that resting coronary vascular resistance was significantly increased whereas coronary vascular resistance during rapid atrial pacing was restored to normal. Resting hyperaemia was restored six months later, and coronary vascular resistance during pacing was unaltered. Ishihara et al\(^\text{36}\) concluded that the impaired coronary flow reserve immediately after angioplasty may be caused by a short-lived but significant increase in rest-
increase in resting coronary blood flow. However, methodological problems in measuring blood flow in the left anterior descending coronary artery by measuring flow in the great cardiac vein by the thermistor technique must be considered as one explanation for the variable results after angioplasty.

Another recent study suggests that it may not be possible to assess the efficacy of coronary angioplasty immediately after angioplasty by coronary flow reserve measurements.40 This study measured coronary stenoses immediately after angioplasty by coronary flow reserve angiograms.

It has been shown that perfusion defects may occur during successful dilation of coronary artery lesions at angioplasty, with subsequent normalization, shown by thallium perfusion images months after the angioplasty.42 The mechanisms involved in the reduction of coronary flow reserve after angioplasty are by no means fully understood.

To sum up, the coronary circulation is very specialized, and able to autoregulate and respond to metabolic demands. Functional alterations in the coronary vascular bed may occur because of atherosclerosis, extravascular stress forces, thrombosis, physical or biochemical endothelial dysfunction, and abnormal myocardium. Coronary flow reserve remains difficult to measure, even with state of the art technology, which, in any case, is not yet available or applicable as a routine clinical tool. Nevertheless, the concept of coronary flow reserve is enabling research cardiologists better to understand physiological and pathological states. Such an understanding may allow the development of therapeutic agents and techniques that will improve treatment of cardiac disease.
Coronary flow reserve.

P Collins

Br Heart J 1993 69: 279-281
doi: 10.1136/hrt.69.4.279

Updated information and services can be found at:
http://heart.bmj.com/content/69/4/279.citation

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/