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,3,4 endothelium derived hyperpolarising factor4 and prostacyclin,5 may all be implicated in the vasodilatation that occurs because of increased metabolic demand. These endothelial 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 shear 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.6 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—eg, 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, intra-
coronary acetylcholine, and substance P. A major crit-
cism 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 blood flow have technical limita-
tions. 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.16 Coronary sinus thermodilution 
catheters have been used to measure coronary blood 
flow.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.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, how-
ever, 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.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.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 thalli-
um-201. This technique cannot distinguish between epi-
cardial 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, appear-
ance time:density ratio, and myocardial washout time. 21 
However, absolute blood flow is not calculated. A mea-
sure of coronary flow reserve can be obtained by calculat-
ing 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.22,23 This 
technique appears to be 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 perfu-
sion in animals.24 Diffusible indicators and inert gas 
clearance techniques with nitrous oxide, hydrogen, heli-
um, xenon133 and krypton45 have also been widely 
used.26 These methods compare the initial concentration 
of the tracer with the arterial and coronary sinus concen-
trations 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 con-
ference intervals, and methodological issues that limit 
their accuracy.27 Other variables affecting coronary blood 
flow must be taken into account, particularly changes in 
heart rate, left ventricular preload, and pharmacological 
interventions.27 Advances in the technology of coronary 
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 var-
ious methods of measuring coronary flow. These include 
coronary atheromatous disease28,29 and left ventricular 
hyppertrrophy.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 angioplas-
ty.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 dur-
ing single vessel angioplasty.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.33,34 Such tech-
nology has been useful because it has been shown that 
immEDIATELY AFTER 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.35,36 As pointed out by Ishihara et al39 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 frac-
ture of the atherosclerotic plaque can make the vessel 
borders indistinct.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.37,38 
During angioplasty, routinely administered medications 
can affect coronary blood flow. These substances include 
glycerol trinitrate, calcium antagonists, and β blockers. 
There may be a temporary increase in resting coronary 
flow, causing an apparent impairment of coronary flow 
reserve after angioplasty.39 This study used measure-
ments of flow in the great cardiac vein at rest and during 
rapid atrial pacing and immediately after angioplas-
ty 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 
artery descending coronary artery. It compared these with 12 
control patients who had minimal narrowing of the left 
artery 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 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 thermodilution tech-
nique must be considered as one explanation for the vari-
able 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 by quantitative coronary angiography in an unselected group of patients. Coronary flow reserve measurements were computed from digitised coronary angiograms performed before, immediately after, and 24 hours after coronary angioplasty. Coronary flow reserve was similar before and immediately after coronary angioplasty, with a slight improvement at 24 hours. Coronary artery dimensions correlated poorly with coronary blood flow reserve before and after angioplasty. It was concluded that there were no changes in the minimal lumen diameter, obstruction area, and percentage diameter stenosis in the first 24 hours after angioplasty. Individual variations in coronary flow reserve measurements from digitised coronary angiograms were only minimal within one day after angioplasty. Coronary flow reserve measurements from digitised coronary angiograms at angioplasty therefore have little value in this setting. It has been shown that perfusion defects may occur despite successful dilation of coronary artery lesions at angioplasty, with subsequent normalisation, shown by thallium perfusion images months after the angioplasty.41 42 The mechanisms involved in the reduc-
tion of coronary flow reserve after angioplasty are by no means fully understood.

To sum up, the coronary circulation is very spe-
cialised, and able to autoregulate and respond to meta-
bolic demands. Functional alterations in the coronary vascular bed may occur because of atherosclerosis, extravascular stress forces, thrombosis, physical or bio-
chemical 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 under-
stand physiological and pathological states. Such an understanding may allow the development of therapeutic agents and techniques that will improve treatment of car-
diac disease.

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