Importance of collateral circulation in coronary heart disease

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Received 14 June 2006; revised 27 November 2006; accepted 30 November 2006; online publish-ahead-of-print 11 January 2007

**Aims** Collateral arteries are a common but inconsistent finding in coronary heart disease (CHD). We endeavoured to review the methods for coronary artery collateral assessment, the predictors and clinical importance of collateral blood flow, and the potential for therapeutic augmentation of collateral anastomoses.

**Methods and results** While many methods have been used to assess collateral blood flow only a few have been formally validated. Collateral flow index, as determined by measurement of intra-coronary pressure or flow velocity, is the most robust measure of collateral flow. These techniques have led to important advances in our understanding of collateral artery function. Coronary collateral arteries may prevent myocardial ischaemia in healthy subjects and in patients with CHD. A functional collateral circulation may lead to reduced ischaemia, preservation of ventricular function, and an improved prognosis. Recent trials have demonstrated that vascular progenitor cell therapies may improve ventricular function following acute myocardial infarction, raising the possibility of effective biological treatments to improve myocardial blood flow and prognosis in CHD.

**Conclusions** Coronary collateral anastomoses represent a prognostically important adaptive response in patients with CHD. Therapeutic augmentation of collaterals with emerging biological therapies represents a desirable goal for treating CHD patients.

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**Introduction**

Coronary collateral arteries serve as alternative conduits for blood flow in obstructive coronary heart disease (CHD). The purpose of this article is to describe the importance of a functional coronary collateral circulation in CHD. We will illustrate how coronary collateral arteries can preserve myocardium and improve prognosis in CHD. Recent trials of biological therapies designed to improve myocardial perfusion in CHD are also discussed.

**Methods**

The assessment, pathogenesis, and therapeutic promotion of coronary collaterals have recently been described by Seiler.1 Respecting this work, our objective was to examine recent research regarding the functional and prognostic importance of coronary collaterals in different clinical settings. We have identified some important post-mortem anatomical publications, and have then identified key angiographic studies from the mid-1980s and informative clinical studies from the mid-1990s till the present time.

To this end, we identified relevant English language publications through a PubMed search using the keywords ‘artery’, ‘collateral’, ‘coronary’, ‘human’, and ‘ischaemic heart disease’. After evaluating these papers, and based on our own practical experiences, we prepared a manuscript which places emphasis on in vivo human investigations, illustrating a contemporary position on collateral function in different patient groups. Owing to word count limitations, we have restricted the citations to, in our view, the most relevant and informative publications.

**Clinical assessment of coronary collateral arteries**

Collateral artery growth is mediated by arteriogenesis (Table 1). Anatomically, collateral arteries may be either epicardial or intramyocardial and serve as contralateral or ipsilateral conduits (Figures 1 and 2).2 Myocardial blood flow is the product of epicardial coronary and collateral artery flow.

**Angiographic evaluation of coronary collateral arteries**

Coronary angiography is the standard method to identify coronary collateral arteries (Table 2). Angiography with ordinary visual detection has limited resolution. Arterioles...
artery opacification, with cine angiography continued until injection of contrast should achieve complete coronary glycerine (100–200 μg) or adenosine (15–40 μg for the left coronary artery and 10–30 μg for the RCA). A graduated injection of contrast should achieve complete coronary artery opacification, with cine angiography continued until coronary sinus opacification is achieved. The X-ray image intensifier may be ‘panned’ during cine acquisition to ensure that collateral flow is fully demonstrated. Collateral filling should be assessed in cine frames obtained during diastole.

Invasive assessment of coronary collateral artery function

Coronary pressure and flow
Invasive studies have demonstrated coronary collateral flow may be bidirectional. The coronary wedge pressure, which is the distal coronary pressure obtained when antegrade flow is prevented by intra-coronary balloon inflation, is a marker of collateral function.

Coronary collateral blood flow can be objectively quantified using an 0.014” (0.36 mm) intra-coronary wire which has either a flow velocity (Doppler) or a pressure measuring capability. Pressure-derived fractional collateral flow reserve is estimated by calculating the collateral pressure index (CFI) during maximal hyperaemia. CFI is based on the premise that coronary perfusion pressure or flow velocity distal to an occlusion are derived from collateral flow.

The Doppler-derived CFI ratio is measured by obtaining distal coronary flow velocity (CFV) during patency and balloon occlusion (Table 3). Distal occlusive collateral flow velocity correlates well with coronary wedge pressure, particularly in non-infarcted myocardium. The CFV reserve (CFVR) is the ratio of maximum hyperaemic average peak velocity (APV) to basal APV, and a CFVR < 2 in the absence of an epicardial artery stenosis (i.e. FFR ≥ 0.75) represents microvascular dysfunction. In collateral-dependent territory, functional measures of collateral flow, such as a basal APV, are positively correlated with collateral size.

The pressure-derived collateral flow index (CFIp or PDCF) depends on the simultaneous estimation of mean aortic pressure (Pao), mean central venous pressure (Pv), and mean distal coronary pressure during balloon occlusion (Pd; Table 3). CFIp is synonymous with the maximum recruitable collateral flow reserve (Qc) expressed as a fraction of normal myocardial perfusion: Qc/Qn = CFIp.

When pressure and Doppler studies are performed successively, the collateral resistance index (RColl, mmHg cm⁻¹ s⁻¹) can be calculated (Table 3) assuming constant vessel diameters before and during balloon occlusion. In other words, RColl is derived from the relationship between the pressure gradient across the collateral bed and collateral-derived flow velocity measured in the recipient artery during balloon occlusion. The components of the collateral pathway (RColl) are the collateral microvascular network resistance (Rc) and the donor artery resistance (Rd; Table 3). RColl is inversely correlated with the extent of functional collateralization. The other resistance networks are those of the obstructed recipient artery (Rcoll) and the peripheral myocardial microcirculation (Ri; Table 3).

Coronary vascular resistances may vary acutely due to, for example, distal embolization or vasoactive drugs. Chronic changes in coronary artery resistance may occur after ‘fixed’ alterations in flow, such as after successful PCI. Collateral flow velocity is influenced by ventricular function. This relationship can probably be explained by variation in microvascular function (or more specifically, microvascular

<table>
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<tr>
<th>Attribute</th>
<th>Definition</th>
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<tr>
<td>Angiogenesis</td>
<td>Formation of new capillaries by sprouting from post-capillary venules</td>
</tr>
<tr>
<td>Arteriogenesis</td>
<td>The transformation of pre-existing arterioles into functional (muscular)</td>
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<td></td>
<td>collateral arteries with vasomotor properties</td>
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<tr>
<td>Collateral blood vessels</td>
<td>Collateral blood vessels are vascular connections linking parallel arteries</td>
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<td>without an intervening capillary</td>
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<100 μm are invisible to the naked eye, and visible collaterals typically have a diameter of 0.5 mm. The angiographic assessment of collateral circulation can be refined by off-line computer analyses.

Angiographic collateral degree
Coronary collaterals may be spontaneously visible or recruitable. Recruitable collaterals may be defined by the absence of visible collaterals before coronary occlusion (grade 0 or 1) and the development of collaterals during coronary occlusion (grade 2 or 3). Spontaneously visible collaterals are present when they are grade 2 or 3 prior to any intervention.

In the setting of a stenosed artery, collaterals may be graded using the Rentrop classification: 0, no visible collateral channel filling; I, faintly visible collaterals with filling of branches but no filling of the distal stenotic (culprit) artery; II, collaterals partially filling the branches of the stenosed artery; III, complete collateral filling of the stenosed artery. In patients with single vessel coronary artery disease (CAD) and preserved left ventricular (LV) function, collateral filling grade increases acutely (within 90 s) during balloon occlusion and diminishes on balloon deflation. When the culprit artery is patent, the assessment of both spontaneously visible and recruitable collaterals requires a double artery approach with balloon occlusion of the culprit (collateral receiving) artery and simultaneous contrast injection in the donor artery (see also Seiler’s review).

Collateral filling should be assessed in cine frames obtained during diastole. The X-ray image intensifier may be ‘panned’ during cine acquisition to ensure that collateral flow is fully demonstrated. Collateral filling should be assessed in cine frames obtained during diastole.

Contrast washout collaterometry is based on the hypothesis that the time to contrast clearance distal to an occluded artery is inversely related to collateral flow. In other words, contrast is cleared more rapidly in a well-collateralized territory. Other angiographic methods for collateral evaluation are summarized in Table 2.

Angiographic demonstration of coronary collateral arteries
The complete angiographic assessment of coronary collateral arteries requires the induction of maximal hyperaemia, which may be achieved by systemic or intra-coronary vasodilator administration. During routine angiography, intra-coronary vasodilator therapy is usually adequate [e.g. nitroglycerine (100–200 μg) or adenosine (15–40 μg for the left coronary artery and 10–30 μg for the RCA)]. A graduated injection of contrast should achieve complete coronary artery opacification, with cine angiography continued until coronary sinus opacification is achieved. The X-ray image intensifier may be ‘panned’ during cine acquisition to ensure that collateral flow is fully demonstrated. Collateral filling should be assessed in cine frames obtained during diastole.

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resistance) according to the presence and severity of ischaemic myocardial damage and contractile dysfunction.\(^\text{24}\) The response to vasodilators varies between collateral types, and recruitable collaterals may be less responsive to vasodilators than spontaneously visible collaterals. This is probably because spontaneously visible collaterals are anatomically and functionally well developed compared with recruitable collaterals which may be less mature.\(^\text{5}\)

Seiler and coworkers\(^\text{20}\) were the first to use three simultaneous intra-coronary sensor wires in different areas to elucidate the mechanisms leading to coronary steal (see in what follows). Clearly, a triple wire approach is not readily applicable to ordinary catheter laboratory practice, and measurement of \(R_{\text{Coll}}\) is usually reserved for research purposes by experienced operators.

Pressure- and velocity-derived assessments of fractional coronary flow are not identical. Each measure is subject to different physical laws and may differentially influence flow resistances in the coronary, microvascular, and collateral systems. For example, Doppler, which measures CFV rather than flow volume, is affected by vessel diameter, tortuosity, branching (due to altered velocity waveform profiles), and distal wire placement.\(^\text{13}\) A constant coronary artery diameter is an important prerequisite for both Doppler and pressure measurements, however, this may be less important for a Doppler approach.\(^\text{13}\) The Doppler wire is very sensitive to phasic alterations in forward and reverse flow, whereas the pressure wire is not. Alternatively, \(C_{\text{Flp}}\) is entirely independent of alterations in heart rate and aortic pressure, whereas the Doppler approach is not.

Collateral blood flow measurements using Doppler and pressure techniques were highly correlated in experimental animal validation studies \((r = 0.96)\);\(^\text{14}\) but the correlations were weaker in human validation analyses \((C_{\text{Fiv}} \text{ vs. } C_{\text{Flp}}: r = 0.8)\).\(^\text{16}\) In the latter, Seiler et al.\(^\text{16}\) studied 51 patients with single or double-vessel CAD and assessed collateral sufficiency according to ECG changes during intra-coronary balloon inflation. The pressure-derived collateral index \((C_{\text{Flp}})\) underestimated fractional collateral flow compared with the velocity-derived index \((C_{\text{Fiv}})\). Thus, compared with the Doppler-derived \(C_{\text{Fiv}}\), the pressure-derived \(C_{\text{Flp}}\) appears to be slightly less sensitive with a weaker positive predictive accuracy for the detection of a functional collateral circulation.\(^\text{16}\) As Doppler- and pressure-derived assessments of coronary blood flow are based on different

Figure 1  (A) RAO 15° and (B) RAO 10° cranial 40° projections. Injection of the left dominant coronary artery results in opacification of ipsilateral collateral connections (CC) from the second marginal (OM; crossed arrows) and posterior descending arteries (PDA; plain arrows) to the distal LAD. (C) RAO 15° view. Injection of the left coronary artery results in opacification of contralateral collateral connections (CCC) from the anterior septal arteries to the posterior descending artery (PDA). (D) RAO 15° caudal 25° view. Opacification of collateral artery connections from a large diagonal artery (DIAG) to an occluded obtuse marginal artery via ipsilateral collateral connections (ICC). Opacification of the coronary sinus (CS) indicates complete collateral artery filling.
Collateral circulation in CHD

Non-invasive evaluation of coronary artery collateral arteries

Although non-invasive methods may hold promise, collateral assessment is most reliable when performed with transient (balloon inflation) or chronic complete occlusion of the culprit artery (Table 2). Myocardial contrast echocardiography (MCE) demonstrated the importance of collateral arteries for recovery of LV function after MI. Myocardial perfusion imaging after 99mTc-Sestamibi radionuclide injection during PCI has also been used to quantify collateral supply by evaluation of the extent of ischaemia. More recently, Vogel et al. demonstrated the feasibility of real-time non-invasive assessment of collateral supply using MCE and systemic administration of contrast. They demonstrated a close relationship between the CFIp and absolute collateral-derived myocardial blood flow (MBF_c) measured by echocardiography in 32 PCI cases (CFIp = 0.62 MBF_c + 0.05; r^2 = 0.75; P < 0.0001).

Collateral-dependent myocardial perfusion can be quantified by magnetic resonance imaging (MRI), however, an angiographic description of the coronary collateral circulation is a prerequisite requirement. Coronary MRI lacks sufficient resolution to delineate collateral arteries which are usually of modest calibre. Multi-slice computed tomography (CT) has emerging potential for the non-invasive assessment of coronary collateral supply. This technique best images proximal and intermediate coronary segments, however, whether collateral connections, which are usually distal, can be delineated by contrast CT remains to be determined. Positron emission tomography (PET) is a powerful research tool for quantification of collateral-dependent myocardial blood flow, but it is an impractical technique for routine clinical practice.

Coronary collateral circulation in selected patient groups and settings

Collaterals in individuals without CHD

The human coronary circulation is not an end-arterial system as it was previously considered in the past. Furthermore, nascent collateral arteries occur in neonates and in healthy individuals. In the 1950s, Fulton undertook three-dimensional post-mortem stereo-angiographic studies of coronary arteries in preserved hearts from subjects who died from non-ischaemic causes and had normal hearts (Figure 3). He demonstrated extensive superficial and deep intercoronary anastomoses, which were particularly abundant in the interventricular septum and in the subendocardial plexus of the left ventricle. This plexus likely contributes to the myocardial 'blush' observed during angiography. Baroldi et al. produced post-mortem coronary artery casts from normal hearts following digestion of cardiac tissue. These casts revealed striking images of inter- and intra-coronary anastomoses. Collateral arteries are more abundant in the LV than in the right ventricle (RV) and are uncommon in the subepicardial territory in man, in contrast to the dog. Return of blood flow in diastole to the deep layers of the LV is favoured by certain vessels which course directly from the epicardial arteries almost without branching to feed the subendocardial plexus.

Collateral blood flow may prevent ischaemia even in healthy subjects. Considerable variation exists in the...
<table>
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<tr>
<th>Method</th>
<th>Strengths</th>
<th>Weaknesses</th>
<th>References</th>
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<tr>
<td><strong>Angiographic</strong></td>
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<tr>
<td>Visual</td>
<td>Visual assessment</td>
<td>Easy to do</td>
<td>Subject to intra and interobserver error; ordinal variable; limited resolution (arterioles &lt; 100 μm invisible)</td>
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<tr>
<td>Visual–computer assisted Contrast appearance time</td>
<td>Visual–computer assisted Visual assessment</td>
<td>Easy to do; time consuming</td>
<td>Not routinely performed</td>
</tr>
<tr>
<td>Angiographic collateral degree (Rentrop’s grade)⁶</td>
<td>Visual assessment. Settings: ipsilateral CAD; patent coronary artery</td>
<td>Easy to do; standard methods</td>
<td>Subject to intra and interobserver error; ordinal variable; validated in setting of single vessel disease (LAD or CX) and preserved LV systolic function;⁶ angiographic assessment for recruitable collaterals requires a double injection technique; a second arterial puncture is required for injection into the donor artery prior to and during balloon inflation in the recipient (culprit) artery</td>
</tr>
<tr>
<td><strong>Collateral connections score</strong></td>
<td>Visual assessment. Setting—chronic total occlusion</td>
<td>Easy to do; standard method; anatomical basis incorporating collateral size</td>
<td>Subject to intra and interobserver error; optimal angiographic views required to avoid foreshortening; ordinal variable</td>
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<tr>
<td><strong>Coronary flow</strong></td>
<td>TIMI frame count; Fourier spectral analysis; Cineangiographic modelling; Washout collaterometry</td>
<td>Standard methods; washout collaterometry does not require a second arterial puncture, is easy to do and is inexpensive</td>
<td>Dedicated software required for Fourier spectral analysis; subject to the effects of variation in contrast injection and alterations in distal microvascular resistance</td>
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<tr>
<td><strong>Physiological</strong></td>
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<tr>
<td>Doppler wire</td>
<td>Doppler frequency collateral flow velocity</td>
<td>Validated; continuous variable</td>
<td>Expensive; relevant technology required; appropriate training</td>
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<tr>
<td>Pressure wire</td>
<td>Pressure wire e.g. RADI®</td>
<td>Validated; CFIp index continuous variable</td>
<td>Expensive; relevant technology required; appropriate training; may only be done during coronary balloon angioplasty</td>
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<td><strong>Perfusion imaging</strong></td>
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<tr>
<td>Contrast echocardiography</td>
<td>Ultrasound contrast agent and standard echocardiography</td>
<td>Easy to do; relatively inexpensive; contrast may be administered by intra-coronary or intravenous injection</td>
<td>Invasive access still required to demonstrate a chronic total occlusion, or if antegrade flow is present in the culprit artery, to obstruct flow by transient balloon occlusion</td>
</tr>
<tr>
<td>MRI</td>
<td>Coronary blood flow and myocardial perfusion</td>
<td>Accurate assessment of myocardial perfusion; may provide information on myocardial viability</td>
<td>Myocardial and epicardial artery measures of collateral function may differ; off-line analyses</td>
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<tr>
<td>PET</td>
<td>Myocardial perfusion</td>
<td>Information on perfusion and metabolic function</td>
<td>Expensive; off-line analyses</td>
</tr>
<tr>
<td>Scintigraphy</td>
<td>Nuclear isotope infusion with comparison of myocardial perfusion at rest and during pharmacological stress or exercise</td>
<td>Assessment of myocardial perfusion</td>
<td>No direct assessment of collateral blood flow</td>
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extent of collateral supply even between individuals with similar severities of CHD. The reasons for this variability are uncertain but may be genetic or acquired (e.g., duration of angina, drug therapy, extent of coronary disease).

**Angina pectoris**

**Pathogenesis of the collateral circulation**

Fulton and Royen demonstrated that in patients with obstructive CAD, functional coronary collaterals develop by enlargement of pre-existing coronary anastomoses. The main stimulus to vessel enlargement was the collateral blood flow generated by differential pressure gradients resulting from coronary artery occlusion or stenosis. He also demonstrated that the extent of coronary artery collateralization was related to angina duration.

**Predictors of coronary collateral supply**

Pohl et al. investigated the predictors of collateral artery supply in 450 patients with obstructive CAD but no history of Q-wave MI. Coronary collateral arteries were assessed by measurement of intra-coronary pressure (n = 328), flow velocity (n = 217), or simultaneously with both techniques (n = 192). In the group with insufficient collateral function [CFI < 0.25; n = 307 (68%)], angina and ST-segment elevation during balloon occlusion developed in 67 and 84% of patients, respectively. The corresponding rates in patients with adequate collateral blood flow [CFI ≥ 0.25; n = 143 (32%)] were 42 and 26%, respectively (P < 0.0001). The only multivariate predictor of functionally important collateral blood flow (CFI ≥ 0.25) was percent diameter stenosis. CAD progression, as measured by quantitative coronary analysis is associated with increase in collateral supply (Rentrop’s grade), whereas regression in disease is associated with reduced collateral formation.

Other studies in angina patients undergoing PCI have demonstrated percent diameter stenosis, duration of angina, and proximal lesion location to correlate with collateral supply. The relationship between LV systolic function and CFI is influenced by several factors, including the severity of CHD, LV end-diastolic pressure, and microvascular function.

**Coronary collateral supply in stable angina**

**Exercise testing**

The extent of coronary collateralization may influence exercise test results. For example, in a study of angina patients with obstructive (stenosis ≥90% reference diameter) single vessel CAD, myocardial perfusion defects revealed by exercise thallium scintigraphy were more common and more extensive than in patients without collaterals. In other words, collateral arteries may predispose to a false negative stress-perfusion scan. In this investigation, collateralization did not influence exercise duration or ST-segment depression, which suggests that factors which influence coronary flow and myocardial ischaemia, such as collateral connections, may affect exercise tests and stress perfusion scans in different ways.

**Severity of angina**

Using invasive methods in patients undergoing PCI of a single coronary stenosis, Billinger et al. demonstrated that the contra-lateral donor artery resistance and collateral microvascular resistance correlated better with the ipsilateral CFVR than ipsilateral stenosis severity. In other words, blood flow velocity in a territory subtended by a stenosed artery may be influenced more by the resistance to blood flow in the donor artery collateral pathway than the percent diameter of the culprit stenosis. This observation indicates that reduced collateral artery blood flow (through increased resistance) may negatively influence myocardial blood flow, which may in turn provoke or exacerbate angina. Altered collateral pathway resistance is an important mechanism to explain coronary artery steal.

A 10-year angiographic follow-up study demonstrated collateral flow capacity to have increased over three-fold in subjects with improved angina, whereas collateral flow remained constant in subjects with no improvement in angina (P = 0.01). In other words, collateral growth correlated with reduced angina. A well-developed collateral supply at the time of elective PCI is associated with an increased risk of subsequent angina. The reasons for why this may be are controversial, and may involve coronary steal and restenosis.

**Collateral supply and ventricular function**

In patients with obstructive CAD, LV regional contractility and relaxation are influenced by collateral blood flow. Furthermore, in angina, the presence of regional myocardial contractile dysfunction, altered oxidative metabolism and increased glucose utilization, are related to inadequate blood flow in collateral artery-dependent territories. In other words, inadequate blood supply in collateral-dependent myocardium may lead to ventricular dysfunction.
Coronary steal in stable CHD

Definition

'Coronary steal’ is a complex phenomenon in which regional myocardial hypoperfusion occurs through diversion of coronary blood flow to adjacent coronary beds. Coronary steal may be mediated by collateral arteries. Seiler and coworkers\(^\text{19,20}\) defined coronary steal as being a fall in coronary blood flow in one collateralized vascular region in favour of another during coronary arteriolar vasodilatation, i.e. a CFVR \(< 1\) during maximal hyperaemia. Werner et al.\(^\text{21}\) defined coronary steal as a reduction in APV\(_{\text{occl}}\) during adenosine infusion, whereas an increase in APV\(_{\text{occl}}\) represented a positive collateral flow reserve. Thus, coronary steal may provoke angina, despite the presence of an apparently adequate collateral supply.

Mechanisms of coronary steal

Coronary steal may be ‘vertical’ between different layers of the myocardium, or ‘lateral’ via branches through adjacent vascular areas originating from a common branch bifurcation.\(^\text{19}\) Coronary steal is not necessarily collateral-dependent,\(^\text{21}\) but it is influenced by CAD severity and ventricular function.\(^\text{21}\)

Seiler et al.\(^\text{19}\) used a Doppler wire to quantify CFVR and CFI in 100 patients undergoing coronary angioplasty. They assessed the occurrence of coronary steal in stenosed, collateralized coronary arteries by measurement of maximal mean CFV before and after intra-coronary adenosine injection. A CFVR \(< 1\) during systemic adenosine-induced hyperaemia occurred in 10% of patients. Coronary steal was associated with angiographic evidence of enhanced coronary artery collateralization, proximal lesion location, and greater percent diameter stenosis. Compared with patients without evidence of coronary steal, fewer patients with steal experienced angina or had intra-coronary ECG changes during balloon inflation. In other words, in patients with coronary steal, preservation of coronary flow distal to the balloon occlusion by collateral blood flow resulted in reduced ischaemia. Collateral flow to the vascular region studied during balloon inflation decreased during adenosine-induced hyperaemia, indicative of a steal effect via extensive collaterals to the donor territory. These findings provided \textit{in vivo} evidence of an association between the presence and extent of steal away from the collateralized coronary territory and the amount of collaterals towards it.

Werner et al.\(^\text{21}\) recently dissected the contribution of individual resistance components in patients with or without steal. Coronary steal occurs in \(~30\)% of chronic totally occluded (CTO) patients.\(^\text{53}\) Their use of CTO patients, rather than patients with a patent culprit artery, enabled a more controlled study of the coronary circulation.\(^\text{21}\) In their cohort of 56 patients undergoing CTO PCI, Werner et al. demonstrated that in patients who manifest a steal phenomenon with adenosine infusion (46%), the donor artery FFR was lower, its resistance (R\(_D\)) was higher, and \(\Delta R_D\) increased further with adenosine, compared with patients without steal. Collateral pathway resistance (R\(_{\text{coll}}\)) increased with adenosine infusion in the steal group, whereas R\(_{\text{coll}}\) and R\(_P\) fell in subjects with a positive collateral flow reserve. Overall, changes in R\(_P\) were strongly correlated with changes in R\(_{\text{coll}}\) (R = 0.8; P < 0.001). Notably, the pressure

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**Figure 3**  
\textit{Ex vivo} arteriogram of a normal human heart. Radiography with the heart submerged in saline virtually eliminated myocardial tissue shadowing an ensured homogenous exposure to all blood vessels. Before injection, a branch of the left CX was doubly ligated. Retrograde filling of the distal artery, in less than 20 s, demonstrated the existence of anastamotic communications. Stereoscopy revealed that the communicating vessels were largely in the deep, subendocardial network. Penetration of the injection medium to 10–15 µm diameter blood vessels with radiological demonstration to 20 µm. Arterio-mediastinal anastomoses are also seen above the heart (>1). Permission granted from Fulton\(^\text{37}\) and from the British Institutes of Radiology.

**Risk of future myocardial infarction**

In a series of 403 patients with stable angina who underwent elective PCI and were then followed-up (mean follow-up period of 94 weeks) for clinical events, those with poorly developed collaterals (CFI\(_v\) < 0.25) experienced a higher incidence of MI (4.1%), compared with the incidence of MI (0%); \(P = 0.02\) in patients with a well-developed collateral supply (CFI\(_v\) \(\geq 0.25\)).\(^\text{49}\) This remarkable finding may be explained by the contribution of collateral-derived myocardial perfusion after an acute coronary thrombosis.

**Survival**

Hansen\(^\text{51}\) explored the natural history of patients with CHD in relation to the presence or absence of coronary collateral arteries. Collateral arteries were evident in 104 (35%) of 300 patients undergoing clinically indicated coronary angiography, with the highest proportion being in patients with an occluded artery [95/101 (94%)]. Over 10 years, 51.1 and 34.5% of patients in the collateral and non-collateral groups survived (adjusted \(P = 0.1\)). Clearly, more studies are required to clarify the prognostic value of collateral supply in stable CHD.
gradient across the collateral networks did not change during hyperaemia. Interestingly, mean (SD) FFR\textsubscript{D} increased progressively between groups [reduced collateral flow reserve (i.e. coronary steal) vs. no change vs. increased collateral flow reserve: 0.78 (0.13) vs. 0.84 (0.17) vs. 0.90 (0.09)]. Therefore, they confirmed that the conditions for provoking coronary steal involve increased collateral channel resistance, and the combination of a flow-limiting donor artery stenosis proximal to the collateral origin and/or an impaired microvascular response to vasodilator stimulus.\textsuperscript{21}

In other words, coronary artery steal is unlikely to occur in large collateral channels (with low resistance).\textsuperscript{21,31}

**Clinical significance of coronary steal**

Holmvang \textit{et al.}\textsuperscript{54} studied the relationships between coronary artery flow, myocardial perfusion, and LV systolic function in 15 patients with symptomatic CHD. Collateral blood flow and myocardial perfusion were assessed by angiography and PET, respectively, and LV function was assessed by echocardiography. They found that the collateral-dependent coronary flow reserve measured during adenosine-induced vasodilatation was reduced in collateral flow-dependent segments. The steal phenomenon was most evident in segments with impaired basal contractility. Werner \textit{et al.}\textsuperscript{21} also reported an association between coronary steal and impaired ventricular function. Their hypothesis that steal could explain regional dysfunction in CTO patients without a history of MI merits prospective assessment.

Coronary collateral steal may explain why blood flow through collateral arteries may not always be beneficial. Diversion of blood flow through a low resistance collateral circuit away from an ischaemic territory could be one explanation for the potential pro-ischaemic effects of nifedipine in angina.\textsuperscript{55} Coronary steal may also give rise to competitive flow which could contribute to restenosis after angioplasty.\textsuperscript{19,56} For these reasons, Seiler \textit{et al.}\textsuperscript{19} questioned the value of PCI in patients with well-developed collateral arteries and suggested medical therapy with beta-blockers as an alternative. Notably, the anti-ischaemic effects of beta-blockers are not influenced by coronary collateral artery supply.\textsuperscript{57}

**Acute myocardial infarction**

Collateral artery connections may serve as a natural bypass after an acute coronary artery occlusion. In this section, regulation of coronary collateralization and its prognostic importance after MI are examined.

**Coronary collateral artery adaptation in acute MI: relationships with ventricular function**

Most,\textsuperscript{32,58–64} but not all,\textsuperscript{65} MI studies have suggested that myocardial perfusion may be maintained and LV function preserved in patients with an adequate coronary collateral circulation.

Sabia \textit{et al.}\textsuperscript{32} used MCE with intra-coronary contrast injections to study the relationships between myocardial viability and collateral blood flow in 43 patients who had earlier experienced an acute MI (mean time = 12 (2) days post-MI). Wall motion in the infarct region improved in 25 (78%) of the 32 patients in whom PCI had been successful ($P < 0.001$), and there was an inverse correlation between collateral flow at baseline and change in wall motion 1 month later ($r = -0.64; P < 0.001$). Subjects with non-reperfused myocardium without collateral blood flow on MCE had larger infarcts, as assessed by creatine kinase concentrations ($r = 0.67; P < 0.01$), and a higher prevalence of Q-wave infarction.\textsuperscript{33}

**Prognostic influence of coronary collateral arteries after thrombolysis for AMI**

The prognostic value of collateral arteries in MI survivors after thrombolysis is controversial. Anterior Q-wave MI survivors with well-developed collaterals may have a worse prognosis than those without adequate collateral arteries. In one angiographic follow-up study of 803 survivors of Q-wave anterior MI, the 8-year mortality rates of patients with adequate collaterals compared with the rates of those with inadequate collaterals were 21 and 8%, respectively ($P < 0.0034$). Collateralization was positively related to the percent residual stenosis in the left anterior descending (LAD) artery and negatively related to LV ejection fraction. In other words, collateral supply post-MI may simply reflect culprit stenosis severity\textsuperscript{66} and impaired antegrade flow, which, in turn, is a major adverse prognostic factor.\textsuperscript{66}

Angiographic follow-up of Thrombolysis In Myocardial-Infarction (TIMI)-4 trial participants demonstrated that the presence of collateral blood flow, in addition to reduced antegrade flow (TIMI grade $\leq 2$ vs. grade 3 flow), lesion ulceration, and greater percent diameter stenosis at 90 min after thrombolytic therapy, predicted early re-oclusion of the infarct-related artery.\textsuperscript{67}

**Coronary collateral arteries and outcome after primary PCI for AMI**

Presence of collateral arteries at the time of primary PCI

Collateral arteries are usually only evident in a minority (10–40%) of MI patients undergoing interventional management.\textsuperscript{64,68–70}

**Temporal evolution of collateral supply after acute coronary artery occlusion**

\textit{De novo} collateral artery formation after an acute coronary occlusion takes at least 24 h to become angiographically evident.\textsuperscript{71} In a series of 393 MI patients undergoing acute intervention, 27% had evidence of a collateral circulation.\textsuperscript{71} At repeat angiography 10–14 days later, the prevalence of angiographically detectable collateral arteries in patients with a persistent coronary occlusion had increased from 33–90%, indicating a second wave of collateral artery recruitment. Whereas, in patients with a complete occlusion at baseline followed by sustained reperfusion, collateral flow had reduced from 38–7%. In fact, collateral arteries may take up to 3 months to become usefully developed.\textsuperscript{72} The temporal evolution of collateral growth after ischaemic injury may result in preservation of myocardium. Thus, collateral growth represents a protective host response.

**Predictors of collateral supply at the time of primary PCI**

Antoniucci \textit{et al.}\textsuperscript{68} evaluated the Rentrop’s collateral grade in 1164 consecutive STEMI patients undergoing primary PCI...
in their centre and found at least grade 2 collateralization evident in 264 (23%) patients. Recruitment of collaterals was more evident in patients in whom the infarct-related artery was the right coronary artery (RCA), indicating more extensive collateral potential from the left coronary artery. Compared with patients without adequate collaterals, the group of patients with evidence of adequate collateralization included fewer diabetic patients (11 vs. 16%; P = 0.033), a higher proportion with pre-infarction angina (43 vs. 32%; P = 0.001), and a lower proportion with anterior MI (41 vs. 55%; P < 0.001) or cardiogenic shock (9 vs. 14%; P = 0.029). Angiographic differences included more multivessel disease (59 vs. 47%; P = 0.001) and chronic occlusions (20 vs. 10%; P < 0.001) in the collateral group, but a lower frequency of antegrade coronary flow (TIMI flow grade 1: 10 vs. 21%; P < 0.001).

In 1059 patients who underwent primary PCI in the Netherlands, Rentrop’s collateral grades 0, 1, and 2/3 at first contrast injection were detected in 53, 37, and 10% of patients, respectively. Increased collateral flow grade (Rentrop grade 2/3 vs. 0/1) at first contrast injection was associated with non-LAD-related infarction, suggesting a greater donor potential from the LAD than the right or circumflex coronary arteries. In a Spanish study of 238 patients with an incident anterior MI due to LAD occlusion, proximal LAD occlusion was more common (55%) in patients with some collateral filling of the LAD or its side branches compared with subjects with no collateral filling (37%; P = 0.01).

In other primary PCI studies, collateral supply was predicted by duration of angina, pre-infarction angina, severity of the infarct-related artery stenosis, level of antegrade flow collateral blood flow, and cholesterol-lowering therapy. Collateral supply and ventricular function after primary PCI

Beygui et al.63 studied 41 patients with an acute MI and single vessel CAD. At the time of angiography, Rentrop’s collateral grades 0, 1, 2, and 3 were evident in 32, 24, 22, and 24% patients, respectively. The myocardial recovery index was calculated as a function of the reduction in the number of hypokinetic segments vs. baseline as measured by thallium scintigraphy 7 (1) days after primary PCI. In a multivariate analysis, pre-reperfusion Rentrop collateral flow grade (r = 0.55; P = 0.0005) and TIMI flow (r = 0.41; P = 0.01) were determinants of myocardial contractile recovery after MI.

In the Dutch study,64 compared with patients with Rentrop’s grade 0/1, patients with Rentrop’s collateral grade 2/3 had a lower incidence of heart failure post-MI (Killip class ≥2), lesser need for intra-aortic balloon pump counterpulsation, improved microvascular perfusion [as assessed by myocardial blush grade (MBG) post-PCI], and smaller infarct size. These benefits were most apparent in LAD infarcts.

Acute MI patients with an occluded coronary artery and functional collateral networks are more likely to subsequently achieve optimal (TIMI 3) flow after PCI. In rescue PCI, CFIP, in the infarct-related artery is inversely related to LVEDP, indicating CFIP may actually reflect microvascular obstruction in acute MI.29,77

Collateral circulation and adverse outcome after primary PCI

The absence of a collateral circulation predicts mechanical complications, such as ventricular septal rupture, after primary PCI.70 In the Spanish study, cardiogenic shock was a complicating factor in 75% of in-hospital deaths. Of the 31 (17%) patients who died, the majority (84%) had no collateral supply, and lack of collaterals was a multivariate predictor of cardiogenic shock (odds ratio (95% CI) 5.6 (1.9–17); P = 0.002). This observation implicates inadequate collateral supply in the aetiology of cardiogenic shock and mortality after anterior MI.69

In Antoniucci et al. 58 study, patients with collaterals had a lower 6-month mortality rate (4%) than those without collaterals (9%) (P = 0.011). In the Dutch study, the 1-year survival rates post-primary PCI for grades 0, 1, and 2/3 were 95 vs. 96.2 vs. 97.2%, respectively (P = 0.66). Reasons for the lack of prognostic importance of collateral arteries in this setting may reflect the effectiveness of early revascularization (<6 h after the onset of symptoms) and the low mortality rate during follow-up.

Coronary collateral arteries and non-primary PCI

The presence of collaterals, and their anatomical distribution and functional adequacy, are important factors when considering PCI, as successful PCI has a fairly high chance of resulting in loss of collateral artery flow.11

Although patients with a well-developed coronary collateral circulation may have an increased risk of angina and restenosis after PCI,49,78 this is controversial. The study by Wahl et al.78 lacked long-term angiographic follow-up in 136 (68%) patients therefore selection bias may have influenced their results. Werner et al.79 prospectively studied 111 consecutive CTO patients and 106 (95%) of these patients had repeat angiography at follow-up [mean (SD) duration of follow-up 5 (1.4)]. The pre-PCI CFIP in patients who subsequently were found to have a patent artery (n = 50), restenosis (n = 38), or re-occlusion (n = 18) at follow-up were 0.39 (0.13), 0.41 (0.11), and 0.41 (0.10), respectively (P = 0.62). Thus, invasive (and angiographic) measures of collateral supply pre-PCI were unrelated to restenosis or re-occlusion.

A recent prospective study of 58 patients undergoing elective PCI for single vessel CAD found that CFIP at baseline did not correlate with either neo-intimal volume, as measured by IVUS, or percent diameter stenosis, at 6 months follow-up.44 Taken together with Werner’s79 study, we conclude that collateral supply does not predict restenosis after PCI. As stenosis severity is correlated with the degree of collateralization,38,40,44,45 and as stenosis severity (or stent length) also predicts future restenosis,44,79 this may explain the historical association between collateral arteries and restenosis.80

Coronary collateral circulation in patients with a chronically occluded artery

Collateral flow to the territory of a CTO artery is influenced by the extent and the anatomical distribution of the donor artery, microvascular function,18,46 the duration of vessel occlusion,72,82 and LV function.11 Collateral flow in myocardium subtended by an occluded artery may be bidirectional with systolic and diastolic components.11
Collateral flow regression associated with an increase in $R_{\text{coll}}$ after CTO PCI may persist in the long-term, and in some patients, collaterals may not be recruitable in response to acute ischaemia (e.g. upon intra-coronary balloon inflation). In the case of acute culprit artery re-occlusion this could represent loss of collateral protection leading to MI. In reality, however, the incidence of MI is lower than that of re-occlusion, and this discrepancy may be explained by the presence of persistent collaterals (i.e. spontaneous visible rather than recruitable) or gradual re-occlusion of the culprit artery post-PCI. The more extensive the collateral network at baseline (pre-PCI) the lower the $R_{\text{coll}}$ at in the longer-term. Collateral recruitment after PCI, as assessed by Doppler or pressure methods, is directly related to baseline collateral supply pre-PCI. In other words, large collateral networks are more likely to remain present and have recruitable function after PCI than small collateral networks.

**Figure 4** Opacification of contralateral collateral arteries to assist the recanalization of a chronically occluded LAD coronary artery. (A) RCA injection in a frontal projection with cranial angulation, illustrating contralateral collateral connections (CC) from an RV branch and inferior septal branches to the distal LAD, which is occluded proximally. (B) RCA injection in an lateral (LAO 90°) projection, illustrating contralateral collateral supply (CC) from the same RV branch of the RCA to the distal LAD. (C) An 0.014" ACS coronary guidewire (Guidant Corp., Santa Clara, CA, USA) and co-axial over-the-wire balloon catheter (Guidant Corp.) are seen in the LAD proximal to its site of occlusion. The distal LAD is opacified by collateral flow from the RCA (lateral projection). (D) The coronary guidewire has been advanced into the LAD lesion. The distal LAD is opacified by contrast at the end of injection into the RCA (RAO 10° Cranial 40°). (E) Opacification of the distal LAD by injection of contrast through the Voyager catheter (RAO 10° Cranial 40° projection). (F) Final result post-PCI. Opacification of the left coronary artery (LAD 10° Cranial 40° projection) after deployment of a Cypher 2.5 × 33 mm (Cordis Inc., Miami, FL, USA) drug-eluting stent in the mid-LAD and a more proximal, overlapping Cypher 3 × 18 mm stent.

**Utility of collateral artery opacification during PCI in a chronically occluded artery**

During CTO PCI, retrograde contrast opacification of the distal artery through ipsi- or contralateral collateral arteries can greatly facilitate the intervention (Figure 4). Advances in CTO PCI include use of collateral connections for retrograde guidewire access to the occlusion, and the availability of equipment, such as specialist coronary guidewires, designed for CTO PCI.

**Fate of collateral arteries after successful PCI**

Collateral blood flow reduces after successful PCI, whereas in patients with restenosis or re-occlusion, collateral supply may return to pre-PCI levels. Acute loss of recruitable collateral flow after CTO PCI is due to augmented resistance in the collateral artery, the distal vascular bed, or both.

**Ventricular function and CTO PCI**

The relationship between collateral supply and recovery of impaired regional LV function after PCI is complex. A functional myocardial microcirculation associated with viable myocardium is a prerequisite for improvement in LV function after CTO PCI.

**Therapeutic improvement of collateral artery supply**

**Exercise**

Senti et al. selected 79 patients with CAD but without a history of MI who were referred for elective PCI. Physical exercise, retrospectively quantified by structured interview, was related to CFI obtained during PCI. The investigators found that long-term physical activity during leisure time, in addition to conventional predictors of collateralization, such as coronary stenosis severity, predicted CFI.

In a randomized trial of exercise therapy in 113 patients, CAD severity was reduced at 1 year (81% follow-up), whereas collateral supply measured with the Rentrop’s collateral grade was unchanged. Collateral supply might have been expected to increase with exercise. However, exercise-induced regression in CAD severity may explain lack of change in collateral supply with exercise, as collateralization is strongly influenced by the presence of flow-limiting stenoses. Furthermore, physiological measures of collateral supply, such as those employed by Senti et al., may be a more appropriate method for collateral artery assessment, rather than an ordinal scale rating in studies with a limited sample size.

**Pharmacological therapies**

Although experimental data suggest statins and ACE-inhibitors promote blood vessel growth, human data are generally lacking. Beta-blockers reduce collateral blood flow, probably by inducing an increase in coronary collateral artery resistance and a reduction in myocardial oxygen demand.

**Biological therapies for CHD**

Biological therapies designed to improve blood vessel growth and myocardial perfusion are a major therapeutic goal. Despite recent concerns about the effectiveness of
emerging therapies, recent trials have reported encouraging results.

The Reinfusion of Enriched Progenitor Cells and Infarct Remodelling in Acute Myocardial Infarction (REPAIR-AMI) trial was a randomized, double-blind, multicentre trial of autologous intra-coronary infusion of either bone marrow-derived cells (BMCs) or placebo medium in acute MI patients with impaired LV systolic function (EF < 45%). The primary endpoint was absolute change in global LVEF at 4 months, as measured by LVEF imaging. The combination of death, myocardial infarction, or coronary revascularization at 12 months was a pre-specified secondary endpoint. A total of 217 patients provided informed consent and 204 were included in the follow-up analysis. The median time from reperfusion therapy to study therapy was 4 days in each group, and the average number (mean (SD)) of CD34+CD45+ cells administered in the BMCs group was 3.6 ± 3.6 x 10^6. The invasive therapy was generally well tolerated, problems were encountered, including air embolism and difficulties with coronary guidewire advancement. Regarding the primary endpoint, mean (SD) LVEF improved by 5.5 ± 7.3% in the BMC group and by 3.0 ± 6.5% in the placebo group (P = 0.01). The BMC-related improvement in LVEF was negatively related to baseline EF (R = -0.21, P = 0.04). Improvements in regional LV contractility were greater for BMC-treated patients than in placebo-treated patients, and end-systolic volumes increased in placebo-treated patients but not in BMC-treated patients. The BMC group had fewer major adverse cardiac events at 12 months (secondary endpoint = 41%) than in the placebo group (24%; P = 0.009), and in an adjusted Cox analysis, BMC treatment was a negative predictor of this endpoint [hazard ratio (95% CI): 0.53 (0.30–0.91); P = 0.022]. The improvements in myocardial function in BMC patients were probably due to enhanced microvascular perfusion, which may have been due to BMC-mediated microvascular repair, new blood vessel growth, or both.

Of the other intra-coronary BMC therapy MI trials, one reported positive effects on regional LV function and infarct size, whereas the other, the ASTAMI trial, did not. Compared with REPAIR-AMI, this trial involved fewer patients (n = 100), lacked a blinded placebo group (no aspiration or sham procedure was performed), and involved administration of smaller doses of progenitor cells (median [interquartile range] number of CD34+ cells (0.7 x 10^6 (0.4–1.6 x 10^6)). These factors may have contributed to this trial’s neutral result.

Granulocyte colony stimulating factor (GCSF)-based interventions for CAD have had less convincing results. Seiler and coworkers first demonstrated that short-term subcutaneous administration of GCSF could lead to enhanced CFI and reduced myocardial ischaemia during coronary artery balloon occlusion. However, in their most recent study, two patients experienced an acute coronary syndrome, and plaque rupture could plausibly have been promoted by GCSF therapy. Another GCSF study in patients with stable chronic CAD has also raised safety concerns. Some controlled clinical trials of GCSF therapy in patients with either acute or recent MI suggest the potential for preservation of LV function, whereas another acute MI trial found no effect of GCSF on LV function. Although GCSF-based therapy may lead to improvements in coronary flow reserve (or microvascular function) in patients with established MI, safety issues remain a concern.

Presently, there are several trials recruiting patients to test growth factor- and cell-based interventions in CAD (www.clinicaltrials.gov: search terms ‘angiogenesis’ and ‘coronary’). Some of these trials are designed to test whether therapeutic angiogenesis can lead to improved cardiac function in patients with advanced CHD unsuitable for revascularization.

Therapeutic improvement in cardiac perfusion and function may be facilitated through careful selection of patients, such as those who have had large infarctions but also some preservation of microvascular function. Therapeutic efficacy may also be achieved through greater retention of viable BMCs in the infarct zone. Technical advances should include improvements in the type, dose, and timing of biological therapies post-MI, and refinements of the stem cell ‘niche’ environment used to support cell therapies for CHD. Larger clinical trials are required to determine whether bone marrow harvesting followed by autologous transfusion may safely lead to meaningful improvements in outcome in acute and chronic CHD.

Conclusion
Coronary collateral blood flow is an important protective response to acute and chronic ischaemia. Catheter laboratory investigations have led to important advances in our understanding of collateral function in CHD. Non-invasive imaging of coronary collaterals and their therapeutic modification by novel biological therapies hold promise for the future.

Acknowledgements
C.B. and K.G.O. receive research funding from the British Heart Foundation.

Conflict of interest: none declared.

References


