Assessment and Impact of the Human Coronary Collateral Circulation on Myocardial Ischemia and Outcome

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Cardiovascular disease is the leading cause of death in industrialized countries and may become the most prevalent reason for mortality worldwide. In the vast majority of patients, death is the consequence of cerebral or myocardial infarction, both of which are characterized by acute vessel occlusion in the context of atherosclerosis. In this situation, outcome depends critically on the extent of infarcted tissue. Myocardial infarct size is reflected by the degree of ECG ST-segment elevation during the acute phase and is directly proportional to the extent that well-developed coronary anastomoses originating from a collateral supplying artery can entirely compensate for the occlusion in the collateral-receiving vessel, thus rendering its area at risk zero (Figure 1). In this event, the duration of coronary artery occlusion also becomes irrelevant. However, in the event of acute and permanent coronary occlusion, myocardium is only salvaged in the presence of a preformed collateral circulation.

In this context, the promotion of well-functioning coronary anastomoses (arteriogenesis) in patients with chronic coronary artery disease (CAD) before a coronary event is an appealing therapeutic principle. The selection of suitable candidates for arteriogenesis should be based on sound assessment of coronary collateral function.

The theoretical aspects relevant to the assessment of coronary collaterals

The basic physiological and physical principles operative in the coronary circulation in general also apply to its anastomoses, that is, the collateral vessels. Oxygen is the main nutrient for the myocardium, whose demand is determined by ventricular wall stress, heart rate, and myocardial contractility. Oxygen extraction from hemoglobin is close to maximal in myocardial tissue under normal metabolic conditions and, therefore, changes in oxygen demand are regulated by altering rates of coronary blood flow (Q in ml/min). According to Ohm’s law, the perfusion pressure drop (ΔP in mmHg) along increasingly smaller tubes can be described as the product of the vascular resistance (R in dyn s cm⁻¹) to flow and the flow rate Q: ΔP=R·Q. In the coronary circulation, ΔP is the difference between mean aortic perfusion pressure (Pao, mmHg) and mean central venous pressure (CVP, mmHg). In the normal coronary circulation, R is mainly attributable to viscous friction between the blood and the endothelium covering the wall of small vessels; this can be appreciated by the fact that the pressure drop in a normal epicardial coronary tree is equal to only ≈5 mmHg. Based on Ohm’s law, pressure drop along the vascular path is further described by Hagen–Poiseuille’s law, which specifies the components of vascular geometry contributing to its resistance against flow (R=8η/lπr⁴; with l being vascular segment length, r being the internal vessel radius, and η is the blood viscosity). The balance between 2 energy-consuming factors related to the transport of blood, that is, the cost of pumping the blood through the circulation as opposed to the cost of building and maintaining the circulation, defines the term minimum energy dissipation, the principle of which is compatible with the structural design of the entire coronary tree including its anastomoses. Using various measurement techniques, normal myocardial perfusion under resting conditions has been documented to be ≈1 mL/min per gram of tissue. Thus numerically (unity between the flow rate and the regional mass in grams), Q in Ohm’s or Hagen–Poiseuille’s law can be replaced by regional myocardial mass (M, supplied by blood at any point of interest in the coronary tree), which is equal to the ischemic area at risk (AR) for myocardial infarction. AR and M can also be defined angiographically in terms of summed coronary artery branch lengths distal to any point in the coronary tree relative to the entire coronary tree length. This definition of AR establishes the relation between collateral vessels and AR as intuitively outlined above (Figure 1).

In the experimental animal model, the function of arterial collateral pathways is ideally assessed by perfusion (Q/M) or conductance measurements (the inverse of R) using the
instrument of microsphere injections. In the clinical setting, direct myocardial perfusion, flow (Q), or conductance measurements during temporary coronary occlusion is possible only by quantitative myocardial contrast echocardiography, which is, however, technically challenging in the acquisition of suitable images. Coronary artery occlusion, either temporary or permanent (as in chronic total occlusion), is required for unequivocal assessment of collateral supply to a vascular region of interest (see below). Thus, the question can be raised, whether obtaining the third parameter of Ohm’s law, ΔP, which is more robust to determine in the coronary circulation, would yield results, which reflect collateral function reliably and quantitatively. In terms of Ohm’s law, the reference for collateral function assessment is myocardial perfusion during coronary artery occlusion (Qocc/M) relative to normal myocardial perfusion during vessel patency (Qn/M; suffix n for normal) for the identical AR or M, that is, a collateral perfusion index, CPI (Table 1):

\[
\text{CPI} = \frac{Q_{occ}}{M} + \frac{Q_n}{M} = \frac{Q_{occ}}{Q_n}
\]

where \( P_{occ} \) is the coronary pressure downstream of the occlusion, CVP is the central venous pressure, \( R_{myo} \) is the vascular, microcirculatory resistance of the myocardium within the AR of interest, and \( P_a \) is the mean aortic pressure \( P_{ao} \). Under the condition of maximal vasodilation using, for example, adenosine, \( R_{myo} \) during coronary occlusion and during vessel patency is minimal and likely similar; from that, it follows that

\[
\text{CPI} = \frac{(P_{occ} - CVP)}{(P_{ao} - CVP)} = \text{CPI}
\]

Thus, a collateral flow index CFI (mm Hg/mm Hg) can be defined (Figure 2), which is based purely on cardiac and systemic pressure measurements, and which has been evaluated clinically (see also below) and found accurate in comparison with simultaneously obtained echocardiographic myocardial perfusion measurements (Table 1):

\[
\text{CFI} = \frac{(P_{occ} - CVP)}{(P_{ao} - CVP)} = \text{CPI}
\]

Considering, on the contrary, unequal microvascular resistances \( R_{myo} \) during vessel occlusion versus patency, it should be directly obtained:

\[
R_{myo} = \frac{(P - CVP)}{Q}
\]

where \( V \) is mean coronary flow velocity, and \( A \) is coronary cross-sectional area at the site, where \( V \) is obtained. If \( A \) is held constant, \( V \) goes along with \( Q \). In comparison with \( Q \), \( V \) can be obtained more easily in the human coronary circulation than \( Q \) (Doppler measurements during coronary occlusion still being challenging). In this context, a coronary collateral resistance index (CRI) can be obtained on the basis of combined coronary pressure and velocity measurements (Table 1; see also below):

\[
\text{CRI} = \left[ \frac{(P_{occ} - CVP)}{V_{occ}} \right] + \left[ \frac{(P_{ao} - CVP)}{V_{non-occ}} \right]
\]

Noninvasive Characterization of the Coronary Collateral Circulation

In the context of the clinical examination, the only specific sign hinting at a well-developed coronary collateral circulation is the patient’s information about developing tolerance to repetitive bouts of myocardial ischemia, that is, relief of angina pectoris during ongoing or briefly interrupted physical exercise. This so-called warm-up or walking-through angina pectoris was first described by Heberden in 1802 (Table 2). As a pathophysiologic alternative to collateral recruitment on increased myocardial oxygen demand, it can be explained by the mechanism of ischemic preconditioning. Indirect and imprecise signs of a functional collateral circulation relate to the fact that severely narrowed coronary arteries are directly, although loosely, associated with more extended anastomoses

Figure 1. Normal left ventricular angio-gram (top middle and right) in a patient with chronic total occlusion of the proximal left anterior descending artery occlusion (top left). Angiography of the right coronary artery (bottom) shows extensive collateral supply to the naturally occluded (left) and to the artificially occluded (right) left anterior descending artery via apical branch collaterals and via septal collaterals.
between vascular territories.\textsuperscript{15,16} In chronic stable CAD, indicators for severe coronary artery stenoses are the degree of angina pectoris, the level of physical effort at which ECG signs of ischemia or chest pain occur, and the incidence of specific ECG signs during exercise. Resting bradycardia, which is unrelated to betablockade, may indicate collateral promoting, that is, arteriogenic effects.\textsuperscript{17}

In comparison with chronic CAD, the setting of acute ECG ST elevation myocardial infarction is more distinctive for the purpose of noninvasive collateral assessment, because the acute total coronary occlusion allows the interpretation of the extent and the degree of ECG ST elevation on the basis of its contributing factors, area at risk, and collateral supply. The initial standard 12-lead ECG provides insight into AR, collateral flow, and can estimate subsequent infarct size.\textsuperscript{18}

**Coronary Occlusion Model: Natural Versus Artificial**

As indicated above, invasive cardiac examination is a prerequisite for reliable quantitative assessment of the human coronary collateral circulation, because without a natural or artificial occlusion of the collateral-receiving artery, the obtained blood flow reaching the downstream vascular bed cannot be distinguished by its origin from either the native or anastomotic path. In patients with CAD, 1/4 of all coronary angiograms show a chronic total (coronary) occlusion (CTO) of a coronary artery, and only about half of these patients have viable myocardium in the collateralized area.\textsuperscript{19} Once an invasive examination has established the diagnosis of a CTO, the viable collateralized myocardial region can be examined noninvasively in this natural occlusion model by different imaging techniques which, in the case of positron emission tomography using ammonia as tracer, can even measure absolute tissue perfusion in ml/min gram (Table 1). Because the invasive examination is needed to confirm CTO in the natural occlusion model (Figure 1), it is, conversely, essential for an artificial occlusion model to briefly block the vessel using an adequately sized angioplasty balloon catheter (Figure 1). The model of permanent or temporary occlusion of the epicardial collateral-receiving artery yields the so-called recruitable as opposed to spontaneously visible collateral flow.

One of the simplest but rather imprecise methods to qualify collateral function is to register the occurrence of angina pectoris shortly before and after a 1-minute coronary occlusion (Table 2). However, the predictive value of absent versus present chest pain for the distinction between collateral function sufficient and insufficient to prevent ECG signs of ischemia is low (sensitivity and specificity to detect sufficient collateral=60%, respectively).\textsuperscript{20} The severity of chest pain during myocardial ischemia depends on several factors, such as the duration of ischemia, the degree of recruitment of collaterals, previous transmural myocardial infarction, autonomic nerve dysfunction, psychological and neurobiological characteristics of the patient, and even the degree of stretching of the coronary arterial wall by the occluding angioplasty balloon. Irrespective of simultaneous quantitative collateral measurement, the intracoronary ECG at a threshold of ST segment elevation ≥0.1 mV is widely accepted as a sensitive tool for the detection of ischemia.\textsuperscript{21} Accordingly, an independent dichotomous definition of coronary collateral vessels insufficient or sufficient to prevent

<table>
<thead>
<tr>
<th>Method</th>
<th>Equation</th>
<th>Measurement Technique</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPI</td>
<td>((\frac{Q_{occl}}{M}))/(\frac{Q}{M})</td>
<td>Myocardial contrast echocardiography</td>
<td>Variable image quality</td>
</tr>
<tr>
<td>CPI\textsuperscript{1}</td>
<td>(\frac{P_{occl}−CVP}{P_{nonoccl}−CVP})</td>
<td>Pressure sensor guidewire (0.014&quot;)</td>
<td>Not in ACS</td>
</tr>
<tr>
<td>CPI\textsuperscript{1}</td>
<td>(\frac{V_{occl}}{V_{nonoccl}})</td>
<td>Doppler sensor guidewire (0.014&quot;)</td>
<td>(V_{occl}) difficult to obtain</td>
</tr>
<tr>
<td>CRI\textsuperscript{1}</td>
<td>([\frac{P_{occl}−CVP}{V_{occl}}][\frac{P_{nonoccl}−CVP}{V_{nonoccl}}])</td>
<td>Combined pressure/Doppler sensor wire</td>
<td>(V_{occl}) difficult to obtain</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; CPI\textsuperscript{1}, pressure-derived collateral flow index; CPI, collateral perfusion index; CRI, collateral resistance index; CTO, chronic total (coronary) occlusion; CVP, central venous pressure; M, regional myocardial mass; \(P_{occl}\), mean aortic pressure; \(P_{nonoccl}\), mean coronary occlusive pressure; \(Q_{occl}\), normal coronary flow during vessel patency; \(Q_{nonoccl}\), coronary flow during vessel occlusion; \(V_{occl}\), coronary flow velocity during vessel patency; and \(V_{nonoccl}\), coronary flow velocity during vessel occlusion.

**Figure 2.** Pressure-derived coronary collateral flow index (CFI) measurement using simultaneous recordings of phasic and mean aortic pressure (\(P_{aortic}\), red line; scale: 200 mmHg), distal coronary occlusive pressure (\(P_{occl}\), black line; scale: 200 mmHg) and central venous pressure (CVP, blue line; scale: 50 mmHg). Additionally, an intracoronary ECG tracing is depicted at the bottom, which shows marked ST-segment elevation during coronary balloon occlusion.
myocardial ischemia of a briefly occluded vascular area is given by the presence (Figure 2) or absence (Figure 3) of intracoronary ECG ST segment elevation ≥0.1 mV. The intracoronary ECG ST-segment shift (ie, elevation or depression) during a 1-minute coronary occlusion is also quantifiable and, as such, independently predictive of all-cause mortality.2,22

Even with several CTOs present, there may be an entirely normal systolic left ventricle (LV) function attributable to a well-developed collateral circulation. However, a substantial number of patients with CTO reveal various degrees of systolic LV dysfunction. The recovery of impaired systolic LV function after revascularization of a CTO seems not to depend on the quality of collateral function, suggesting that collateral development does not depend on the presence of viable myocardium. In patients with CAD without CTO and viable myocardium, simultaneous assessment of regional LV function using transthoracic tissue Doppler imaging and invasive collateral function has shown an association between systolic as well as diastolic LV function and collateral function24 (Table 2).

### Angiographic Collateral Assessment

The most widely used invasive method for assessing the coronary collateral circulation is contrast angiography because of its availability and the superior imaging quality concerning the often small-sized collateral vessels (Figure 1). As opposed to the coronary patency method used during single vessel intubation with assessment of spontaneously visible collateral vessels, the coronary occlusion model images recruitable collateral pathways. In the presence of a CTO, predominant angiographic collateral pathways run via septal collaterals,1/3 via atrial collaterals with proximal connection, and 1/3 via distal branch collaterals and 1/5 via distal septal collaterals in >2/5 of patients, close to 1/5 via distal branch collaterals, and 1/10 via atrial collaterals with proximal takeoff.23 The normal human heart and that affected by CAD contain numerous anastomotic vessels ranging between 40 and 200 μm. Hence, the size of the majority of these vessels is below the spatial resolution even of analog angiographic imaging chains.

The conventional angiographic grading system is that originally described by Rentrop et al,27 who distinguished 4 degrees of collateral recipient artery filling by radiographic contrast medium: grade 0=no collaterals; grade 1=side branch filling of the recipient artery without filling of the main epicardial artery; grade 2=partial filling of the main epicardial recipient artery; grade 3=complete filling of the main epicardial recipient artery (Figure 1). Of note, occlusion of the collateral-receiving artery clearly augments the sensitivity of detecting collateral vessels using angiography but renders the method of artificial occlusion technically more demanding, because of the necessity of double coronary ostial intubation (Figure 1).

A semiquantitative angiographic method for collateral assessment in patients undergoing CTO recanalization has been introduced25 using the recipient filling grade according to Rentrop et al,27 their predominant anatomic location, and a new grading of collateral connections (CC grade 0=no continuous connection between collateral supplying and receiving vessel, in 14%; CC1=threadlike continuous connection, in 51%; CC2=side-branch like connection, in 35%). Similarly, but without the difficulty of identifying collateral versus recipient vessels, the time to clearance of radiographic contrast medium (washout) trapped distal to a balloon-occluded collateral-receiving artery can be determined. Washout at a

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**Table 2. Methods for the Assessment of the Coronary Collateral Circulation**

<table>
<thead>
<tr>
<th>Method</th>
<th>Precision</th>
<th>Advantage</th>
<th>Disadvantage</th>
<th>Conclusions/Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm-up angina</td>
<td>Qualitative</td>
<td>Obtainable during history taking</td>
<td>Low prevalence not reflecting prevalence of sufficient collaterals</td>
<td>Specific for sufficient collaterals</td>
</tr>
<tr>
<td>Angina at occlusion</td>
<td>Qualitative</td>
<td>Easy and costless; no technical equipment needed</td>
<td>Large interindividual and likely intraindividual variability</td>
<td>Helpful for crude risk stratification</td>
</tr>
<tr>
<td>ECG during occlusion</td>
<td>Qualitative</td>
<td>Easy and costless; more accurate than AP</td>
<td>Large interindividual variability; variable with artery examined</td>
<td>Helpful for crude risk stratification</td>
</tr>
<tr>
<td>Regional LV function</td>
<td>Qualitative</td>
<td>With CTO and normal LV function no further assessment necessary</td>
<td>Not applicable in stenotic arteries without 2nd catheter or simultaneous echo</td>
<td>Applicable in CTOs, otherwise too elaborate for limited information</td>
</tr>
<tr>
<td>Angiography</td>
<td>Qualitative</td>
<td>With natural coronary occlusion easy and costless to perform</td>
<td>Otherwise too elaborate for limited information (2nd catheter)</td>
<td>Appropriate only for natural occlusions and crude risk stratification</td>
</tr>
<tr>
<td>Washout angiography</td>
<td>Semiquantitative</td>
<td>Easy and costless to perform; assesses ipsilateral and contralateral collaterals; no second catheter needed</td>
<td>Only semiquantitative</td>
<td>Applicable in all coronary arteries; more accurate risk stratification</td>
</tr>
<tr>
<td>Pressure (CFI) and Doppler sensor (CFI) measurements</td>
<td>Quantitative</td>
<td>Feasible in most arteries; robust pressure measurements</td>
<td>Challenging in the acquisition of Doppler signals during occlusion</td>
<td>Current gold standard; appropriate for risk stratification and clinical studies</td>
</tr>
<tr>
<td>Collateral perfusion measurement (CPI)</td>
<td>Quantitative</td>
<td>Noninvasive assessment with CTO</td>
<td>Complex procedure; variable image quality; extensive postprocessing; operator-dependent</td>
<td>Appropriate for risk stratification and clinical studies</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; AP, angina pectoris; CFIp, pressure-derived collateral flow index; CFIv, velocity-derived collateral flow index; CPI, collateral perfusion index; CTO, chronic total (coronary) occlusion; and LV, left ventricle.
threshold of 11 heartbeats accurately distinguishes between collateral supply sufficient or insufficient to prevent myocardial ischemia during a brief occlusion (sensitivity of 88%, specificity of 81%; Table 2).

Quantitative Coronary Pressure and Doppler Sensor Measurements

In addition to their principle angiographic results, Rentrop et al. first described an angioplasty balloon occlusion model using the ratio between distal coronary occlusive or wedge pressure ($P_{occl}$) and aortic pressure ($P_a$), which correlates with angiographic collateral score groups in patients with 1-vessel CAD (Table 2). In 1987, Meier et al. found that a $P_{occl} \geq 30$ mm Hg accurately predicted the presence of spontaneously visible or recruitable collaterals. However, $P_{occl}$ is not dependent only on the amount of collateral flow to the occluded vascular region. Determinants of $P_{occl}$ are the driving pressure across collateral pathways (ie, the pressure difference between the coronary pressure in the collateral supplying and receiving artery), the venous back pressure (central venous or right atrial pressure), but also extravascular pressure related to compression of intramural vessels by cardiac contraction and to transmission of diastolic LV pressure to the epicardial circulation. In this context, in that of microembolization of the collateral-dependent vascular area, $P_{occl}$ should not be used for collateral assessment in the acute coronary syndrome because collateral function is substantially overestimated. In the setting of chronic CAD, LV filling pressure has, however, no influence on $P_{occl}$ unless it exceeds values of 30 mm Hg.

In 1993, Pijls et al. provided the experimental basis for the determination of maximum coronary and myocardial fractional blood flow by coronary pressure measurements; importantly, the contribution to myocardial blood flow by collateral pathways was assumed negligible. In this study, microvascular resistance during pharmacologically induced hyperemia was postulated to be constant and minimal, and, thus, no longer dependent on the degree of epicardial stenoses. As a consequence, coronary pressure should directly reflect coronary flow, the former of which is more easily obtainable during invasive examination than the latter. Therefore, myocardial flow $Q$ distal to a stenosis (the sum of flow through the stenotic vessel plus collateral flow as assumed to be zero) relative to myocardial flow without the stenosis $Q_N$ ($Q/Q_N$=fractional flow reserve, FFR) could be calculated on the basis of distal coronary pressure and aortic pressure both after subtraction of central venous backpressure (CVP). The model was tested in dogs, whereby Doppler-derived measurements of stenotic coronary flow $Q_s$ to normal flow $Q_N$ was directly compared with ($P_{d}-CVP$)/($P_{a}-CVP$). However, the situation of a complete coronary occlusion ($Q_s=0$, ie, the setting where $P_{d}=P_{occl}$) was not tested. In fact, direct and simultaneous evaluation of the coronary parameters quantitative for collateral function ($[P_{occl}-CVP]/[P_{a}-CVP]$; Figures 2 and 3) in comparison with occlusive coronary flow velocity was not performed until 1998: coronary pressure- and Doppler-derived ratios indicative of collateral function during PCI were compared in patients with CAD and termed pressure-derived (CFI$_p$) and velocity-derived collateral flow index, respectively (CFI$_v$; see also Table 1). Figure 2 shows an example of CFI$_p$ values insufficient to prevent ECG signs of myocardial ischemia as indicated by the intracoronary ECG (lowest lead).
definition of myocardial ischemia (ST elevation ≥0.1 mV) provide the best cutoff of 0.217 for the most accurate detection of sufficient and insufficient collaterals (76% sensitivity and 76% specificity),20 which is in close agreement with a study among patients with acute myocardial infarction undergoing single photon emission tomography before primary PCI.34

Potential Pitfalls, Limitations, and Risks
Mean CVP should be obtained systematically as temporal average during several respiratory cycles. During pressure recordings, the patient should be asked to breathe normally and not to speak to maintain physiological CVP variations. As further technical aspects, $P_d$ or $P_{out}$ pressure shifts attributable to leakage of electric current and artificial systolic pressure peaks in relation to looping of the pressure guidewire have to be considered. Both problems occur more often during prolonged use and technically demanding maneuvering of the wire. Doppler- or velocity-derived collateral assessment by Doppler-tipped guide wires is much less robust than pressure-derived CFI measurement (Tables 1 and 2). This is mainly because of difficulties of differentiating low occlusive coronary flow velocity signals from vascular wall motion artifacts, respectively, to time-consuming efforts of wire repositioning to obtain true flow velocity signals.

In ≈2/3 of patients with chronic CAD, coronary occlusion causes myocardial ischemia,16 which is considered a strong hyperemic stimulus. An additional pharmacological hyperemic stimulus (eg, by intravenous adenosine) most likely does not induce further reduction of microvascular resistance in this population, that is, it does not alter CFI. However, among individuals not revealing signs of ischemia during occlusion, pharmacological vasodilation may further decrease collateral and peripheral vascular resistance and increase CFI. Alternatively, microvascular resistance in the collateral supplying region may predominantly decline, and collateral flow may be redirected away from the collateral-receiving area (ie, collateral steal).15 The maximum vasodilatory stimulus is specifically important when assessing the natural occlusion model of a CTO. In this situation, we cannot assume the presence of spontaneous maximum hyperemia because the occlusion is permanent. Vasodilation using systemic adenosine in these patients provides a wide variation of responses of the collateral flow and pressure recordings, which are not unidirectional.16

Angioplasty balloon occlusion of a normal coronary artery for the purpose of CFI measurement may pose a risk for endothelial injury and development of a de novo stenosis. Aside from the shortness of a 1-minute vessel occlusion, the principal feature of our protocol with regard to preventing vessel injury is the use of a low balloon inflation pressure just sufficient to occlude the artery. This minimal occlusion pressure is reached slowly, and imminent occlusion is sensed using the start of pressure decline obtained distal to the balloon and not primarily angiographic detection of occlusion, which only follows later. In angiographically normal arteries, an analysis of 426 measurements revealed a dissection in 1 vessel (1/426≈0.2%), subsequently treated by stent implantation.37 In 35% of all vessels investigated (n=150; mean follow-up of 10 months), angiography was repeated most often because of planned exams. In 2 out of 150 patients (≈1.3%) both having progressive CAD, a new stenosis at the site of balloon occlusion occurred 14 and 72 months after the initial occlusion, respectively.37

Quantitative Collateral Perfusion Measurements
A direct verification of CFIp, versus the reference of myocardial blood supply has been performed recently: Myocardial perfusion (ml/min per gram), defined as blood flow Q into a region relative to its mass M, can be obtained by positron emission tomography and lately by myocardial contrast echocardiography (MCE; see below for description of the technique; Table 1).11 Direct comparison of CFIp and absolute myocardial perfusion to a briefly and artificially occluded vascular region requires a bedside quantitative method for blood flow measurements, a condition fulfilled by MCE. Two human studies with coronary occlusion to avoid concomitant contrast flow via the native vessel, compared MCE and invasive collateral assessment.38,39 In patients with recent acute myocardial infarction, angiographically visible collaterals correlated poorly with the size of the collateralized area as well as normalized ultrasound contrast agent transit rates.38 This is not unexpected because angiographic collateral vessels develop only late in about half the patients after infarction. In patients with stable CAD undergoing PCI, CFIp has been shown to correlate modestly with peak signal intensity of ultrasound contrast agent transit curves but not with contrast transit rates.39

Based on the MCE technique of ultrasound contrast agent destruction by high mechanical index with subsequent observation of contrast refill (expressed by the volume exchange rate $\beta$) within a vascularized myocardial region of interest (providing the parameter of relative myocardial blood volume, rBV), absolute collateral myocardial perfusion or collateral myocardial blood flow has been obtained during coronary angioplasty balloon occlusion in 30 patients undergoing PCI12 (Table 2). Myocardial blood flow has been calculated according to the continuity equation as the product of $\beta$ and rBV divided by myocardial tissue density. The precision of this MCE method has been previously documented in comparison with a perfusion phantom model, to positron emission tomography and to invasive coronary flow velocity measurements.31 In the context of our study with side-by-side comparison of 2 different quantitative methods for collateral assessment,12 it is reasonable to state that CFIp measurements accurately reflect collateral relative to normal antegrade flow in humans with chronic stable CAD, even in the low range. The overestimation of MCE-derived collateral perfusion index (collateral relative to normal myocardial perfusion; CPI) by pressure-derived CFI is much less than that of Doppler-derived CFI,33 and it amounts to ≈2% to 7% depending on whether the CFIp-intercept or the standard error of estimate of the CFIp–CPI relation is considered. However, MCE-derived collateral assessment may be limited by insufficient image quality, and an elaborate postprocessing image analysis (Table 2).

Impact of the Collateral Circulation on Myocardial Ischemia
As a surrogate for the prognostically relevant infarct size, studies on myocardial salvage and on myocardial injury attributable to PCI have used the magnitude of intracoronary ECG
ST-segment shift during or after coronary balloon occlusion. Intracoronary ECG recording from the angioplasty catheter guidewire is more sensitive and reliable in detecting regional myocardial ischemia during balloon inflation than standard ECG. As outlined above, the degree of myocardial ischemia during coronary occlusion is not only dependent on collateral supply (Figures 2 and 3), but also on factors such as the occlusion duration, the size of the ischemic area, the occurrence of preconditioning episodes of ischemia, and the actual level of oxygen consumption, which itself is determined by heart rate, blood pressure, and myocardial contractility. Thus, the relation between the degree of ischemia during occlusion and collateral supply can be expected to be inverse but not absolutely tight. In this context, a recent study on the determinants of quantitatively assessed intracoronary ECG ST-segment shift during a 1-minute coronary occlusion has been performed in 765 patients with stable CAD undergoing simultaneous CFI measurement. Absence of ECG ST-segment shift (<0.1 mV) during coronary occlusion has been found to be independently related to a well-functioning collateral supply to the occluded region (i.e., CFI≥0.217; Figure 4), to a low heart rate during occlusion, to the right coronary artery territory as the ischemic area, and to the absence of arterial hypertension in the patient’s history.

**Impact of the Collateral Circulation on Outcome**

There is a hierarchy of end points defining clinical outcome, which consists of all-cause mortality, cardiac mortality, cardiovascular mortality, myocardial infarction, unstable angina pectoris, repeat revascularization, and the combination of those events. In addition, surrogate end points used in studies on the prognostic relevance of collaterals are infarct size, LV aneurysm formation, LV systolic function, and myocardial viability. The beneficial effect of well-developed collaterals on all surrogate end points has been recognized. To influence the pathophysiological prognosticator of outcome beneficially, infarct size, collaterals need to be preformed for preventing LV remodeling and aneurysm formation, whereas they may

<table>
<thead>
<tr>
<th>Study</th>
<th>Good CCC</th>
<th>Poor CCC</th>
<th>RR</th>
<th>95%-CI</th>
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<td>61</td>
<td>6</td>
<td>0.57</td>
<td>[0.22; 1.47]</td>
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<tr>
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<td>0.72</td>
<td>[0.49; 1.06]</td>
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</tbody>
</table>

**Figure 4.** Association between collateral flow index (CFI, x axis) and intracoronary (i.c.) ECG ST-segment shift (y axis). y=1.0–0.55x; n=809, r=0.129, P<0.0001. The red broken lines indicate the ECG ST shift of 0.1 mV above which ischemia is defined, and the (best) CFI threshold of 0.217 for the distinction between well and poorly functioning collaterals.

**Figure 5.** Impact of the coronary collateral circulation (CCC) on survival related to all-cause mortality as analyzed in a meta-analysis including 12 studies. Reproduced from Meier et al. with permission of the European Society of Cardiology. Copyright ©2012, Meier et al.
develop only after myocardial infarction (see above). During the first 3 to 6 hours of acute coronary syndrome, angiographically well visible collateral vessels are present in ~50%, a number increasing to ~100% in the presence of continuing vascular occlusion.49 Late angiographic appearance signifies no prognostic benefit because collaterals supplying necrotic myocardium do not salvage it. In this context, the impact of the collateral circulation on outcome has to be interpreted differently depending on whether the focus is on chronic stable or on various phases of acute CAD (see below).

The association between the angiographic presence of collateral vessels and medium-term outcome in patients with chronic CAD has been investigated as early as 1971. The risk to die from any cause during a follow-up of ~2 years in that study by Helfant et al50 was reduced to almost half in the presence versus the absence of angiographic collaterals. However, the 95% confidence interval of the relative risk (0.22–1.47) found in that study rendered the survival benefit of patients with good collateral supply uncertain and exemplified the triple limitation of many subsequent studies on the same topic: low number of recruited patients with a brief observation time and use of a blunt method for collateral assessment, that is, coronary angiography. The range of patients included in 13 studies on the prognostic effect of the coronary collateral circulation is equal to 22 to 2173 (mean 866), the range of follow-up duration is between 30 days and 16 years, and the majority of these studies have used angiographic grading of spontaneously visible collaterals as the method for assessment.20,51 The investigation of Antoniucci et al52 and that of Steg et al53 illustrate that the use of a vague method for collateral assessment can be compensated for by including more patients in a setting, in which mortality is genuinely higher than in the population with chronic stable CAD (2%/yr): acute, respectively, subacute myocardial infarction. The relative risk for mortality from any cause in these studies among patients with spontaneously visible collateral arteries has been reduced to 0.47 (95% confidence interval 0.25–0.87) in the former and to 0.72 (95% confidence interval 0.49–1.06) in the latter investigation, respectively (Figure 5).50,52–62 The fact that in the study by Steg et al53 angiographic collaterals were only marginally beneficial on all-cause mortality is directly related to the inclusion of about half the patients in this subacute infarction population with delayed arteriogenesis occurring only after the myocardial-salving window of the 1st 3 to 6 hours after symptom onset.

The main result of a recently published study among 1181 patients with chronic CAD has been that a growing collateral function as quantitatively assessed by CFI is an independent beneficial prognosticator.20 The relative risk to die from any cause in patients with high CFI during this 16-year follow-up study (Figure 6) was reduced to 0.206 (95% confidence interval 0.067–0.637; \(P=0.0061\)).20 This is consistent with the principal finding of a recent meta-analysis documenting a relative risk reduction for all-cause mortality to 0.64 (95% confidence interval 0.45–0.91) among patients with a well-developed coronary collateral circulation.51

### Conclusions

In patients with CAD, a well-developed coronary collateral circulation is related to reduction of infarct size, LV dysfunction, and all-cause mortality. Concerning future clinical research, accurate and quantitative assessment methods are needed for a reliable distinction between patients with collateral function sufficient or insufficient to prevent ischemia during coronary occlusion. Invasive methods are inevitable for collateral assessment with pressure-derived CFI measurements being the current gold standard.

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None.

### References

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Assessment and Impact of Coronary Collaterals


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