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.\(^1\)\(^2\) 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.\(^2\) In this situation, outcome depends critically on the extent of infarcted tissue.\(^3\) Myocardial infarct size is reflected by the degree of ECG ST-segment elevation during the acute phase\(^4\) and is directly compensated for the occlusion in the collateral-receiving artery 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.\(^5\) 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 purpose of this article is to review the theoretical background and the different methods for the assessment of collateral function, and to provide an overview of its impact on myocardial ischemia and outcome.

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.\(^4\) 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 mm Hg) along increasingly smaller tubes can be described as the product of the vascular resistance (R in dyn s cm\(^{-5}\)) to flow and the flow rate Q: ΔP=RQ. In the coronary circulation, ΔP is the difference between mean aortic perfusion pressure (P\(_a\), mm Hg) and mean central venous pressure (CVP, mm Hg). 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 mm Hg. 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=8ηπr\(^4\), 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 artery tree including its anastomoses.\(^7\) Using various measurement techniques, normal myocardial perfusion under resting conditions has been documented to be ≈1 mL/min per gram of tissue.\(^8\) 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 artery tree length.\(^9\) 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

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instrument of microsphere injections.\textsuperscript{10} In the clinical setting, direct myocardial perfusion, flow (Q), or conductance measurements during temporary coronary occlusion is possible only by quantitative myocardial contrast echocardiography,\textsuperscript{11} 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, \( \Delta P \), 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 (\( Q_{\text{occl}}/M \)) relative to normal myocardial perfusion during vessel patency (\( Q_n/M \); suffix n for normal) for the identical AR or M, that is, a collateral perfusion index, CPI (Table 1):

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

(1)

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

\[
\text{CPI} = \frac{(P_{\text{occl}} - \text{CVP})}{(P_n - \text{CVP})}
\]

(2)

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\textsuperscript{12} (Table 1):

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

(3)

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

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

(4)

\[
Q = V \cdot A
\]

(5)

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 (CFI) can be obtained on the basis of combined coronary pressure and velocity measurements (Table 1; see also below):

\[
\text{CFI} = \frac{(P_{\text{occl}} - \text{CVP})}{V_{\text{occl}}} + \frac{(P_{ao} - \text{CVP})}{V_{\text{non-occl}}}
\]

(6)

**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\textsuperscript{13} (Table 2). As a pathophysiologic alternative to collateral recruitment on increased myocardial oxygen demand, it can be explained by the mechanism of ischemic preconditioning.\textsuperscript{14} 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.
between vascular territories. 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 beta-blockade, may indicate collateral promoting, that is, arteriogenic effects.

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.

### 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. 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 the end of 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 collaterals=60%, respectively). 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. Accordingly, an independent dichotomous definition of coronary collateral vessels insufficient or sufficient to prevent

![Figure 2. Pressure-derived coronary collateral flow index (CFI) measurement using simultaneous recordings of phasic and mean aortic pressure (P_a, red line; scale: 200 mm Hg), distal coronary occlusive pressure (P_occl, black line; scale: 200 mm Hg) and central venous pressure (CVP, blue line; scale: 50 mm Hg). Additionally, an intracoronary ECG tracing is depicted at the bottom, which shows marked ST-segment elevation during coronary balloon occlusion.](http://circinterventions.ahajournals.org/content/47/2/721/F2)

| Table 1. Equations for the Derivation of Quantitative Coronary Collateral Function |
|------------------|------------------|------------------|------------------|
| Method           | Equation         | Measurement Technique   | Disadvantage                      |
| CPI              | \( \frac{Q_{occl}}{Q_{n}} \) | Myocardial contrast echocardiography | Variable image quality |
| CPI_p            | \( \frac{Q_{occl}}{Q_{n}} \) | Positron emission tomography | Only in CTO |
| CRI             | \( \frac{P_{occl} - P_{CVP}}{V_{occl}} \) | Pressure sensor guidewire (0.014") | Not in ACS |
| CRI_v            | \( \frac{V_{occl}}{V_{n}} \) | Doppler sensor guidewire (0.014") | V_{occl} difficult to obtain |
| CPI_v            | \( \frac{Q_{occl}}{Q_{n}} \) | Combined pressure/Doppler sensor wire | V_{occl} difficult to obtain |

ACS indicates acute coronary syndrome; CFI, pressure-derived collateral flow index; CRI, velocity-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_{a}, mean aortic pressure; P_{occl}, mean coronary occlusive pressure; Q, normal coronary flow during vessel patency; Q_{occl}, coronary flow during vessel occlusion; V_{n}, coronary flow velocity during vessel patency; and V_{occl}, coronary flow velocity during vessel 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.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,23 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 vessels using angiography but renders the method 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 connection, in 14%; CC1=threadlike continuous connection, in 25%; 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
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%28; Table 2).

Quantitative Coronary Pressure and Doppler Sensor Measurements
In addition to their principle angiographic results, Rentrop et al27 first described an angioplasty balloon occlusion model using the ratio between distal coronary occlusive or wedge pressure (Poccl) and aortic pressure (Pao), which correlates with angiographic collateral score groups in patients with 1-vessel CAD (Table 2).29 In 1987, Meier et al30 found that a Poccl ≥30 mm Hg accurately predicted the presence of spontaneously visible or recruitable collaterals. However, Poccl is not dependent only on the amount of collateral flow to the occluded vascular region. Determinants of Poccl 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.31 In this context, in that of microembolization of the collateral-dependent vascular area, Poccl 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 Poccl unless it exceeds values of 30 mm Hg.

In 1993, Pijls et al32 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, 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 QN (Q/QN=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 Qs to normal flow QN was directly compared with (Pd−CVP)/(Pao−CVP). However, the situation of a complete coronary occlusion (Qs=0, ie, the setting where Pd=Poccl) was not tested.32 In fact, direct and simultaneous evaluation of the coronary parameters quantitative for collateral function ([Poccl−CVP]/[Pao−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 (CFIp) and velocity-derived collateral flow index, respectively (CFIv33; see also Table 1). Figure 2 shows an example of CFIp 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, Pd or Pwse 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 pro-
longed 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 coro-
nary 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 physiological 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 indi-
viduals not revealing signs of ischemia during occlusion, phar-
omacological 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 impor-
tant when assessing the natural occlusion model of a CTO.
In this situation, we cannot assume the presence of spontane-
ous maximum hyperemia because the occlusion is permanent.
Vasodilation using systemic adenosine in these patients pro-
vides 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 occlu-
sion pressure is reached slowly, and imminent occlusion
is sensed using the start of pressure decline obtained dis-
tal 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 myocar-
dial 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 echo-
cardiography (MCE; see below for description of the tech-
nique; Table 1).11 Direct comparison of CFIp and absolute
myocardial perfusion to a briefly and artificially occluded vas-
cular 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 col-
lateral assessment.38,39 In patients with recent acute myocar-
dial infarction, angiographically visible collaterals correlated
poorly with the size of the collateralized area as well as nor-
malized 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 cor-
relate modestly with peak signal intensity of ultrasound con-
trast 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 observ-
ation of contrast refill (expressed by the volume exchange
rate β) within a vascularized myocardial region of interest
(providing the parameter of relative myocardial blood vol-
ume, rBV), absolute collateral myocardial perfusion or collat-
eral myocardial blood flow has been obtained during coronary
angioplasty balloon occlusion in 30 patients undergoing PCI12
(Table 2). Myocardial blood flow has been calculated accord-
ing to the continuity equation as the product of β 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 tomog-
raphy 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 overestima-
tion 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 CPI-
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, studi-
ies on myocardial salvage and on myocardial injury attribut-
able to PCI have used the magnitude of intracoronary ECG
Because heart rate reduction has been consistently found more prevalent during ischemia of the right than the left coronary territory, the abovementioned determinants low heart rate and right coronary artery territory cannot be called independent parameters in a biological sense. Alternatively to intracoronary ECG ST-segment shift, other ECG parameters such as QT interval could be used as markers for the degree of ischemia. QT interval would be reasonable because evidence has accumulated that QT prolongation or time variability are markers or triggers of myocardial electric instability and sudden cardiac death. A study among 150 patients with stable CAD undergoing a standardized 1-minute coronary balloon occlusion with simultaneous intracoronary ECG recording has documented a QT prolongation during ischemia in the left, but not the right coronary territory, whereby it has been inversely associated to CFI, thus indicating a protective effect of the collateral circulation not only against infarct size expansion, but also against ischemia-related risk of sudden cardiac death. The threshold of arterial blood supply in absolute terms has been determined using quantitative myocardial contrast echocardiography. Using this method, the distinction between patients with and without intracoronary ECG signs of myocardial ischemia (0.1 mV cutoff) during 1 minute of coronary occlusion has been found to be most accurate at a threshold of 0.374 mL/min per gram of perfusion.

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 pathophysiologic prognosticator of outcome beneficially, infarct size, collaterals need to be preformed for preventing LV remodeling and aneurysm formation, whereas they may

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*Heterogeneity: I-squared=66.5%, tau-squared=0.2097, p=0.0006*
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 al54 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-salvaging 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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Disclosures
None.

References


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