Assessment of the Human Coronary Collateral Circulation

Tobias Traupe, MD; Steffen Gloekler, MD; Stefano F. de Marchi, MD; Gerald S. Werner, MD; Christian Seiler, MD

Cardiovascular disease is the leading cause of death in industrialized countries and may become the most important reason for mortality worldwide. In patients suffering from coronary artery disease (CAD), the size of myocardial infarction mainly determines outcome. Accordingly, the primary strategy to reduce cardiovascular mortality is by shrinking infarct size (IS) (Figure 1A). In the clinical setting of acute myocardial infarction, Antoniucci et al. documented in 1164 patients undergoing primary percutaneous coronary intervention (PCI) that the presence of angiographic collaterals before PCI purported a survival benefit compared with the situation without them (Figure 2). As a surrogate for IS, studies on the effect of myocardial salvage procedures have employed the magnitude of ECG ST-segment elevation during coronary balloon occlusion (Figure 3). IS, measured as the degree of ECG ST-segment elevation during a 1-minute coronary occlusion, is influenced by the following factors: duration of occlusion, ischemic area at risk for myocardial infarction (AR), collateral blood supply to the ischemic zone, ischemic preconditioning, and myocardial oxygen consumption. In the context of a single brief artificial coronary occlusion of uniform duration without preceding bouts of ischemia (Figure 3), ECG signs of ischemia are influenced predominantly by the AR and by collateral supply to this region. Furthermore, Figure 1B illustrates that AR and collateral supply are inversely related to each other (ie, AR tends to shrink toward zero in the presence of well-functioning collaterals). They are termed sufficient if they prevent an ECG ST-segment elevation of ≥0.1 mV during a 1-minute coronary balloon occlusion; otherwise, they are termed insufficient collaterals.

The functional relevance of coronary collaterals in humans was a matter of debate for decades, most likely because of inadequate means for gauging collaterals and study populations that were too small and thus not representative of all patients with CAD. In the individual patient, the functional relevance of collaterals with myocardial salvage is evident in the presence of preserved left ventricular (LV) systolic function without regional wall motion abnormalities despite total proximal occlusion of a coronary artery (Figure 4). In regard to the collective prognostic impact of collaterals, the cumulative 10-year survival rates of patients with chronic stable CAD are significantly higher in patients with versus those without sufficient collaterals or high collateral relative to normal flow (collateral flow index [CFI]; Figure 5). On the basis of these prognostic benefits and the given therapeutic options of collateral growth promotion (termed arteriogenesis) and in the context of frequently unfeasible conventional revascularization options, an individual quantitative assessment of collateral function is important. The purpose of this article is to review the theoretical background and the different methods for assessment of collateral function, with a specific focus on quantitative methods (for a summary, see the Table).

Theoretical Aspects Relevant to Assessment of Coronary Collaterals

The basic theoretical characteristics operative in the coronary circulation in general also apply to its anastomoses (ie, the collateral vessels). Oxygen is the principal nutrient for the myocardium, whose demand is determined by ventricular wall stress, heart rate, and myocardial contractility. Under normal metabolic conditions, oxygen extraction is close to maximal in myocardial tissue, and therefore changes in oxygen demand are regulated by altering rates of coronary blood flow (Q). According to Ohm’s law, the drop in perfusion pressure (P) along increasingly smaller tubes can be described as the product of the vascular resistance (R) to flow and the flow rate Q: ΔP = R · Q. In the systemic circulation, ΔP is the difference between aortic perfusion pressure (Pao; mm Hg) and central venous pressure (CVP; mm Hg). R is mainly due to viscous friction between the blood and the vascular wall of small vessels, which can be appreciated by the fact that the pressure drop in a normal epicardial coronary tree is equal to only ≈5 mm Hg. On the basis of 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 = 8ηl/r4, with l being vascular segment length, r being the vessel radius, and η being the blood viscosity). The balance between 2 energy-consuming factors related to the transport of blood (ie, 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.

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From the Department of Cardiology, University Hospital Bern, Bern, Switzerland (T.T., S.G., S.F.d.M., C.S.); and Department of Cardiology and Intensive Care Medicine, Medizinische Klinik I, Klinikum Darmstadt, Darmstadt, Germany (G.S.W.).

Correspondence to Christian Seiler, MD, Department of Cardiology, University Hospital Bern, CH-3010 Bern, Switzerland. E-mail christian.seiler@insel.ch

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dissipation, the principle of which governs the structural design of the entire coronary artery tree, including its anastomoses. With the use of various measurement techniques, normal myocardial perfusion under resting conditions has been documented to be close to 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 AR for myocardial infarction (Figure 1A). 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. This definition of AR illustrates the relation between collaterals and AR (see immediately below).

With regard to the absence or presence of epicardial anastomoses within the coronary tree, the traditionally held view of the normal human coronary circulation as an end-arterial system would have no adjacent myocardial regions with overlapping supply (Figure 1A). Thus, AR (M) would correspond to the summed coronary artery branch lengths distal to any point within the coronary tree. In contrast, an anastomotic system would be built with overlapping areas at risk by collateral arteries or arterioles extending beyond the vascular territorial borders (Figure 1B). Acutely increased oxygen requirements must be met by instantaneous augmentation of coronary blood flow, whose regulation occurs via coronary microvascular resistance changes. In the absence of collateral flow, a brief coronary artery occlusion of 1 minute normally induces a 4- to 5-fold increase in flow or flow velocity above resting level immediately after release of the occlusion. Analogous to possible collaterals crossing the boundaries of vascular territories, there also might be a functional or vasomotor response of collateral vessels to hyperemic stimuli such as brief vascular occlusion. The clinical equivalent of such functional collateral response or recruitment would be the development of tolerance to repetitive bouts of myocardial ischemia (eg, a relief of angina pectoris usually termed warm-up or walking-through angina pectoris, first described by Heberden in 1802). Aside from collateral recruitment in response to multiple episodes of ischemia, a biochemical mechanism responsible for myocardial tolerance to ischemia (ischemic preconditioning), exercise-induced permanent structural growth of coronary anastomoses (arteriogenesis), and a combination of all 3 could explain the phenomenon described by Heberden.

**Noninvasive Characterization of Collaterals**

The aforementioned “warm-up” or “walking-through” angina pectoris is information obtained easily during the patient’s history taking, which is quite specific for the presence of well-developed coronary collaterals (Table). However, its prevalence is low, and, accordingly, the sensitivity to detect well-grown collaterals is limited.
Well-established determinants of collateralization are the duration of angina pectoris and the severity of coronary artery stenoses. In chronic stable CAD, indicators for severely narrowed coronary arteries 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. All of the ECG signs are markers for myocardial electric stability (bradycardia) or instability during ischemia. Resting bradycardia, which is unrelated to β-blockade, may indicate collateral-promoting (ie, arteriogenic) effects due to augmented (ie, prolonged) coronary blood flow, leading to extended tangential vascular shear stress. Because of prolongation of diastole, bradycardia prolongs the period of longitudinal stretch of endothelial cells, increasing the expression of various proarteriogenic signaling pathway components. Indicators of repolarization heterogeneity have been documented to be valuable for assessing the collateral circulation: ECG U-wave appearance at rest or during exercise is known to point to CAD with critical arterial narrowing. In stable effort angina pectoris, patients with exercise-induced U-wave changes exhibit fewer ischemic ECG ST changes and less chest pain during coronary occlusion than those without. Additionally, the QT-interval dispersion (maximal minus minimal QT interval on a 12-lead ECG) has become a noninvasive measure for assessing the degree of myocardial repolarization heterogeneity and may also identify patients with sufficient coronary collaterals.

In comparison to chronic CAD and except for chronic total coronary occlusion (CTO), the setting of acute ECG ST-segment elevation myocardial infarction is much more distinctive for the purpose of noninvasive collateral assessment.

Figure 3. Mean aortic (Pao) and distal coronary pressure tracings during 3 consecutive 2-minute angioplasty balloon occlusions (Poccl) with corresponding intracoronary (i.c.) ECG recordings (top) showing diminishing ST-segment elevation with increasing Poccl during subsequent occlusions (ie, coronary collateral recruitment). Reprinted from Billinger et al with permission of the publisher. Copyright © 1999, Elsevier.

Figure 4. Normal LV angiogram (top middle and right panels) in a patient with proximal left anterior descending coronary artery occlusion (LAD; black arrow; top left panel). Angiography of the right coronary artery (RCA; bottom panel; anteroposterior cranial view) shows extensive collateral supply to the left anterior descending coronary artery via apical branch collaterals (white arrow) and via septal collaterals. Reprinted from Seiler with kind permission of Springer Science and Business Media. Copyright © 2009, Springer Science and Business Media.
because the acute total coronary occlusion allows interpretation of the extent and the degree of ST-segment elevation on the basis of its contributing factors, AR and collateral supply. The initial standard 12-lead ECG provides insight into AR and collateral flow and can estimate subsequent IS,\textsuperscript{31} as follows. For anterior myocardial infarction, AR (in percentage) = 4.5 (number of leads with ST elevation ≥1 mm) − 1.2; for inferior myocardial infarction, IS/AR = 1.8 (mm of ST elevation in leads II, III, aVF) + 6.0. However, infarct location may no longer identify the coronary artery responsible for the event when abundant collaterals are present.

The Coronary Occlusion Model: Natural Versus Artificial

At present, invasive cardiac examination is a prerequisite for reliable quantitative assessment of the human coronary collateral circulation (Figure 6)\textsuperscript{5} because without a natural or artificial occlusion of the collateral receiving artery, the obtained blood flow reaching the downstream vascular bed or regional myocardium cannot be distinguished by its origin from the native or anastomotic path (Figure 6). In patients with CAD, approximately one third of all coronary angiograms show a CTO of a coronary artery, and only approximately half of these patients have viable myocardium in the

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<td>Large interindividual and likely intraindividual variability</td>
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<td>Applicable in CTOs, otherwise too elaborate for limited information</td>
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<tr>
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<tr>
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<td>Quantitative</td>
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Figure 5. Cumulative survival rates related to all-cause (left) and cardiac (right) mortality in patients with low and with high CFI. Reprinted from Meier et al\textsuperscript{11} with permission of the publisher. Copyright © 2007, the American Heart Association.
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 an array of different imaging techniques, which potentially can even measure the reference parameter for coronary blood supply, absolute tissue perfusion in milliliters per minute per gram. Because the invasive examination is needed to confirm CTO in the natural occlusion model (Figure 4), it is, on the other hand, essential for an artificial occlusion model to briefly block the vessel with an adequately sized angioplasty balloon catheter (Figure 7). The model of permanent or temporary occlusion of the epicardial collateral receiving or ipsilateral artery yields the so-called recruitable, as opposed to spontaneously visible, collateral flow (Figures 4, 6, and 7). It is most reasonable to perform the angioplasty balloon occlusion at the site of the stenosis to be treated. However, and on purely theoretical grounds, it would be most advantageous to assess the collateral circulation in an AR as large as possible (ie, at a most proximal occlusion site) because then one would account for the sum of all supplying collateral vessels.

In studies focusing on a single value of collateral degree or flow, there is just 1 occlusion lasting exactly 1 minute, and the measurement is obtained at the end of the occlusion. However, if the focus is on ischemic preconditioning and collateral recruitment (Figure 3), the duration of 1 minute for each of the repetitive occlusions is very likely insufficient to initiate protection from ischemia. One of the simplest but rather imprecise ways to qualify collateral function is to ask the patient about the presence of angina pectoris shortly before the end of occlusion.

Figure 6. Schematic drawing illustrating the hemodynamic parameters needed for quantitative collateral assessment. Pressure-derived collateral quantification requires coronary occlusion and measurement of mean aortic pressure (Pao), mean distal coronary pressure (Pocc; coronary wedge pressure), and central venous or right atrial pressure (CVP). In addition, coronary volume flow rate (Q) for the calculation of coronary conductance can be obtained by Doppler-derived coronary flow velocity and the respective vascular caliber at the same site (combined coronary pressure/velocity measurement) or, alternatively, by myocardial contrast echocardiography–derived perfusion measurement. Curved arrows between the left anterior descending artery (LAD) and the left circumflex coronary artery (LCX) symbolize collateral arteries. Reprinted from Seiler with kind permission of Springer Science and Business Media. Copyright © 2009, Springer Science and Business Media.

Figure 7. Right coronary angiogram with double-intubation technique (anteroposterior cranial view) in a patient with normal systolic LV function and chronic total occlusion of the proximal left anterior descending coronary artery (same patient as in Figure 4). The purpose of the left coronary intubation is to perform a balloon occlusion at the site of the recanalized chronic occlusion with positioning of a pressure sensor wire distal to the inflated balloon (see also the pressure tracings of Figure 9). The left panel is an image taken early after contrast injection; if this would be an image taken late after injection, the angiographic collateral degree would be equal to 2 (ie, part of the main artery [left anterior descending coronary artery] is filled via collaterals). The right panel is an image taken late after contrast injection; it shows complete filling of the main artery (left anterior descending coronary artery) up to the occlusion site (ie, an angiographic collateral degree of 3). The filling of only side branches of the left anterior descending coronary artery without the main artery via collaterals would be equal to an angiographic degree of 1 (not shown in this figure).
However, the predictive value of absent or present chest pain for the distinction between high and low quantitative collateral function is low (sensitivity and specificity to detect sufficient collaterals = 60%; Table). It should be remembered that the severity of chest pain developed during myocardial ischemia depends on several factors, such as the duration of ischemia, the degree of recruitment of collaterals, prior 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 sufficient or insufficient to prevent myocardial ischemia of a briefly occluded vascular area is given by the presence or absence of intracoronary ECG ST-segment elevation ≥0.1 mV (Figure 8). Despite the limitation of a 1-minute compared with a 2-minute balloon occlusion, the intracoronary ECG ST-segment qualification of coronary collaterals is helpful in predicting long-term survival in patients with chronic CAD (Figure 9).

Even with several CTOs present, there may be an entirely normal systolic LV function because of a well-developed collateral circulation (Figure 4 and Table). However, a substantial number of CTO patients reveal various degrees of systolic LV dysfunction. The possibility of LV functional recovery with its beneficial effect on survival provides the rationale for the technically demanding attempt to recanalize a CTO. The recovery of impaired systolic LV function after revascularization of a CTO appears not to depend on the quality of collateral function, suggesting that collateral development...
Angiographic Collateral Assessment: Often Used but Overrated?

The most widely used invasive method for assessing the coronary collateral circulation is contrast angiography because of its availability and the superior imaging quality in regard to the often small collateral vessels (Table). As opposed to the coronary patency method employed during single-vessel intubation with assessment of spontaneously visible collateral vessels, the coronary occlusion model images recruitable collaterals. With the exception of the one quarter of CAD patients with CTO encountered during coronary angiography and patients undergoing primary PCI in acute myocardial infarction, collaterals are not assessed with the occlusion model in the majority of coronary angiographies. In the presence of a CTO, predominant angiographic collateral pathways run via septal collaterals in more than two fifths of patients, in close to one fifth via distal branch collaterals, and in approximately one third via atrial collaterals with proximal take-off. The normal human heart and the heart affected by CAD contain numerous anastomotic vessels with proximal take-off. Hence, the size of the majority of these vessels is below the spatial resolution of even analog angiographic imaging chains. With modern-day digital storage media and a resolution of >0.2 mm, quantitative coronary angiography of collaterals, which would be ideal, is not applicable.

The most widely used angiographic grading system is that originally described by Rentrop et al, 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; and grade 3=complete filling of the main epicardial recipient artery (Figure 7). Current qualitative methods consider further aspects of coronary collateral angiographic appearance, such as collateral flow grade, frame count, bifurcation count, collateral length grade, the relation between AR and collaterals, and collateral recipient vessel filling. Of note, occlusion of the collateral receiving artery clearly augments the sensitivity of detecting collateral vessels with the use of angiography (Figure 7) but renders the method of artificial occlusion technically much more demanding because of the necessity of double coronary ostial intubation (Table).

A recently reported quantitative angiographic analysis of collateral diameters on high-resolution cine films has underscored the relevance of the collateral diameter for its capacity to supply blood flow in relevant volume rates. Moreover, a semiquantitative assessment of collaterals in patients undergoing CTO recanalization has been introduced with the use of the recipient filling grade according to Rentrop et al, their predominant anatomic location, and a new grading method of collateral connections (collateral connection grade 0=no continuous connection between collateral supplying and receiving vessel, in 14%; collateral connection grade 1=thread-like continuous connection, in 51%; collateral connection grade 2=side-branch-like connection, in 35%). A close association between collateral connection grade and invasively determined parameters of collateral hemodynamics and function has been demonstrated in the same study. Similarly, but without the difficulty of identifying collateral versus recipient vessels, the time (or heartbeat count or frame count) 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 sufficient and insufficient collateral supply (sensitivity of 88%, specificity of 81%+; Table).

Quantitative Coronary Pressure and Doppler Sensor Measurements: Current Gold Standards

In addition to their principal angiographic results, Rentrop and coworkers 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. In 1987, Meier and coworkers published their work in CAD patients undergoing coronary wedge pressure measurements during PCI: A Poccl ≥30 mm Hg was found to accurately predict the presence of spontaneously visible or recruitable collaterals. However, Poccl is not only dependent on the amount of collateral flow to the temporarily or permanently occluded vascular region. Potential 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), venous back pressure (CVP or right atrial pressure), and also extravascular pressure related to compression of intramural vessels by cardiac contraction and/or to transmission of diastolic LV pressure to the epicardial circulation. In the setting of chronic CAD, LV filling pressure has, however, no influence on Poccl unless it exceeds values of ≥30 mm Hg (Table).

In 1993, Pijs and coworkers provided the experimental basis for the determination of maximum coronary, myocardial, and collateral blood flow by coronary pressure measurements. In this study, it was assumed that minimal microvascular resistance during pharmacologically induced hyperemia is constant, minimal, and 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. However, the assumption of constant and minimal coronary resistance may be principally flawed. Therefore, myocardial flow Q in the presence of a stenosis (the sum of flow through the stenotic vessel plus collateral flow) relative to myocardial flow without a stenosis Qss (Q/Qss=fractional flow reserve) could be calculated on the basis of distal coronary pressure and aortic pressure after subtraction of CVP. The model was tested in dogs, whereby Doppler-
derived measurements of stenotic coronary flow $Q_S$ to normal flow $Q_N$ was compared directly with $(P_d - CVP)/(P_{occl} - CVP)$ but without testing the situation of a complete coronary occlusion ($Q_S = 0$; ie, the setting in which $P_d = P_{occl}$). A direct and simultaneous evaluation of the coronary parameters measured for collateral function ($[P_{occl} - CVP]/[P_{occl} - CVP]$; Figure 8) in comparison to occlusive coronary flow or directly obtained flow velocity was not performed until 1998: Coronary pressure- and Doppler-derived ratios indicative of collateral flow during PCI were compared in CAD patients and termed pressure-derived collateral flow index ($CFI_p$) and velocity-derived collateral flow index ($CFI_v$), respectively. Figure 8 shows 2 examples of $CFI_p$ values sufficient and insufficient to prevent ECG signs of myocardial ischemia (ST-segment shift $\geq 0.1$ mV) during coronary occlusion. With the use of a threshold of $CFI_p = 0.30$, sufficient (ie, no surface lead or intracoronary ST-segment changes $\geq 0.1$ mV during occlusion) and insufficient coronary collaterals could be correctly detected with 75% sensitivity and 92% specificity. In comparison, $>1400$ $CFI_p$ measurements using the definition of myocardial ischemia (ST-segment elevation $\geq 0.1$ mV) provide a cutoff of 0.215 for the most accurate detection of sufficient and insufficient collaterals (76% sensitivity and 76% specificity), which is in close agreement with a study among patients with acute myocardial infarction undergoing single-photon emission computed tomography before primary PCI.

Potential Pitfalls, Limitations, and Risks

Mean CVP should be obtained systematically as a temporal average over several respiratory cycles. During pressure recordings, the patient should be asked to breathe normally and not to speak in order to maintain physiological CVP variations. As additional technical aspects, $P_d$ or $P_{occl}$ shifts due to leakage of electric current and artificial systolic pressure peaks in relation to looping of the pressure guidewire must 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 guidewires is much less robust than pressure-derived CFI measurement. This is mainly due to difficulties of differentiating low occlusive coronary flow velocity signals from vascular wall motion artifacts, as well as time-consuming efforts of wire repositioning to obtain true flow velocity signals.

In approximately two thirds of patients with chronic CAD, coronary occlusion causes myocardial ischemia, which is regarded as a very strong hyperemic stimulus. An additional pharmacological hyperemic stimulus (eg, by intravenous adenosine) probably does not induce further reduction in microvascular resistance in this population (ie, it does not alter CFI). However, among individuals not revealing signs of ischemia during occlusion (Figure 8), pharmacological vasodilation may further decrease collateral and peripheral vascular resistance and increase CFI, and thus CFI may be underestimated in the absence of pharmacological hyperemia. 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). Nevertheless, it can be argued that performing CFI measurements with and without pharmacological hyperemia provides more information than without vasodilation and that induction of maximal vasodilation is theoretically sound. 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 maximum hyperemia because the occlusion is constant. Vasodilation with the use of systemic adenosine in these patients provides a wide variation of responses of the collateral flow and pressure recordings, which are not unidirectional. The differential assessment shows that collateral flow is determined by the serial resistance of the collateral donor segment, by the collateral proper, and also specifically by the peripheral microvascular resistance. Such a differential assessment requires the use of both pressure and flow velocity recordings.

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 stenotic lesion at the occlusion site. 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 balloon inflation pressure just sufficient to occlude the artery. This minimal occlusion pressure is reached very slowly, and imminent occlusion is sensed with 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 (performed in our department from 1996 to 2008) revealed a dissection in 1 vessel (1/426 = 0.2%), which was subsequently treated by stent implantation. In 35% of all vessels investigated (n = 150; mean follow-up, 10 months), angiography was repeated most often because of planned examinations. In 2 of 150 patients (1.3%) both suffering from progressive CAD, a new stenosis at the site of balloon occlusion occurred 14 and 72 months after the initial occlusion, respectively.

Quantitative Collateral Perfusion Measurements

A direct verification of $CFI_p$ versus the reference of myocardial blood supply has been shown only recently. Measurement of myocardial blood flow, defined as blood flow (mL/min) into a region relative to its mass (g), can be obtained by positron emission tomography and lately by myocardial contrast echocardiography (MCE) (see below for description of the technique). Direct comparison of $CFI_p$ 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 (Table). Two human studies with documented CTO to avoid concomitant contrast flow via the native vessel compared MCE and invasive collateral assessment. 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. In patients with stable CAD undergoing PCI, $CFI_p$ has been shown to correlate modestly with peak
signal intensity of ultrasound contrast agent transit curves but not with contrast transit rates.\textsuperscript{59}

On the basis of 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), absolute collateral myocardial perfusion or collateral myocardial blood flow has been obtained during coronary angioplasty balloon occlusion in 30 patients undergoing PCI.\textsuperscript{60} Myocardial blood flow has been calculated according to the continuity equation as the product of $\beta$ and relative myocardial blood volume divided by myocardial tissue density. The precision of this MCE method has been documented previously in comparison to a perfusion phantom model, to positron emission tomography, and to invasive coronary flow velocity measurements.\textsuperscript{57} The distinction between patients revealing ECG signs or no signs of myocardial ischemia during 1 minute of coronary occlusion appears to be most accurate with the use of absolute MCE-derived collateral myocardial blood flow at a threshold of 0.374 mL/min per gram.\textsuperscript{61} In the context of our study with side-by-side comparison of 2 different quantitative methods of collateral assessment,\textsuperscript{60} it is reasonable to state that CFI\textsubscript{p} measurements accurately reflect collateral relative to normal antegrade flow in humans with chronic CAD, even in the low range. The overestimation of MCE-derived collateral perfusion index (collateral relative to normal myocardial perfusion) by pressure-derived CFI is much less than that of Doppler-derived CFI,\textsuperscript{50} and it amounts to $\approx$2% to 7% depending on whether the CFI intercept or the standard error of estimate of the CFI\textsubscript{p}–collateral perfusion index relation is considered.

Options for Coronary Collateral Growth Promotion (Arteriogenesis)

Invasive cardiologists have long been aware of the occurrence of large epicardial branch or septal collateral vessels after total or subtotal occlusion of a major coronary artery (Figure 4). These usually become visible within 2 weeks after an occlusion, and they arise from preformed arterioles. The remodeling process involved in this recruitment of already existing collateral vessels has been termed arteriogenesis.\textsuperscript{62} Large bridging collaterals are much more effective in salvaging ischemic myocardium at risk for necrosis than small peri-ischemia capillaries. The complete obstruction of a coronary artery leads to a fall in poststenotic pressure and to a redistribution of blood to preexisting arterioles. The resulting stretch and shear forces may lead to an increased expression of certain endothelial chemokines, adhesion molecules, and growth factors. Within days, circulating monocytes attach to the endothelium of the bridging collateral vessels, causing a local inflammatory reaction.\textsuperscript{63} Matrix dissolution occurs, and the vessels undergo a growth process with active proliferation of their endothelial and smooth muscle cells. In this context, several candidates for effective coronary collateral arteriogenesis have been found recently in small but controlled clinical trials: granulocyte-macrophage colony-stimulating factor (which may not be safe enough, however),\textsuperscript{54,65} granulocyte colony-stimulating factor,\textsuperscript{12} physical endurance exercise training,\textsuperscript{66} and external counterpulsation triggered by the ECG to occur during diastole.\textsuperscript{13,67}

Conclusions

In patients with CAD, a well-developed coronary collateral circulation contributes to reduction of infarct size,\textsuperscript{68} LV dysfunction,\textsuperscript{69} and mortality.\textsuperscript{11} Coronary collaterals are present in one fourth of patients with normal coronary arteries or nonobstructive CAD.\textsuperscript{71} Therapeutic promotion of collateral function is not only feasible but also effective\textsuperscript{12,13} and represents an important therapeutic option in CAD patients not eligible for revascularization. In regard to future clinical research, accurate and quantitative assessment methods are needed for a reliable distinction between patients with sufficient versus insufficient collateral function. Invasive methods are still inevitable, with pressure-derived CFI measurement being the current gold standard.

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Disclosures

None.

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