Beneficial Effect of Recruitable Collaterals
A 10-Year Follow-Up Study in Patients With Stable Coronary Artery Disease Undergoing Quantitative Collateral Measurements

Pascal Meier, MD*; Steffen Gloekler, MD*; Rainer Zbinden, MD*; Sarah Beckh, BS; Stefano F. de Marchi, MD; Stephan Zbinden, MD; Kerstin Wustmann, MD; Michael Billinger, MD; Rolf Vogel, MD, PhD; Stéphane Cook, MD; Peter Wenaweser, MD; Mario Togni, MD; Stephan Windecker, MD; Bernhard Meier, MD; Christian Seiler, MD

Background—The prognostic relevance of the collateral circulation is still controversial. The goal of this study was to assess the impact on survival of quantitatively obtained, recruitable coronary collateral flow in patients with stable coronary artery disease during 10 years of follow-up.

Methods and Results—Eight-hundred forty-five individuals (age, 62±11 years), 106 patients without coronary artery disease and 739 patients with chronic stable coronary artery disease, underwent a total of 1053 quantitative, coronary pressure–derived collateral measurements between March 1996 and April 2006. All patients were prospectively included in a collateral flow index (CFI) database containing information on recruitable collateral flow parameters obtained during a 1-minute coronary balloon occlusion. CFI was calculated as follows:

\[
\text{CFI} = \frac{P_{\text{occl}} - \text{CVP}}{P_{\text{ao}} - \text{CVP}},
\]

where \(P_{\text{occl}}\) is mean coronary occlusive pressure, \(P_{\text{ao}}\) is mean aortic pressure, and \(\text{CVP}\) is central venous pressure. Patients were divided into groups with poorly developed (CFI < 0.25) or well-grown collateral vessels (CFI ≥ 0.25). Follow-up information on the occurrence of all-cause mortality and major adverse cardiac events after study inclusion was collected. Cumulative 10-year survival rates in relation to all-cause deaths and cardiac deaths were 71% and 88%, respectively, in patients with low CFI and 89% and 97% in the group with high CFI (\(P = 0.0395, P = 0.0109\)). Through the use of Cox proportional hazards analysis, the following variables independently predicted elevated cardiac mortality: age, low CFI (as a continuous variable), and current smoking.

Conclusions—A well-functioning coronary collateral circulation saves lives in patients with chronic stable coronary artery disease. Depending on the exact amount of collateral flow recruitable during a brief coronary occlusion, long-term cardiac mortality is reduced to one fourth compared with the situation without collateral supply. (Circulation. 2007;116:975-983.)

Key Words: angiogenesis ■ collateral circulation ■ coronary circulation ■ prognosis ■ survival

The coronary collateral circulation has long been recognized as an alternative source of blood supply to a myocardial area jeopardized by ischemia. Well-grown versus poorly grown collateral arteries in humans have been suggested to exert a beneficial effect on infarct size,1-5 ventricular aneurysm formation,6,7 and ventricular function.2,7,8 A reduction in nonfatal cardiovascular events during various follow-up durations has been demonstrated among patients with versus those without angiographic coronary collaterals in the setting of chronic stable coronary artery disease (CAD).9,10 Conversely, a study performed in a population with more extended CAD has found that the angiographic presence of collaterals may mark an unfavorable prognosis.11

In the setting of acute myocardial infarction treated by primary percutaneous coronary intervention (PCI), there have been also controversial results regarding the effect of angiographically present collaterals, including 1 investigation without a beneficial effect on 6-month survival rate12 and another study showing reduced in-hospital mortality.13 This debate on the relevance of the human coronary collateral circulation has a long-lasting “tradition.”14 Much of the argument was and still is likely due to the blunt method of gauging human
coronary collaterals by angiography and to the investigation of populations that were too small or followed up too briefly to be representative.\textsuperscript{15,16} Therefore, the aim of the present study was to assess the impact on survival of quantitatively obtained, recruitable coronary collateral flow in a large patient population with stable CAD during 10 years of follow-up.

**Methods**

**Patients**

Eight-hundred forty-five individuals (age, $62 \pm 11$ years; 647 men, 98 women)—106 patients without CAD and 739 patients with 1- to 3-vessel chronic stable CAD—underwent a total of 1053 quantitative, coronary pressure–derived collateral measurements between March 1996 and April 2006. Coronary angiography was performed for diagnostic purposes in the context of chest pain. All of the patients were prospectively included in our collateral flow index (CFI, for calculation, see below) database, which contains $\sim 55$ demographic, clinical, and hemodynamic variables besides the information on recruitable collateral flow parameters obtained during a 1-minute angioplasty balloon coronary occlusion (first occlusion if several were performed). Criteria for measuring collateral flow parameters were as follows: (1) no previous Q-wave myocardial infarction in the area of collateral assessment, (2) no baseline ECG ST-segment abnormalities, and (3) the absence of acute myocardial infarction or unstable angina pectoris. For the purpose of data presentation, the study population was split into 2 groups, a group with poorly developed (CFI $<0.25$) and a group with well-grown (CFI $\geq 0.25$) collateral vessels. Part of the database has been described elsewhere.\textsuperscript{17–19}

Follow-up information on the occurrence of all-cause mortality and major adverse cardiac events after study inclusion was obtained by telephone interview of the patients, their relatives, or their family physicians or by examination of hospital charts. A major adverse cardiac event was defined as death resulting from a cardiac cause, myocardial infarction, unstable angina pectoris, recurring PCI, coronary artery bypass grafting, cerebrovascular stroke, and rehospitalization for cardiac reasons. Cardiac death was defined as any death with an immediate cardiac cause (myocardial infarction, low cardiac output failure, fatal arrhythmia) or unwitnessed death. Myocardial infarction was diagnosed as one of the following criteria: typical rise and fall of cardiac biochemical markers (troponin, creatine kinase-MB) with at least 1 ischemic symptom (development of new Q waves on ECG, ECG changes indicative of ischemia) or new Q waves on ECG without biomarker assessment during the acute event.\textsuperscript{20} The present investigation was approved by the institutional ethics committee, and the patients gave informed consent to participate in the study.

**Cardiac Catheterization and Coronary Angiography**

Patients underwent left heart catheterization and coronary angiography for diagnostic purposes from the right femoral artery approach. Biplane left ventriculography was performed, followed by coronary angiography. Coronary artery stenoses were determined quantitatively as percent diameter reduction with the guiding catheter used for calibration. Aortic pressure was obtained by a 6F coronary artery guiding catheter. Central venous pressure (CVP) was measured via the femoral vein.

**Coronary Collateral Assessment**

**Coronary Pressure–Derived Collateral Flow Index**

In all patients, recruitable coronary collateral flow during a 1-minute vascular balloon occlusion relative to normal antegrade flow through the nonoccluded coronary artery was determined from coronary pressure measurements. A 0.014-in fiberoptic pressure monitoring wire (RadiWire, Radi, Upsala, Sweden) was set at 0, calibrated, advanced through the guiding catheter, and positioned distal to the site of collateral flow index (CFI) assessment. CFI was determined by simultaneous measurements of mean aortic pressure ($P_{ao}$ in mm Hg via the angioplasty guiding catheter), distal coronary occlusive pressure ($P_{occl}$ in mm Hg), and CVP (right atrial pressure):

$$CFI = \frac{P_{ao} - CVP}{P_{occl} - CVP}$$

(CFI calculation at the end of the first 1-minute balloon occlusion; Figure 1). Sensor-derived CFI measurements have previously been validated\textsuperscript{21–24} and are regarded as the gold standard for collateral assessment in humans.

As a dichotomous method for collateral assessment, a unipolar intracoronary ECG was obtained during coronary occlusion in all patients from the angioplasty guidewire (Figure 1) in addition to the surface leads. For that purpose, an alligator clamp was attached close to the end of the wire and connected to ECG lead V$_{1}$.\textsuperscript{25} Thus, coronary collaterals with or without intracoronary ECG signs of ischemia (ie, ST-segment elevation of $>1$ mm or $>0.1$ mV) at the end of the 1-minute coronary occlusion were determined (Figure 1). In addition, at the end of the coronary occlusion, the patient was asked whether he or she experienced chest pain.

**Study Protocol**

After diagnostic coronary angiography, an interval of at least 10 minutes was allowed for dissipation of the effect of the contrast medium on coronary vasomotion. Before CFI measurement, 5000 U heparin was given. Two puffs of oral nitroglycerin spray were applied shortly before coronary pressure measurements. The pressure guidewire was positioned distal to the site of the imminent angioplasty balloon occlusion. During the entire protocol, the intracoronary ECG obtained from the pressure guidewire and the surface lead ECG were recorded. Simultaneous recording of $P_{ao}$, $P_{occl}$, CVP, and the ECG was started before and continued throughout the 1-minute balloon occlusion. Coronary occlusion was performed with an appropriately sized angioplasty balloon. If indicated, PCI for treatment of a stenotic lesion was performed after CFI measurement. If the CFI measurement was performed in a normal coronary artery, an adequately sized balloon was inflated at a low pressure ($\sim 1$ atm) just sufficient to occlude the vessel.

**Statistical Analysis**

The study population was divided into a group with poorly developed collateral vessels (CFI $<0.25$) or a group with well-grown collateral vessels (CFI $\geq 0.25$). Between-group comparisons of continuous demographic, clinical, angiographic, hemodynamic, and collateral flow data were performed by a 2-sided unpaired Student $t$ test. A $\chi^2$ test ($2 \times 2$ table) was used for comparison of categorical variables among the study groups. Cumulative survival and event rates were calculated through Kaplan-Meier analysis; statistical comparison between the groups was done by a log-rank test (Mantel-Cox). Cox proportional hazards analysis was carried out to determine independent predictors for cardiovascular mortality.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Patient Characteristics and Clinical Data**

There were no statistically significant differences between the 2 groups regarding age, gender, duration of chest pain before CFI measurement, body mass index, and frequency of most of the cardiovascular risk factors, as well as the use of most cardiovascular drugs (Table 1). The frequency of prior remote myocardial infarction was higher, that of ECG changes indicative of ischemia during an exercise test was lower, and the occurrence of smoking was lower in patients with low than in those with high CFI. Statins were used less often in the group with low CFI.
Coronary Angiographic Data
The coronary arteries undergoing CFI measurement were distributed similarly between groups (Table 2). There was no difference between groups in the number of coronary arteries diseased or in the vascular site of CFI measurement. Average percent diameter stenosis at the site of CFI measurement and the total number of stenotic lesions in patients with CAD were significantly less in the group with low than with high CFI (Table 2).

Hemodynamic and Collateral Circulation Data
Heart rate, arterial blood pressure, left ventricular ejection fraction, left ventricular end-diastolic pressure, and CVP were similar between groups (Table 3).

CFI Measurement Variability
Serial CFI measurements in the absence of altering hemodynamic conditions between the measurements (ie, no change of stenosis severity) and without any intervention during follow-up were performed in 53 patients (66 vessels; follow-up duration, 2 weeks and 3 months). CFI was 0.203±0.081 at baseline and 0.185±0.076 at follow-up (P=0.75).

The occurrence of angina pectoris during the 1-minute coronary occlusion and ST-segment elevation/1 minute intracoronary ECG (ie, signs of ischemia) were observed significantly more often in the group with low than with high CFI. By group definition, CFI was lower in the group with CFI <0.25 than in the group with CFI ≥0.25; a comparable result was obtained among the 45 patients with chronic total coronary occlusion (Table 3). Figure 2 shows the CFI frequency distribution among the study individuals without and with differently severe forms of CAD.

Cardiovascular Events
Follow-up duration ranged from 0.5 to 128 months (average, 58.8±36.2 months). Follow-up duration was significantly shorter in patients with low than in those with high CFI (Table 4). Follow-up was complete in 801 patients (95%). The number of deaths due to all causes (n=83; 2 of them in the group without CAD) tended to be higher and the number of cardiovascular deaths (n=42) was significantly higher in the group with low versus high CFI (Table 4). The raw numbers of other major adverse cardiac events did not differ between groups. Cumulative survival rates in relation to all-cause and cardiovascular deaths were significantly lower in patients with low versus high CFI (Figure 3). The composite event-free rates of cardiac death or myocardial infarction and of cardiac death, infarction, or unstable angina pectoris were significantly lower in the group with low versus high CFI (Figure 4). Among patients with chronic total coronary occlusion, the 5-year cumulative survival rate in

![Insufficient coronary collaterals](image1.png) ![Sufficient coronary collaterals](image2.png)

Figure 1. Determination of collateral function in a patient with insufficient (left) and a patient with sufficient (right) coronary collaterals. CFI is calculated by dividing the mean distal coronary occlusive pressure ($P_{occl}$; mm Hg; scale, 0 to 200 mm Hg) minus CVP (mm Hg; scale, 0 to 50 mm Hg) by mean aortic pressure ($P_{ao}$; mm Hg; scale, 0 to 200 mm Hg) minus CVP. CFI of 0.176 (left) is insufficient to prevent myocardial ischemia during a 1-minute coronary balloon occlusion as indicated by ST-segment elevations on the intracoronary (V1) and peripheral ECG leads (arrows). Conversely, CFI of 0.236 (right) is sufficient to prevent myocardial ischemia during a 1-minute coronary balloon occlusion as indicated by the absence of ST-segment elevations on the intracoronary (V1) and peripheral ECG leads (arrowheads).
relation to cardiac deaths was 80% in the group with CFI <0.25 and 96% in the group with CFI ≥0.25 (P=0.03). Using the intracoronary ECG definition of collateral flow insufficient or sufficient to prevent signs of myocardial ischemia during coronary occlusion shows that cumulative survival related to cardiac deaths was lower in the group with than in the group without signs of ischemia (Figure 5). Proportional hazards analysis showed the following parameters to be independent predictors of cardiovascular mortality (Table 5): CFI <0.25 as a group, low CFI as a continuous variable, advanced age, and smoking.

### Discussion

The novel result of this study is that a well-functioning coronary collateral circulation saves lives in patients with a common and potentially fatal disorder, ie, chronic stable CAD. Depending on the exact amount of collateral flow recruitable during a brief coronary occlusion relative to

### Table 1. Patient Characteristics and Clinical Data

<table>
<thead>
<tr>
<th></th>
<th>Insufficient Collaters (CFI &lt;0.25)</th>
<th>Sufficient Collaters (CFI ≥0.25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study individuals, n</td>
<td>618</td>
<td>227</td>
<td>...</td>
</tr>
<tr>
<td>CFI measurements, n</td>
<td>803</td>
<td>250</td>
<td>...</td>
</tr>
<tr>
<td>Individuals without CAD</td>
<td>83 (13)</td>
<td>23 (10)</td>
<td>...</td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>62±11</td>
<td>61±11</td>
<td>0.30</td>
</tr>
<tr>
<td>Male gender</td>
<td>467 (76)</td>
<td>180 (79)</td>
<td>0.19</td>
</tr>
<tr>
<td>Duration of chest pain, mo, mean±SD</td>
<td>17±40</td>
<td>16±33</td>
<td>0.71</td>
</tr>
<tr>
<td>Prior myocardial infarction in remote area</td>
<td>130 (21)</td>
<td>32 (14)</td>
<td>0.0324</td>
</tr>
<tr>
<td>ECG changes during exercise test</td>
<td>358 (58)</td>
<td>160 (71)</td>
<td>0.05</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean±SD</td>
<td>28±11</td>
<td>28±11</td>
<td>0.65</td>
</tr>
<tr>
<td>Smoking</td>
<td>218 (35)</td>
<td>102 (45)</td>
<td>0.0148</td>
</tr>
<tr>
<td>Hypertension</td>
<td>336 (54)</td>
<td>139 (61)</td>
<td>0.09</td>
</tr>
<tr>
<td>Obesity</td>
<td>360 (58)</td>
<td>111 (49)</td>
<td>0.0210</td>
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<tr>
<td>Family history of CAD</td>
<td>220 (36)</td>
<td>70 (31)</td>
<td>0.18</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>94 (15)</td>
<td>39 (17)</td>
<td>0.49</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>429 (69)</td>
<td>176 (78)</td>
<td>0.06</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>315 (51)</td>
<td>132 (58)</td>
<td>0.12</td>
</tr>
<tr>
<td>Nitrates</td>
<td>116 (19)</td>
<td>44 (19)</td>
<td>0.10</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>254 (41)</td>
<td>91 (41)</td>
<td>0.69</td>
</tr>
<tr>
<td>Statin</td>
<td>353 (57)</td>
<td>155 (68)</td>
<td>0.0088</td>
</tr>
</tbody>
</table>

Values are expressed as n (%) unless otherwise noted.

### Table 2. Coronary Angiographic Data

<table>
<thead>
<tr>
<th></th>
<th>Insufficient Collaters (CFI &lt;0.25)</th>
<th>Sufficient Collaters (CFI ≥0.25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel undergoing CFI measurement, n (%)</td>
<td>...</td>
<td>...</td>
<td>0.12</td>
</tr>
<tr>
<td>Left anterior descending coronary artery</td>
<td>303 (49)</td>
<td>98 (43)</td>
<td>...</td>
</tr>
<tr>
<td>Left circumflex coronary artery</td>
<td>133 (22)</td>
<td>56 (25)</td>
<td>...</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>182 (29)</td>
<td>73 (32)</td>
<td>...</td>
</tr>
<tr>
<td>0</td>
<td>83 (13)</td>
<td>23 (10)</td>
<td>...</td>
</tr>
<tr>
<td>1</td>
<td>202 (33)</td>
<td>68 (30)</td>
<td>...</td>
</tr>
<tr>
<td>2</td>
<td>226 (36)</td>
<td>84 (37)</td>
<td>...</td>
</tr>
<tr>
<td>3</td>
<td>107 (18)</td>
<td>52 (23)</td>
<td>...</td>
</tr>
<tr>
<td>Site of CFI measurement, n (%)</td>
<td>...</td>
<td>...</td>
<td>0.42</td>
</tr>
<tr>
<td>Proximal segment</td>
<td>306 (49)</td>
<td>109 (48)</td>
<td>...</td>
</tr>
<tr>
<td>Mid segment</td>
<td>270 (44)</td>
<td>104 (46)</td>
<td>...</td>
</tr>
<tr>
<td>Distal segment</td>
<td>42 (7)</td>
<td>14 (6)</td>
<td>...</td>
</tr>
<tr>
<td>Diameter stenosis at CFI site, %</td>
<td>59±33</td>
<td>69±34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stenoses in patients with CAD, n</td>
<td>2.2±1.8</td>
<td>2.6±2.0</td>
<td>0.0152</td>
</tr>
</tbody>
</table>
normal antegrade flow during vessel patency (ie, CFI), cardiac mortality is reduced to one fourth compared with the situation without collateral supply.

**Coronary Collateral Circulation and Adverse Events**

Recently, the prognostic impact of the collateral circulation in ischemic heart disease has regained heightened interest. However, as in earlier investigations, the focus has been on widely varying aspects of the terms “prognosis” and “ischemic heart disease” such as surrogate end points for worse outcome in the course of CAD, “soft” and “firmer” cardiac end points, respectively, and the setting of acute myocardial infarction versus chronic stable CAD. Thus, the ongoing controversy over whether coronary collateral vessels are protective against future adverse events is substantially influenced by the solidity of the definition of the terms “prognosis” and “collateral supply.” In addition, whether the focus of the study is on patients with acute or chronic CAD affects the degree of how statistically relevant “prognosis” can be determined because the occurrence of severe incidences in the hierarchy of adverse events is

<table>
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<th>TABLE 3. Hemodynamic and Collateral Circulation Data</th>
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<tr>
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<tr>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
</tr>
<tr>
<td>LV end-diastolic pressure, mm Hg</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
</tr>
<tr>
<td>Coronary collateral circulation</td>
</tr>
<tr>
<td>Angina pectoris during balloon occlusion, n (%)</td>
</tr>
<tr>
<td>IC ECG ST elevation &gt;1 mm during occlusion, n (%)</td>
</tr>
<tr>
<td>CFI</td>
</tr>
<tr>
<td>CFI in patients with chronic total occlusion (n)</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD unless otherwise noted. LV indicates left ventricular; IC, intracoronary.

**Figure 2.** Frequency distribution (vertical axes in percent) of CFI (horizontal axes) values in all the individuals included in the study.
different. With respect to the increasing solidity of end points, they range from surrogate end points (left ventricular ejection fraction, ventricular aneurysm formation, ventricular remodeling) to soft cardiac end points (eg, coronary reintervention) to the occurrence of unstable angina pectoris, myocardial infarction, and cardiac death to the only unequivocal adverse event, all-cause mortality. All-cause mortality in the present study occurred in 83 of the 845 study individuals (2 deaths among those without CAD) during an average follow-up of 5 years (2.0% mortality per year), a number almost identical to the recently reported frequency of 1.7% in a comparable population.\textsuperscript{30} Thus, chronic stable CAD is primarily a benign disease, and gauging the real prognostic impact of a well-developed collateral circulation requires sizeable patient populations and/or long follow-up durations. Both are met in the present study. Regarding the statistical power of the event rate of total mortality, the only comparable investigation in a similar study population overseeing 5985 patient-years (the present study, 3907 patient-years) has reported an annual mortality of 4.9%.\textsuperscript{16} The higher total mortality in that study compared with this study is explained in part by the very low number of 2 deaths among the 106 individuals in our control group without CAD (mortality rate, 0.6% per year). Other very recent investigations in patients with chronic CAD undergoing PCI have included insufficient numbers of individuals with brief observation times, so the number of the only indisputable end point, all-cause mortality, has been <10.\textsuperscript{10,11} Thus, the present investigation is unique in demonstrating that a well-developed collateral circulation reduces all-cause annual mortality from 2.3% (group with low CFI) to a level reached by individuals without CAD (0.6%). In this context, mortality in the presence of well-developed collaterals continues to be diminished beyond a follow-up of 5 years (Figure 3), which can be explained by the increasing importance of natural bypasses during the progression of CAD. The study by Abbott et al\textsuperscript{16} has reported a lower and statistically irrelevant difference in mortality between patients without (annual mortality, 4.7%) and those with (annual mortality, 4.1%) visible collateral vessels during coronary angiography to the artery undergoing PCI. In this

<table>
<thead>
<tr>
<th>Insufficient Collaterals (CFI&lt;0.25)</th>
<th>Sufficient Collaterals (CFI≥0.25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean follow-up duration, mo, mean±SD</td>
<td>56±36</td>
<td>65±37</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>28 (5)</td>
<td>16 (7)</td>
</tr>
<tr>
<td>All-cause deaths</td>
<td>66 (11)</td>
<td>17 (7)</td>
</tr>
<tr>
<td>Cardiac deaths</td>
<td>37 (6)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>27 (4)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
<td>42 (7)</td>
<td>14 (6)</td>
</tr>
<tr>
<td>PCI</td>
<td>135 (22)</td>
<td>55 (24)</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>21 (3)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Stroke</td>
<td>8 (1)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>152 (25)</td>
<td>55 (24)</td>
</tr>
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</table>

Values are expressed as n (%) unless otherwise noted.

![Figure 3](http://circ.ahajournals.org/)

Figure 3. Cumulative survival rates related to all-cause (left) and cardiac (right) mortality in patients with low and high CFI.
context, an explanation for the reason of this discrepancy is warranted, and more generally, the solidity of the definition of “coronary collateral supply” has to be discussed.

Clinical Definition of Coronary Collateral Supply

Our notion is that the inconsistency in annual mortality data between the Abbott et al study and the present study relates to the angiographic qualification of collateral structure in general used in the former investigation and to the way that angiographic collateral characterization was used in particular in that study. Except for only a few recent investigations on the topic, the vast majority have used structural qualitative assessment of collaterals by angiographically dividing the patients into those with or without spontaneously visible collateral supply to the area of interest. Investigations directly comparing the “traditional” angiographic scoring system (according to Rentrop et al) and quantitative functional measures of collateral supply such as pressure- or Doppler-derived CFI or a collateral resistance index have revealed no or only a very weak correlation (ie, angiographic collateral score is equal to \( 0.3, \) with a large SE of \( 0.8 \)). Quantitative functional measures of relative or absolute collateral flow obtained during a brief vascular occlusion (PCI model of recruitable collateral supply to the area of interest) currently serve as the reference for assessing the human coronary collateral circulation. Coronary angiographic data on collateral channels during vessel patency are readily available, but they represent the actual status of “natural bypasses” very imprecisely. Consequently, the blurred measure of collateral supply contributes further to

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient collateral flow (CFI = 0.25)</td>
<td>4.555 (1.345 to 15.425)</td>
<td>0.0148</td>
</tr>
<tr>
<td>CFI</td>
<td>0.028 (0.001 to 0.795)</td>
<td>0.0362</td>
</tr>
<tr>
<td>Age</td>
<td>1.053 (1.008 to 1.100)</td>
<td>0.0195</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.196 (0.422 to 3.392)</td>
<td>0.74</td>
</tr>
<tr>
<td>No diabetes mellitus</td>
<td>0.649 (0.241 to 1.749)</td>
<td>0.39</td>
</tr>
<tr>
<td>No smoking</td>
<td>0.362 (0.165 to 0.793)</td>
<td>0.0111</td>
</tr>
<tr>
<td>No family history of CAD</td>
<td>1.341 (0.582 to 3.093)</td>
<td>0.49</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.987 (0.914 to 1.066)</td>
<td>0.74</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.997 (0.977 to 1.018)</td>
<td>0.80</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>1.016 (0.730 to 1.414)</td>
<td>0.92</td>
</tr>
<tr>
<td>No. of vessels with CAD</td>
<td>0.936 (0.599 to 1.462)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Figure 4. Cumulative event-free survival rates related to major adverse cardiac events: cardiac death or myocardial infarction (left) or cardiac death, myocardial infarction, or unstable angina pectoris (right) in patients with low and high CFI.

Figure 5. Cumulative survival rates related to cardiac mortality in patients without and in those with ECG signs of myocardial ischemia on intracoronary ECG during a 1-minute coronary balloon occlusion. Myocardial ischemia was defined as ECG ST-segment elevation >0.1 mV (ST↑).
the above-mentioned increased number of study individuals required to determine the term “prognosis.” Aside from this conceptual problem of collateral assessment inherent in most studies on the prognostic impact of coronary collaterals, the only statistically powerful investigation has used an even fuzzier angiographic feature of collaterals, ie, the distinction among coronary arteries treated by PCI getting no collaterals, those supplying other vessels (supplying collaterals), and those receiving collaterals from other vessels. The discrimination between the absence of angiographic collaterals to the artery of interest and collaterals taking off that vessel (supplying collaterals) lacks any clear definition and has to be regarded as very difficult, especially in the context of a data registry. Therefore, the particular methodology used in that study has not allowed a firm conclusion as to whether collaterals are protective or not.

As an alternative to the continuous, pressure-derived collateral measure (CFI), the present study also used the dichotomous, intracoronary ECG-detected presence or absence of signs of myocardial ischemia during vascular occlusion for collateral definition. Cardiac deaths and the composite of cardiac death or myocardial infarction occurred more often in the group with than among patients with high CFI. Other study parameters and analyses argue against this suggestion. The rate of 3-vessel CAD among coronary arteries treated by PCI getting no collaterals, shorter follow-up in the group with low than with high CFI most likely reflects the higher fatality rate in the absence of well-developed collaterals.

Five percent of patients were lost to follow-up, which may have influenced the outcome of the study. However, the rate of patients with missing information on the course of the disease can be regarded as very low, and it did not differ between groups.

Conclusions
A well-functioning coronary collateral circulation saves lives in patients with chronic stable CAD. Depending on the exact amount of collateral flow recruitable during a brief coronary occlusion, long-term cardiac mortality is reduced to one fourth compared with the situation without collateral supply.

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

The coronary collateral circulation has been recognized as an alternative source of blood supply to a myocardial area jeopardized by ischemia. However, the prognostic relevance of this system of natural cardiac bypasses in patients with chronic stable coronary artery disease has been controversial. This is likely due to the blunt, qualitative method of angiographic collateral assessment used in previous studies and to the investigation of populations too small or followed up too briefly to be representative. The novel result of the present investigation in 845 individuals undergoing quantitative collateral measurement is that a well-functioning collateral circulation is able to reduce all-cause annual mortality from 2.3% in patients with coronary artery disease and low collateral flow to a level reached by individuals without coronary artery disease (0.6%). Well-developed or sufficient coronary collaterals are defined as a collateral flow during a 1-minute angioplasty balloon occlusion amounting to >0.25 of normal flow during vessel patency (so-called collateral flow index) because this value corresponds well to the absence of ECG signs of myocardial ischemia during coronary occlusion. Accordingly, the present study found not only a beneficial effect of collaterals with a collateral flow index >0.25 but also a reduced rate of cardiac deaths and acute myocardial ischemia when there were no ECG signs of myocardial ischemia during coronary occlusion. The main implication of this study is that therapeutic promotion of collateral growth has great potential to have an impact on the prognosis of patients, even in the low-risk group with chronic coronary artery disease.
Beneficial Effect of Recruitable Collaterals: A 10-Year Follow-Up Study in Patients With Stable Coronary Artery Disease Undergoing Quantitative Collateral Measurements
Pascal Meier, Steffen Gloekler, Rainer Zbinden, Sarah Beckh, Stefano F. de Marchi, Stephan Zbinden, Kerstin Wustmann, Michael Billinger, Rolf Vogel, Stéphane Cook, Peter Wenaweser, Mario Togni, Stephan Windecker, Bernhard Meier and Christian Seiler

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