Is There Functional Collateral Flow During Vascular Occlusion in Angiographically Normal Coronary Arteries?

Kerstin Wustmann, MD; Stephan Zbinden, MD; Stephan Windecker, MD; Bernhard Meier, MD; Christian Seiler, MD

Background—Thus far, it is unknown whether there is functional collateral flow through preexisting anastomoses in patients with angiographically normal coronary arteries. Such preformed coronary collateral vessels could form the basis for subsequently developing protective natural bypasses in the presence of coronary artery disease.

Methods and Results—Among 100 patients, the collateral flow index (CFI) was measured in coronary arteries without stenotic lesions. The CFI was determined by simultaneous measurement of mean aortic pressure, central venous pressure, and coronary wedge pressure via a sensor-tipped guidewire at the end of a 1-minute balloon occlusion. Patients were divided in 2 groups according to complete angiographic absence (51 patients) or partial presence (49 patients) of stenotic lesions in coronary arteries other than that undergoing collateral measurement. CFI in all patients (61.006 10 years; men/women, 69/31) amounted to 0.18 0.08 (range, 0.04 to 0.36). It showed a normal Gaussian frequency distribution; 22 individuals had a CFI 0.25, a value that was empirically found to represent well-developed collaterals protective against myocardial ischemia during coronary occlusion. Accordingly, 17 patients did not reveal signs of myocardial ischemia during coronary balloon occlusion, as assessed from an intracoronary ECG, and 26 patients did not experience angina pectoris during occlusion.

Conclusion—In humans with angiographically normal coronary arteries, there are functional collateral vessels to the extent that one fifth to one quarter of them do not show signs of myocardial ischemia during brief vascular occlusions. (Circulation. 2003;107:2213-2220.)

Key Words: circulation collateral circulation angiogenesis

In the presence of obstructive or occlusive coronary artery disease, anastomoses between different vascular regions may serve as natural bypasses for blood to reach myocardial territories distal to occlusions, thereby preventing or mitigating myocardial infarction.1 In an experimental animal model, well-conducting coronary collateral arteries in the presence of a blocked native vessel develop via remodeling of preformed interconnecting arterioles.2 Among patients with coronary artery disease, about one third have functionally sufficient coronary collaterals that are able to prevent signs of myocardial ischemia during brief vascular occlusions.3 Thus far, the question of whether humans possess preformed, functionally adequate coronary anastomoses has not been investigated in a population without cardiac disease.

Historically, channels connecting the right and left coronary arteries were first described by Richard Lower of Amsterdam in 1669,4 the fact of which was later confirmed by the Swiss anatomist Albrecht von Haller using gross anatomic dissection of the coronary arteries.5 After initial controversy regarding the structural existence of coronary anastomoses in human hearts,6,7 it was recently generally recognized that collateral arterioles occur frequently in the presence of occlusive coronary artery disease.8-10 However, the response of collateral development to a certain obstructive stimulus is highly variable and in only a minority of patients is it adequate to prevent myocardial ischemia during coronary occlusion. It may be hypothesized that a certain amount of preformed, sufficiently large collateral vessels (Figure 1) have to be present so that a later developing pressure gradient between a nonobstructed and a stenotic vascular territory will lead to functionally “sufficient” anastomoses. Pathoanatomically, the existence of structural intercoronary connections (>40 μm in diameter) in normal hearts has been a matter of dispute, with estimates of their occurrence ranging between 6%11 and 100%.12 It is, however, generally assumed without ever having been investigated that functionally, coronary arteries are end-arteries.11

The purpose of the present study was to test the hypothesis that in individuals with entirely or partially normal coronary arteries, there is functionally relevant collateral flow to a nonstenotic recipient vessel.

Methods

Patients
One hundred patients (age, 61±10 years; 69 men and 31 women) referred for diagnostic coronary angiography were included in the
study if they presented with one or more coronary arteries with entirely normal angiographic appearance (ie, no wall irregularities, no stenotic lesions). Patients underwent coronary angiography because of chest pain or a positive treadmill exercise test. Patients with acute coronary syndrome, valvular heart disease, left ventricular ejection fraction <40%, previous coronary artery bypass surgery, abnormal conduction on ECG, previous myocardial infarction in the area undergoing collateral flow measurement, chronic lung disease,

Figure 1. Coronary angiogram of a patient without stenotic lesions in both RCA and LCA but with spontaneously visible collateral vessels between the RCA (left panel; projection: left anterior oblique, 10°; cranial, 15°) and the retrogradely filled marginal branch of the LCX (left and right panels; projection for left coronary angiogram: left anterior oblique, 40°; caudal 20°).

Figure 2. Coronary collateral assessment: Collateral flow index (CFI) expressing collateral flow to the balloon-occluded coronary artery relative to normal antegrade flow during vessel patency is determined using aortic pressure, coronary pressure, and CVP measurements (phasic recordings of these pressures obtained during coronary patency are shown on the left middle and lower side of the figure). After vascular occlusion, phasic and mean coronary artery occlusive or wedge pressure (P_{occl}) starts to decrease and plateaus at a level of 36 mm Hg (right lower side of the figure). Note the different scale for mean aortic pressure (P_{a0}), mean occlusive pressure, and CVP. CFI is calculated as (P_{occl}/CVP)/(P_{a0}/CVP). During contrast medium injection, complete coronary balloon occlusion is ascertained; this is a moment during which aortic pressure cannot be obtained via the angioplasty guiding catheter. On the surface lead ECG (I, II, aVF) and on the intracoronary (i.c.) ECG lead recorded via the sensor guidewire, no signs of myocardial ischemia (ie, ST-segment changes) can be observed during vessel occlusion when compared with the period before coronary occlusion (ie, definition of sufficient collateral vessels).
or renal insufficiency were excluded. Patients were divided in 2 groups according to the complete angiographic absence (termed entirely normal coronary arteries; n=51) or presence of stenotic lesions (termed partially normal coronary arteries; n=49) in coronary arteries other than the one undergoing collateral assessment.

The local ethics committee approved the investigation, and all patients gave written, informed consent to participate in the study. In addition, the ethical issue of briefly and softly (see below) occluding a normal coronary artery was considered as follows: in the literature, data on the risk of neointima formation through a vascular balloon occlusion as we specifically performed it in our protocol are absent, and the senior author of the investigation (C.S.) served as a study subject during a baseline and follow-up invasive examination. The coronary angiogram was normal during both exams. A 3.0-mm balloon was inflated in the normal mid-left anterior descending coronary artery (LAD) in August 2000 and in September 2002 (only the data of the first examination are included in the study). Using adenosine for functional assessment of the coronary artery investigated before both balloon occlusions showed the artery was normal.

### Cardiac Catheterization and Coronary Angiography

Patients underwent diagnostic left heart catheterization via the right femoral artery. Before biplane coronary angiography, 2 puffs of oral isosorbidedinitrate were given. Biplane left ventriculography was performed after completion of coronary angiography, and left ventricular end-diastolic pressure was determined. Aortic pressure was recorded using a 5 to 6 French guiding catheter for percutaneous transluminal coronary angioplasty. In all patients, central venous pressure (CVP) was obtained as right atrial pressure via the right femoral vein. Percent diameter stenosis in coronary vessel(s) other than the one assessed for collateral flow and the diameter of the normal vessel at the occlusion site were determined by quantitative coronary angiography using the guiding catheter for calibration.

### Coronary Collateral Flow Measurement

Collateral flow to an angiographically normal coronary artery relative to normal antegrade blood flow was determined by simultaneous measurements of mean aortic pressure (Pao), mean distal...
coronary occlusive or wedge pressure ($P_{occl}$) obtained via a 0.014-inch sensor-tipped pressure guidewire (PressureWave, Jomed), and mean CVP at the end of a 1-minute balloon occlusion. Collateral flow index (CFI) was calculated using the following formula:

$$\text{CFI} = \frac{P_{occl}}{P_{a} \times CVP}$$

Sensor-guidewire–derived CFI measurements have been validated previously. An intracoronary ECG obtained via the sensor guidewire was recorded in addition to the limb lead ECG for the detection of absent (Figure 2) or present signs of myocardial ischemia during coronary occlusion (defined as ST-segment changes ≥ 0.1 mV).

**Study Protocol**

After completion of the diagnostic angiographic procedure and intravenous administration of 5000 IU heparin as well as two additional puffs of oral isosorbidedinitrate, the pressure guidewire was set at zero, calibrated, advanced through the guiding catheter into the coronary ostium, and equalized with aortic pressure obtained via the guiding catheter. Subsequently, the pressure guidewire was inserted into the angiographically normal coronary artery of interest and placed distally. Coronary occlusion sites were chosen based on the criterion of an easy and fast access with both the sensor-tipped guidewire and the angioplasty balloon. An adequately sized angioplasty balloon for proximal (in 65 patients) or midvascular (in 34 patients) occlusions was positioned and inflated at a pressure of 1 to 2 atm to occlude the artery without impacting the vessel wall. The principal feature of the protocol with regard to preventing vessel injury was the use of a balloon inflation pressure just sufficient to occlude the artery (always ≤ 2 atm). This minimal occlusion pressure was reached slowly, and imminent occlusion was sensed using the start of decline of the pressure obtained distal to the balloon and not angiographic detection of occlusion, which only followed later. During the 1-minute vessel occlusion, simultaneous mean distal coronary occlusive or wedge pressure, mean aortic pressure, and mean CVP (with phasic and mean curves for the calculation of CFI) and the intracoronary guidewire–derived ECG in addition to the 3 surface ECG leads were recorded (Figure 2). Patients were asked about chest pain or discomfort. After balloon deflation and pullback, a biplane coronary angiogram was performed to ascertain vessel integrity. In 3 patients, a transient coronary vasospasm proximal to the briefly occluded site was observed and was successfully treated by intracoronary nitroglycerin. After the procedure, all patients received a transdermal nitroglycerin patch for the following 12 hours per protocol. Patients with a focal, hemodynamically relevant stenotic lesion in another vessel than that undergoing CFI measurement underwent angioplasty before (n = 28) or after (n = 21) collateral assessment in the normal coronary artery.

**Statistical Analysis**

For comparison of continuous demographic, angiographic, and hemodynamic variables between the 2 groups, as well as for correlations between CFI and intracoronary ECG and angina pectoris categories, an unpaired Student’s t test was used. Categorical variables between the 2 populations were compared with the χ² test. ANOVA was performed to compare CFI related to the collateral recipient vessel. Linear regression analysis was carried out to detect statistically relevant correlations between CFI (dependent variable)

<table>
<thead>
<tr>
<th>Vessel selected for CFI measurement, n (%)</th>
<th>Angiographically Entirely Normal Coronary Arteries (n=51)</th>
<th>Angiographically Partially Normal Coronary Arteries (n=49)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>21 (41)</td>
<td>11 (22)</td>
<td>0.05</td>
</tr>
<tr>
<td>LCX</td>
<td>16 (31)</td>
<td>26 (53)</td>
<td>0.03</td>
</tr>
<tr>
<td>RCA</td>
<td>14 (28)</td>
<td>12 (25)</td>
<td>NS</td>
</tr>
<tr>
<td>Balloon size used during CFI measurement, mm</td>
<td>3.2±0.4</td>
<td>3.1±0.4</td>
<td>0.10</td>
</tr>
<tr>
<td>Vessel size at CFI measurement site, mm</td>
<td>3.0±0.4</td>
<td>2.9±0.4</td>
<td>0.10</td>
</tr>
<tr>
<td>No. of vessels diseased</td>
<td>0</td>
<td>1.3±0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No. of stenotic lesions, n (%)</td>
<td>0</td>
<td>51 (100)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
<td>0.0013</td>
</tr>
<tr>
<td>Stenotic vessel, n (%)</td>
<td>0</td>
<td>30 (52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>LAD</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>LCX</td>
<td>0</td>
<td>0.0007</td>
</tr>
<tr>
<td></td>
<td>RCA</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Site of stenosis, n (%)</td>
<td>0</td>
<td>12 (21)</td>
<td>0.0003</td>
</tr>
<tr>
<td></td>
<td>Proximal segment</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Mid segment</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Distal segment</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>0</td>
<td>69±11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Site of occlusion in the normal vessel, n (%)</td>
<td>36 (71)</td>
<td>29 (59)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Proximal segment</td>
<td>15 (29)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Distal segment</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

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TABLE 2. Coronary Angiographic Data
and potential predictors of CFI (independent variable). Data are expressed as mean±SD. Statistical significance was defined as P<0.05.

Results

Patient Characteristics
Among the 100 patients included in the study, 51 patients had angiographically entirely normal coronary arteries, and 49 patients had ≥1 stenotic lesion(s) in 1 or 2 other coronary arteries (ie, partially normal coronary arteries). Demographic and clinical characteristics for both patient groups are presented in Table 1.

Coronary Angiographic Data
Table 2 shows that the angiographically normal vessels selected for collateral measurement were the left coronary artery in 37 of 51 cases and the right coronary artery (RCA) in 14 of 51 cases among patients with entirely normal vessels, and the left coronary artery in 37 of 49 cases and the RCA in 12 of 49 cases among patients with partially normal coronary arteries, respectively (P=NS). Balloon sizes used during CFI measurement ranged between 2.0 to 4.0 mm in diameter (4.0 and 3.5 mm in 32%, 3.0 mm in 63%, and 2.5 and 2.0 mm in 5%).

Hemodynamic and Coronary Collateral Circulation Data
Hemodynamic parameters included heart rate, left ventricular end-diastolic pressure, left ventricular ejection fraction (range, 40% to 89%), mean arterial blood pressure during coronary occlusion, mean coronary occlusive pressure, and occlusive central venous pressure and were similar between the groups (Table 3).

Collateral Circulation Data
Coronary collateral assessment obtained by a 1-minute occlusion of the entirely normal vessel revealed that about one fourth of individuals in both groups did not suffer chest pain during occlusion and that about one fifth to one sixth of them, at the same time, did not show ECG signs of ischemia (defined as “sufficient” collateral flow; Table 3 and Figure 2). When performing the vessel occlusion proximally, 18 of 65 patients (28%) remained without chest pain, and when performing occlusion in the midsection, the respective number was 7 of 34 patients (21%; P=NS). There was a significant difference between CFI values in patients with and without angina pectoris (0.17±0.08 versus 0.21±0.09, respectively; P=0.01), and in those with and without intracoronary ECG ST-segment changes during coronary balloon occlusion (Figure 3). CFI ranged between 0.044 and 0.363 in

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

**Figure 3.** CFI values (vertical axis; bar graphs indicating mean values and 75% confidence intervals, error bars indicating 90% confidence intervals, and individual values beyond the error bars) are depicted in relation to the presence (horizontal axis, left side) or absence of ECG ST-changes of ≥0.1 mV (right side) during coronary balloon occlusion.
both groups, and it was not statistically different between them (Table 3). CFI did not differ statistically in the group with partially normal coronary arteries depending on whether it was measured before or after angioplasty of the contralateral vessel (0.16±0.07 versus 0.18±0.06, respectively; \(P=\text{NS})\). Figure 4 illustrates the normal frequency distribution of CFI in the 100 patients in the present study, including the 22 individuals with a CFI ≥0.25, which is a value that was empirically found to predict best the absence of signs of ischemia during coronary occlusion.\(^3\) For comparison, a panel is inserted showing the (Poisson) distribution of CFI measured in coronary arteries with hemodynamically relevant stenoses of patients in a previous study at our institution\(^4\) (mean values were significantly different at \(P=0.01)\).

CFI with regard to the collateral recipient vessels did not differ significantly; it was 0.17±0.08, 0.19±0.09, and 0.17±0.08, respectively, in the LAD, the left circumflex (LCX), and the RCA. There were no differences in CFI among the 3 major coronary arteries in the groups with entirely normal and partially normal coronary arteries, respectively (0.19±0.09 [LAD], 0.20±0.11 [LCX], and 0.19±0.1 [RCA], and, respectively, 0.15±0.06 [LAD], 0.18±0.07 [LCX], and 0.16±0.05 [RCA]).

**Discussion**

This first investigation of direct in vivo assessment of coronary collateral flow in angiographically normal human coronary arteries and, in part, in entirely normal hearts provides clear evidence that blocked coronary arteries cannot be the only factor determining the level of functional collateral flow capacity to a vessel receiving “natural bypasses.” One fifth of individuals without stenotic lesions do have immediately recruitable collateral flow to the respective vascular area sufficient to prevent myocardial ischemia during a brief coronary occlusion.

**Structural Appearance of Collateral Vessels in Normal Coronary Arteries**

Sufficient collateral flow to prevent signs of myocardial ischemia during coronary occlusion can be reasonably regarded as a definition of useful, efficient, or functional collateral flow, and it has been found to amount to one fourth of the normal antegrade flow through the patent collateral recipient vessel.\(^3\) Conversely, there is and has been no definition of efficient collateral vessels based on their structural appearance, because the vessel caliber being the main determinant of vascular resistance against flow is dependent on factors varying with the imaging techniques used, such as perfusion pressure or the contrast medium employed. Epicardial coronary collaterals spontaneously visible on angiography in an individual with an entirely normal heart can likely be regarded as efficient if they fill the major part of the contralateral artery, as illustrated on Figure 1. However, because that patient refused to undergo collateral flow measurement, proof of the just-mentioned assumption could not be provided in this extremely rare case of angiographically visible collaterals. In comparison, pathoanatomic studies have variably reported a high occurrence of intercoronary communications (>20 to 40 \(\mu\)m), whereby most of them have been observed to be located intramyocardially and to be <200 \(\mu\)m in diameter.\(^{12}\) Considering that coronary angiography has a similar resolution of ~100 to 200 \(\mu\)m, the above-mentioned singularity of in vivo imaging of coronary collateral vessels comes unexpected only at first. The iterative debate among (patho)anatomists of whether coronary arteries in the absence of obstructive lesions are end-arteries has likely been founded in different techniques used to explore anastomoses, such as the use of various injection pressures, materials, viscosity of the injectate, or in the fact that the postmortem examination of the organ took place under various time frames and preservation protocols.

**Collateral Function in Patients With Angiographically Normal Coronary Arteries**

An in vivo investigation of the function as opposed to the (postmortem) imaged structure of coronary collaterals circumvents all the caveats described above and, in addition, definitely and individually answers the question of the relevance of collaterals in the event of vascular occlusion. In the case of stenotic coronary arteries, such clinical studies have
been performed repeatedly, and the obstruction’s severity has consistently been found to be related to collateral function.3,15 This is in perfect agreement with experimental data revealing the biophysical force of a pressure gradient between a potential collateral supplying and receiving vascular area as the protagonist in arteriogenesis (ie, the forming of well grown and highly conductive collateral arterioles).2 Pathophysiological, a pressure gradient requires a substrate to act on to achieve development of collaterals. The substrates are small, preformed anastomotic channels that can be remodeled in response to augmented vascular shear forces produced by the mentioned pressure gradient. On the basis of previous work from our laboratory (with one third of well-developed collaterals in the presence of a stenosis3) and the present investigation (with one fifth of well-developed collaterals in the absence of a stenosis), it can be estimated that such remodeling takes place in up to 2 of 3 individuals having any level of collateral flow to start with (Figure 4). Accordingly, the median CFI value among patients without compared with those with a stenotic lesion shifts from 0.2 to 0.4. Of course, it cannot be determined but only speculated on the basis of the present study that patients ultimately growing copious collaterals in response to a coronary obstruction are those having extensive preformed anastomoses.

The question ensuing from this study is which factors could influence the degree to which collateral vessels to a normal coronary artery are preformed. On the basis of the observation that coronary collateral arteries may serve as 2-way conduits,16 it could be hypothesized that among patients in the group with stenotic lesions in other vessels than the one undergoing collateral assessment, CFI is higher than in the group with entirely normal coronary arteries. Obviously, such a hypothesis ought not be generated in the context of our results showing similar CFIs between the study groups. In patients with only partially normal coronary arteries, the point in time of CFI measurement with regard to balloon dilatation of the stenosis in the contralateral vessel could theoretically influence the result of the measurement, the fact of which could not be verified. It has been reported that left ventricular hypertrophy may exert a positive effect on the state of intercoronary connections.11 This could not be confirmed in either group of patients, either by ECG or by echocardiographic criteria for left ventricular hypertrophy.

Collateral Function in Patients Without Cardiac Disease

Taking into account only the 51 patients with angiographically entirely normal coronary arteries and the low occurrence of ECG signs of left ventricular hypertrophy, there were ≈50 individuals without gross appearance of cardiopulmonary disease undergoing functional collateral assessment, the population of which did not reveal a difference in immediately recruitable collateral flow to a normal coronary artery when compared with the other half of our study population with heart disease. A similar result was found (data not shown) even when adopting a more conservative definition of patients without heart disease as being those 20 individuals without systemic hypertension and entirely normal coronary arteries. In the entire study population or in one of the described subgroups, no clinical variable, such as those previously described (eg, hemoglobin level),10 was associated with the degree of functional collateral flow. Because patients with valvular heart disease were excluded from our study, the investigation of Goldstein et al17 in 7 patients undergoing aortic valve replacement is difficult to compare with ours, despite the fact that it is the only case collection using similar in vivo functional collateral assessment. Unfortunately, the study protocol of Goldstein et al17 did not assess central venous pressure, which may heavily influence CFI, particularly in the lower range of values.13

Study Limitations

It is evident that the different methods used to estimate collateral vessels (ie, angina pectoris and ECG ST-segment shifts during coronary occlusion) vary in comparison with the reference method (ie, CFI measurements). This is not unexpected, keeping in mind the changeable perception of chest pain, the rather arbitrary definition of ECG signs of myocardial ischemia, and the level of precision of pressure-derived CFI measurement, which is not absolute but has a standard error of estimate of 0.08 when compared with Doppler-derived CFI measurement.13 In comparison with 99m Tc-sestamibi scores of the extent and severity of myocardial ischemia during coronary balloon occlusion, pressure-derived CFI measurements have revealed similar values for the standard error of estimate.14 A considerable amount of variability in the frequency of hemodynamically relevant collaterals can also be attributed to rounding errors when 2 instead of 3 decimal digits are used for CFI differentiation between insufficient or sufficient collateral flow; for example, CFI ≥0.25 in 21 of 100 cases, but CFI ≥0.250 in only 17 of 100 cases.

By defining “normal” coronary arteries on the basis of coronary angiography, vessels may have been selected for CFI measurement that were actually atherosclerotic. Although this is possible in the group with partially stenotic coronary arteries, it is less likely in the 51 patients with angiographically entirely normal vessels. However, the results and, thus, conclusions of the present study would not have been influenced by the presence of nonstenotic coronary atherosclerosis, because it has not been previously reported to cause collateral development.

Acknowledgments

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References

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