Angiographic Assessment of Collateral Connections in Comparison With Invasively Determined Collateral Function in Chronic Coronary Occlusions

Gerald S. Werner, MD; Markus Ferrari, MD; Stephan Heinke, MD; Friedhelm Kuether, MD; Ralf Surber, MD; Barbara M. Richartz, MD; Hans R. Figulla, MD

Background—The evaluation of new therapeutic modalities to induce collateral growth in coronary artery disease require improved methods of angiographic characterization of collaterals, which should be validated by quantitative assessment of collateral function.

Methods and Results—In 100 patients with total chronic occlusion of a major coronary artery (duration >2 weeks) collaterals were assessed angiographically by the Rentrop grading, by their anatomic location, and by a new grading of collateral connections (CC grade 0: no continuous connection, CC1: threadlike continuous connection, CC2: side branch–like connection). The interobserver variability was 10%. Collateral function was assessed by Doppler flow (average peak velocity) and pressure recordings distal to the occlusion before recanalization. A collateral resistance index (R_coll) was calculated. Recruitable collateral flow was measured during a final balloon inflation >30 minutes after the baseline measurement. The comparison of the anatomic location, the Rentrop, and the collateral connection grade showed only for the latter an independent and significant relation with R_coll. CC2 collaterals preserved regional left ventricular function better than did CC1 collaterals and provided a higher collateral flow reserve during adenosine infusion. CC0 collaterals were predominantly observed in recent occlusions of 2 to 4 weeks’ duration, with the highest R_coll. During balloon reocclusion, recruitable collateral function was best preserved with CC2 and least with CC0.

Conclusions—The angiographic grading of collateral connections in total chronic occlusions could differentiate collaterals according to their functional capacity to preserve regional left ventricular function and was closely associated with invasively determined parameters of collateral hemodynamics. (Circulation. 2003;107:1972-1977.)

Key Words: collateral circulation • angiography • occlusion

Therapeutic approaches to induce collateral development in humans require refined methods to assess collaterals in vivo. The most widely used method to assess coronary collaterals is contrast angiography. The direct measurement of collateral function with the use of miniaturized sensors of coronary flow and pressure distal to an occlusion is superior to angiographic assessment, but it can be performed only during a coronary intervention. In principal, this method can evaluate the induction of collateral development, but it requires balloon occlusion to assess collateral function, which limits its applicability.

A recently reported quantitative angiographic analysis of collateral diameters on high-resolution cine films underscored the relevance of the collateral diameter for the collateral function. Aside from the complexity of this approach, its applicability to modern digital storage standards with lower resolutions is limited. Still, a semiquantitative assessment of the collateral diameters as suggested three decades ago in this journal may improve the angiographic assessment of collaterals. The aim of our study was to evaluate in a well-defined patient group of total chronic coronary occlusions (TCO) whether such a semiquantitative assessment of collateral diameters would improve the prediction of collateral function and be of clinical relevance. It should be compared with established angiographic criteria by using the invasively measured collateral function as the reference.

Methods

Patients

Collateral flow was analyzed in 103 patients during recanalization of a TCO in one of the major coronary arteries. All TC0s had a duration of >2 weeks, TIMI grade 0 flow, and spontaneously visible collaterals. The duration of the occlusion was defined by a prior myocardial infarction (MI) or the onset of chest pain before the diagnostic angiography. Three patients had been excluded from the subsequent analysis because angiograms were of insufficient quality to clearly define the collateral pathways as described below, leaving 100 patients for the data analysis. The study was approved by the institutional ethics committee, and informed consent obtained from all patients.
After the lesion was crossed by a guidewire, an exchange catheter was exchanged for a Doppler guidewire (FloWire, EndoSonics Corporation). The first 21 patients of this consecutive series were assessed by Doppler measurements only and subsequent patients by both Doppler and pressure measurements. In these patients, the Doppler wire was exchanged for a pressure wire (PressureWire, RADI Medical Systems). After these recordings, the occlusion was dilated and treated by stent implantation. Finally, the Doppler guidewire was reintroduced and the antegrade coronary flow was recorded.

Doppler flow signals were analyzed as described previously. A collateral flow index (CFI) was obtained before and after PTCA as the ratio of average peak velocity (APV) distal to the occlusion and antegrade APV recorded after completion of PTCA. From the ratio of the mean distal coronary pressure (Pd) and the mean aortic pressure (Pa), obtained through the fluid filled guiding catheter, the collateral pressure index (CPI) was calculated at baseline and during balloon reocclusion (Figure 2). The collateral resistance index Rcoll was calculated, assuming steady laminar flow and constant vessel diameters, as (Pao−Pd)/APV (12,19,20) (with a physical dimension of mm Hg/cm per second).

Assessment of Recruitable Collateral Function

The above-described recordings were repeated during reinflation of the stent balloon to obtain the recruitable collateral flow in 87 patients with Doppler and in 72 with additional pressure recordings. These measurements were done 38±13 minutes after the baseline recording. The identical location of the sensor wires for all recordings was ascertained by fluoroscopy.

Collateral Flow Reserve

In 51 patients, collateral flow was assessed before balloon dilation during intravenous administration of adenosine (140 μg/kg per minute) over a period of 3 minutes by Doppler and pressure recordings, as previously described. The ratio of APV during adenosine and APV at baseline was the collateral flow reserve, a value <0.95 indicated coronary steal.

Quantitative Angiography

Biplane left ventricular (LV) angiograms were obtained in all patients at the time of the baseline diagnostic angiography. The quantitative LV analysis was done with standard software (LVA 4.0, Pie Medical Imaging). LV ejection fraction (LVEF) was calculated, and the centerline method was applied to analyze the territory of the occluded artery by the regional wall motion severity index (SD/chord) and the extent of regional dysfunction (number of chords).

Statistics

Data are mean±SD if not indicated otherwise. Group differences of continuous variables were evaluated by ANOVA and of categoric variables by Fisher’s exact test. A GLM ANOVA was used to analyze covariate effects of the angiographic criteria of collateral grading on quantitative parameters of collateral function. Post hoc analysis was done with the Scheffé test. A level of P<0.05 was considered significant. All calculations were done with SPSS for Windows (Version 10, SPSS Inc).

Results

Angiographic Assessment of Collateral Pathways

In 100 patients, 211 different collateral pathways were identified; 86% of patients had more than one distinct pathway (Table 1). The subsequent analysis included only one principal pathway per patient, which was through septal connections in 44%, atrial epicardial connections in 32%, distal interarterial connections in 18%, and bridging connections in 6%. Collateral connection grade CC0 was observed in 14%, CC1 in 51%, and CC2 in 35%. CC2 was observed less than two others. The physiological data on collateral function were not known to the investigators at the time of review. The agreement in grading was 88%, 92%, and 91% among the 3 investigators.

Doppler and Pressure Recordings

The recanalization procedure was done as previously described. After the lesion was crossed by a guidewire, an exchange catheter (Transit Cordis) or a low-profile over-the-wire balloon catheter (Bandit, Scimed) was passed distal to the occlusion. The guidewire was exchanged for a Doppler guidewire (FloWire, EndoSonics Corporation). The first 21 patients of this consecutive series were assessed by Doppler measurements only and subsequent patients by both Doppler and pressure measurements. In these patients, the Doppler wire was exchanged for a pressure wire (PressureWire, RADI Medical Systems). After these recordings, the occlusion was dilated and treated by stent implantation. Finally, the Doppler guidewire was reintroduced and the antegrade coronary flow was recorded.

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frequently in septal than in epicardial pathways (23% versus 45%) and CC0 more frequently (23% versus 7%; \( P = 0.02 \)). The filling of the occluded epicardial segment was graded as Rentrop grade 2 in 22% and grade 3 in 78%. There was a significant but weak correlation between CC grade and the Rentrop grading \( (r = 0.32; \ P < 0.001) \).

Collateral Pathways and LV Function

The relation of regional LV function and the collateral size could be assessed in 35 patients in whom the collaterals had prevented a Q-wave MI. None had CC0 collaterals, and the duration of occlusion tended to be longer in CC2 collaterals \( (P = 0.13) \). Patients with CC2 collaterals had less severe wall motion abnormalities than with CC1 collaterals (Figure 3). In patients with prior Q-wave MI, the extent of regional wall motion abnormality was not related to the CC grades. In the latter patients, the CC grade was closely related to the duration of TCO, with CC0 observed predominantly in TCOs of \(<4\) weeks’ duration and CC2 predominantly in TCOs of \(>12\) weeks’ duration (Table 2).

Collateral Pathways and Collateral Function

The parameters of collateral function were characteristically different in the three CC grades (Table 3). The Doppler parameter APV and CFI were lowest in CC0 but comparable between CC1 and CC2, whereas the pressure parameter \( P_d \) and CPI were comparable between CC0 and CC1 but highest.

### TABLE 1. Clinical Characteristics of 100 Patients With Chronic Total Coronary Occlusions

<table>
<thead>
<tr>
<th>Age, y</th>
<th>63.4 ± 10.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, %</td>
<td>76</td>
</tr>
<tr>
<td>No. of diseased arteries, 1/2/3</td>
<td>40/40/20</td>
</tr>
<tr>
<td>Occluded coronary artery, right/LAD/LCX</td>
<td>57/38/5</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>65</td>
</tr>
<tr>
<td>Angina pectoris (CCS 0–4)</td>
<td>0/40/55/1</td>
</tr>
<tr>
<td>Heart failure (NYHA 0–4)</td>
<td>2/37/42/19/0</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>37</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>67</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>73</td>
</tr>
<tr>
<td>History of smoking, %</td>
<td>44</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>56.6 ± 17.8</td>
</tr>
</tbody>
</table>

CCS indicates Canadian Cardiovascular Society classification of chest pain; LAD, left anterior descending; LCX, left circumflex; and NYHA, New York Heart Association classification of heart failure.
in CC2. R_{Coll} was highest in CC0 and lowest in CC2 (Figure 4). A potential influence of the LV end-diastolic pressure on intracoronary pressure measurements was unlikely because it was similar in the 3 groups (CC0: 16±7; CC1: 14±8; CC2: 14±10 mm Hg; P=0.7).

A univariate ANOVA comparing the influence of Rentrop grades, CC grades, and anatomic location on R_{Coll} showed that the CC grade was a better predictor of a low R_{Coll} (r²=0.32; P<0.001) than Rentrop grade (r²=0.10; P=0.12) or anatomic location of the collaterals (r²=0.07; P=0.65). The number of individual collateral connections within each CC group did not further improve the prediction based on the CC grade.

**Pharmacological Modulation of Collateral Flow**

Maximum decrease of the peripheral microvascular resistance during adenosine infusion in 51 patients did not change APV with CC0 collaterals. Adenosine caused a decrease of APV with CC1 collaterals from 10.0±5.4 to 8.8±4.3 cm/s and an increase with CC2 collaterals from 11.7±5.5 to 13.6±9.4 cm/s (ANOVA: P=0.06). A collateral flow reserve <0.95 indicating coronary steal was observed in 33% of patients with CC2 collaterals and in 61% with CC1 collaterals (P=0.16).

**Recruitable Collateral Function and Collateral Connection Size**

The recruitable collateral function after recanalization showed considerable and specific differences between the collateral connection grades (Table 3). The APV that had been similar for CC1 and CC2 at baseline decreased significantly in CC1, and it was further decreased in CC0. The recruitable R_{Coll} increased in all three groups as compared with baseline, but the amount of increase was lowest with CC2 and highest with CC1 (Figure 5).

**Discussion**

The present study analyzed the relation of collateral pathway anatomy, the collateral diameter, and the recipient artery filling with the invasively assessed collateral function in TCOs. We propose a visual grading of the size of collateral connections that discriminates collaterals with different functional capacity.

**Angiographic Assessment of Collaterals**

The most accurate way to assess collaterals would be a quantitative angiography, which is not applicable to modern-day digital storage media with a resolution limit >0.2 mm given the small diameter of collaterals and the often tortuous course of the collateral connections.16 In TCOs with well-developed, spontaneously visible collaterals, the widely used Rentrop grading lacks further differentiation because most collaterals are grade 3. A measure of the collateral diameter should enhance the semiquantitative assessment as first suggested by Carroll et al.17 Therefore a visual grading of the diameter of collateral connections was used in our study, with an interobserver variability of about 10%.

The Rentrop grading shows only a weak correlation with invasive parameters of collateral function.13,14 Other methods for the angiographic assessment of collaterals such as the bifurcation count, collateral length estimation, and collateral frame count have not been compared with invasive methods.4,23 A frame counting of contrast medium washout distal to a balloon occlusion by recruitable collaterals was shown to correlate well with invasive collateral function, but it requires an interventional procedure.24 The goal of the present study was instead to evaluate an angiographic grading that would be applicable during diagnostic angiography. Furthermore, attempts to induce collateral development will aim at vascular territories in need of constant collateral perfusion distal to TCOs not accessible to revascularization, and the TCOs of our study represent a model for this situation.

**Clinical Relevance of the Collateral Connection Grade**

Well-developed collaterals should preserve LV function in the incidence of an occlusion, but many collaterals develop after an occlusion had already caused an acute MI.25,26 Therefore, we assessed the prediction of collateral adequacy to preserve LV function by this new grading system in a subgroup of patients without a prior MI. Only CC1 and CC2 collaterals were found in these patients, and the regional wall motion was best preserved with grade CC2 collaterals.

**TABLE 2. Collateral Connection Grades and Duration of Occlusion in 65 Patients With Prior Q-Wave MI**

<table>
<thead>
<tr>
<th>Collateral Connection Grade</th>
<th>Duration of Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2–4 Weeks</td>
</tr>
<tr>
<td>CC grade 0</td>
<td>12</td>
</tr>
<tr>
<td>CC grade 1</td>
<td>9</td>
</tr>
<tr>
<td>CC grade 2</td>
<td>5</td>
</tr>
</tbody>
</table>

χ² Value=23.4; P<0.001.
In patients with a prior MI, collaterals had not been sufficient to prevent the MI and most likely developed fully after the occlusion. We have recently shown that collateral function improves between 4 and 12 weeks after an acute MI. This is further supported by the present study, which contained also patients 2 to 4 weeks after an occlusion. There was a significant relation between the collateral connection grade and the duration of the occlusion with CC0 collaterals representing early stages of collateral development and CC2 collaterals representing mature collaterals.

The relevance of the collateral connection grades was further supported by the differential response to adenosine. An increase of collateral flow by adenosine occurred predominantly in CC2 collaterals. However, these changes showed wide variations, which is explained by the multiple factors influencing the adenosine response such as the donor artery resistance and the peripheral vasodilation of the donor and recipient vascular beds.

Collaterals in TCOs lose part of their functional capacity immediately after recanalization. The observation that patients who had CC2 collaterals before recanalization had the best and those with CC0 collaterals had the lowest recruitable collateral function is further support for the clinical relevance of this new grading. In CC2 collaterals, invasive function indexes remained above the values reported to prevent ischemia. In analogy to animal studies, CC2 collaterals probably will have a well-developed vascular wall structure, whereas CC0 collaterals represent those with only a rudimentary wall structure. CC2 collaterals retain their responsiveness to influences such as increased shear stress during reocclusion, whereas CC0 collaterals probably collapse after recanalization and do not immediately reopen during reocclusion.

**Limitations of the Study**

The $R_{coll}$ is not identical to the collateral resistance derived from quantitative angiographic data, but it describes the resistance of the combined collateral network including the donor artery segment proximal to the collateral takeoff. The majority of patients show multiple collateral pathways, and the location of the Doppler sensor distal to the occlusion will detect flow that may enter this segment at various locations.

**TABLE 3. Quantitative Assessment of Collateral Function in Chronic Total Coronary Occlusions With Different Collateral Size Grades Before and After Recanalization**

<table>
<thead>
<tr>
<th>Collateral Connection</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$APV, \text{cm/s}$</td>
<td>$6.3\pm3.6^#$</td>
<td>$11.9\pm6.5$</td>
<td>$11.8\pm5.0$</td>
</tr>
<tr>
<td>$P_D, \text{mm Hg}$</td>
<td>$35\pm12^\dagger$</td>
<td>$41\pm11^\dagger$</td>
<td>$54\pm13$</td>
</tr>
<tr>
<td>$CFl$</td>
<td>$0.32\pm0.26$</td>
<td>$0.44\pm0.27$</td>
<td>$0.44\pm0.27$</td>
</tr>
<tr>
<td>$CPI$</td>
<td>$0.33\pm0.09^#$</td>
<td>$0.39\pm0.11^\dagger$</td>
<td>$0.52\pm0.09$</td>
</tr>
<tr>
<td>$R_{coll}, \text{mm Hg/cm per second}$</td>
<td>$14.5\pm7.1^\dagger$</td>
<td>$7.2\pm4.4$</td>
<td>$5.2\pm3.0$</td>
</tr>
<tr>
<td><strong>Reocclusion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$APV, \text{cm/s}$</td>
<td>$3.5\pm2.3^\dagger$</td>
<td>$5.6\pm2.7^\dagger$</td>
<td>$8.7\pm5.6$</td>
</tr>
<tr>
<td>$P_D, \text{mm Hg}$</td>
<td>$26\pm9^\dagger$</td>
<td>$32\pm10^\dagger$</td>
<td>$45\pm14$</td>
</tr>
<tr>
<td>$CFl$</td>
<td>$0.17\pm0.11^#$</td>
<td>$0.19\pm0.11^\dagger$</td>
<td>$0.33\pm0.26$</td>
</tr>
<tr>
<td>$CPI$</td>
<td>$0.25\pm0.08^#$</td>
<td>$0.29\pm0.09^\dagger$</td>
<td>$0.44\pm0.12$</td>
</tr>
<tr>
<td>$R_{coll}, \text{mm Hg/cm per second}$</td>
<td>$33.9\pm21.7^\dagger$</td>
<td>$16.8\pm9.2^\dagger$</td>
<td>$9.5\pm6.1$</td>
</tr>
</tbody>
</table>

$P_D$ indicates distal coronary pressure; $R_{coll}$, collateral resistance index. Significant differences compared with grade 1: *$P<0.001$, †$P<0.05$; compared with grade 2: ‡$P<0.001$, §$P<0.01$, ||$P<0.05$.

**Figure 4.** Individual data and group mean±SD of average peak velocity (left), collateral pressure index (middle), and collateral resistance index (right) for the three collateral size grades.
Figure 5. Increase of $R_{\text{Coll}}$ from baseline to reocclusion (mean±SEM). $R_{\text{Coll}}$ increased more with CC0 compared with CC1 and CC2 (repeated-measures ANOVA: *P<0.001). It increased least with CC2 compared with CC1 (*P=0.019).

and will not be the result of one but rather the sum effect of all relevant collaterals. Therefore, the interindividual variability (Figure 4) may be explained by this collateral interference. During reocclusion, a lower APV was recorded, which may be influenced by a changed vascular diameter at the site of measurement both at baseline and during reocclusion. However, the drop of $P_{\text{D}}$ supports the conclusion of genuine differences in recruitability. A limitation of the pressure-derived indexes is that we did not simultaneously record the central venous pressure.

We used only one principal pathway with the highest CC grade of the coexisting multiple pathways to categorize our patients. Theoretically, the 2 to 3 largest collateral connections would determine the collateral conductance,16 but the additional consideration of the number of collaterals in each CC grade did not further improve the discrimination of collateral function parameters.

Conclusions

The angiographic collateral connection grades provide an additional parameter to describe spontaneously visible collaterals in TCOs. This grading showed a close association with clinical determinants of collateral adequacy. It could be also of clinical relevance because CC2 collaterals identified patients with well-recruitable collaterals, which may protect myocardium in the case of an acute reocclusion. These observations were made in TCOs, and the applicability of this angiographic method to collaterals in nonocclusive lesions and to the assessment of pharmacologic agents or growth factors on collateral function is not yet established.

References

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