The functional reserve of collaterals supplying long-term chronic total coronary occlusions in patients without prior myocardial infarction

Gerald S. Werner1*, Ralf Surber2, Markus Ferrari2, Michael Fritzenwanger2, and Hans R. Figulla2

1Department of Cardiology and Intensive Care Medicine, Medizinische Klinik I, Klinikum Darmstadt, Grafenstrasse 9, D-64283 Darmstadt, Germany and 2Clinic for Internal Medicine I, Friedrich-Schiller-University Jena, Erlanger Allee 101, D-07740 Jena, Germany

Aims Chronic total coronary occlusions (CTOs) with angiographically well-developed collaterals may be considered to provide sufficient blood supply to the occluded segment, and the indication for revascularization may be questioned. Therefore, the collateral function and functional reserve in patients with a CTO without a prior Q-wave myocardial infarction (MI) were assessed.

Methods and results Invasive assessment of collateral function was done during successful percutaneous coronary intervention in 107 patients with a CTO and no prior Q-wave MI. Intracoronary Doppler flow velocity and pressure recordings were obtained distal to the occlusion before the first balloon inflation and collateral function indexes calculated. In 62 patients, additional pharmacological stress testing was done by intravenous adenosine (140 μg/kg/min) to assess the collateral flow reserve. Patients with normal and impaired regional dysfunction were compared. Collateral function was similar in patients with and without regional left ventricular (LV) dysfunction. In both groups, 78% collaterals provided a collateral pressure index at baseline $>0.3$, sufficient to prevent ischaemia during a balloon occlusion, with a minimum of 0.2 in those with preserved LV function. A Doppler-derived function index showed a wider variation due to the high prevalence of microvascular dysfunction in CTOs. Only 7% of patients had an increase in collateral flow reserve $>2.0$ during pharmacological stress, whereas coronary steal occurred in one-third independent of regional LV function.

Conclusion A limited increase in collateral flow and the high prevalence of coronary steal during stress underscore the functional limitation of collaterals in CTOs without prior Q-wave MI. Even presumably 'well-collateralized' CTOs may benefit from a revascularization.

KEYWORDS Collateral function; Chronic total occlusion; Revascularization; Intracoronary Doppler; Intracoronary pressure

Introduction

The recanalization of a chronic total coronary occlusion (CTO) leads to relief of angina and to recovery of left ventricular (LV) function with a favourable effect on survival.1-3 In contrast, the recanalization of a CTO is a cost-intensive, lengthy, and often complex procedure4-6 with a high recurrence rate.6,7 On the basis of experimental animal models, well-collateralized CTOs must be considered equivalent to a 90% stenosis of an epicardial artery,8 which would generally be considered an indication for revascularization.

Clinical practice shows that collaterals will be sufficient to maintain full systolic contractile function in some patients, whereas in others, they may be just sufficient to provide a minimum nutritional supply to hibernating myocardium. The limits of collateral function to either uphold functional competence of the myocardium or at least prevent irreversible myocardial damage are unknown in man. The hypothesis to be tested in this study was whether there were distinctive differences in collateral function between patients with preserved normal LV function and those with impaired LV function but without a prior Q-wave MI. For this purpose, we assessed collateral function invasively by intracoronary pressure and flow recordings in the collateralized arterial segment.9,10

Methods

Patients

All consecutive CTOs (duration $>2$ weeks; TIMI flow 0) of a major coronary branch (diameter $\geq 2.5$ mm) between August 1999 and November 2004 were eligible for this study except for (i) an indication for a surgical revascularization (e.g. presence of left main disease, concomitant severe valvular disease), (ii) absence of collaterals to the occluded artery (Rentrop grade 0), and (iii) an aneurysm distal to the CTO. The recanalization was successful in 234 of 289 consecutive patients (81%). In 26, collateral flow and pressure could not be obtained before balloon dilatation due to inability to

© The European Society of Cardiology 2006. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org
cross the lesion with an exchange catheter (discussed sub-
sequently), leaving 208 patients with invasive assessment of the col-
lar function. A subset of these patients had been included in
previous studies. The study protocol had been approved by the
university’s Ethics Committee, and written informed consent was
obtained from all patients.

Definition and selection of study group
Out of the 208 patients, the study patients were selected if there
was no evidence of a Q-wave myocardial infarction (MI) in the
area supplied by the occluded artery and an occlusion duration
 greater than 3 months (Figure 1). The criteria for a Q-wave MI were: for
a right coronary occlusion, Q-waves in leads III and aVF of a duration
 greater than 30 ms and amplitude greater than 0.1 mV (small R-waves
less than 0.05 mV were also considered Q-wave equivalents); for a left anterior descending cor-
nary occlusion, Q-wave in leads V3 and V4 defined as any negative
extension at the beginning of the QRS complex (reduced R-waves
less than 0.2 mV were also considered as Q-wave equivalent). Patients
with circumflex occlusions were excluded because of unreliable
ECG criteria.

The study group of 107 patients was subdivided according to the
extent of regional LV dysfunction as measured by the wall motion
severity index (WMSI) (SD/chords) using a standard software (LVA
4.0, Pie Medical Imaging). Patients with a normal regional LV func-
tion (WMSI < 1 SD/chord) were compared with patients with an
impaired regional LV function (WMSI ≥ 1 SD/chord). An improve-
ment of WMSI > 1 was considered a significant LV function improve-
ment during follow-up.12

Angioplasty procedure
The recanalization was done as described before.9,10 All patients
were on aspirin (100 mg) and received clopidogrel (75 mg) starting
on the day of the procedure for 4 weeks. After the lesion
was crossed by a guide wire, an exchange catheter (Transit
TM, Cordis,
or.014 Support Catheter, Spectranetics) or a low-profile
over-the-wire balloon catheter was advanced distally of the occlu-
sion. Then the guide wire was exchanged for a 0.014
Doppler flow velocity, and subsequently for a 0.014
Support Catheter, Spectranetics) or a low-profile
implantation followed.

Protocol for intracoronary Doppler and pressure
recordings of collateral flow
The Doppler wire was advanced to a position where a clearly defined
and stable velocity signal could be recorded. These Doppler record-
ings of baseline collateral flow were done before the first balloon
inflation. They were analysed as described before to obtain the
average peak velocity (APVD) as the area under the flow velocity
curve.9,10,13 The absence of antegrade flow was ascertained by the
lack of distal opacification after proximal contrast injection and
no interference with the distal Doppler signal. After stent
implantation, the antegrade APV was recorded at the same position
as APVD. The collateral flow index (CFI) was calculated as the ratio
of APVD and antegrade APV.14

For the pressure recording, the transducer was positioned at the
same spot where the Doppler wire tip had been located. The mean
pressure of Pd and the aortic pressure (Pao) were used for further
computation. A collateral pressure index (CPI) was calculated.14

The formula includes the central venous pressure (CVP): CPI =
(Pd - CVP)/(Pao - CVP). In 71 of 107 patients (66%), CVP was
measured directly with a mean of 9.5 ± 4 mmHg. Accordingly, a
value of 10 mmHg was substituted for CVP in 36 patients without
direct measurement. The collateral resistance index (Rcoll) was cal-
culated as (Pao - Pd)/APVD, and the peripheral resistance index R P
as Pd/APVD.10,15

Pharmacological stress testing
In 62 of the 107 patients, the above-mentioned measurements were
repeated during intravenous adenosine infusion (140 μg/kg/min).
Patients did not undergo stress testing if the preceding recanaliza-
tion procedure was already taking exceedingly long. As pressure
recordings are less affected by the exact sensor position than the
Doppler flow signal, the pressure recording was obtained first, and
then the Doppler wire was advanced and the baseline APV recorded.
Without changing the position of the Doppler wire, the adenosine
infusion via a femoral central venous access was started and APV
recorded for 3 min. During continuing adenosine infusion, the
Doppler wire was exchanged for the pressure wire and Pd and Pao
were obtained. The adenosine infusion was stopped, and Pd and
Pao recorded until they had returned to their baseline values
(Figure 2). The collateral flow reserve was calculated as APVD during
adenosine infusion divided by APVD at baseline.

Angiographic analysis
Pre-interventional angiograms showed either collateral flow grade 2
(partial epicardial filling of the occluded artery) or 3 (complete epicar-
dial filling of the occluded artery). The angiographically visible
diameter of the collateral connection was graded as CC0 (no con-
tinuous visible connection between donor and recipient branch,
CC1 (continuous thread-like connection), and CC2 (continuous
small side-branch like connection).17 Angiograms were assessed
independently by two investigators, and in the case of discordance,
a consensus was obtained.

Definition of functionally sufficient collateral supply
Studies in non-occluded coronary lesions provided thresholds of col-
lar function parameters to discriminate a necessary level to
prevent ischaemia during balloon occlusion: (i) a Pd ≥ 45 mmHg,18
(ii) a CPI ≥ 0.30,14,19 and (iii) a CFI ≥ 0.30.14 During adenosine infu-
sion, the collateral fractional flow reserve (FFRcol) would be analo-
gous to the FFR for evaluating epicardial arteries.19,20 The collateral
 coronary flow velocity reserve (CFVR) was determined analogous to
the CFVR in non-occlusive lesions.21 If the collateral flow reserve
dropped below 0.85, this would represent coronary steal.15
Statistics

Data are given as the mean value ± SD if not indicated otherwise. Group differences of continuous variables were evaluated by an analysis of variance. Group differences of categorical variables were tested by a $\chi^2$-test. A correlation analysis was done to assess the relation between collateral function parameters and WMSI. A multivariable regression analysis was done to assess the relation between CFI and CPI, with WMSI and LV end-diastolic pressure (LVEDP) as additional independent variables. Possible differences in changes of collateral haemodynamics during adenosine infusion between two groups were assessed by a $t$-test, changes within each group by a paired $t$-test. All tests were two-sided, and a level of $P < 0.05$ was considered significant. All calculations were done with SPSS for Windows (Version 11.5, SPSS Inc.).

Results

Clinical characteristics

Among patients with a CTO and no prior Q-wave MI, 66 patients had a normal regional LV function and 41 an impaired regional function (Table 1). The duration of the occlusion was >3 months (median 10.3 months, range 3.4–165 months), as assessed by either a previous angiography or the timing of new onset of symptoms. One-third of patients had diabetes in both groups. Patients with an impaired regional LV function tended to have less often hypertension and more often hypercholesterolaemia and a history of smoking than patients with normal LV function. They also had more often a prior non-Q-wave MI and more pronounced symptoms of congestive heart failure, despite a similar LVEDP. Collateral filling was predominantly of Rentrop grade 3 in both groups, and there was no difference regarding the collateral connection size (Table 1).

Collateral function and coronary haemodynamics

The relation of invasive parameters of collateral function with the extent of regional myocardial dysfunction was assessed by a correlation analysis. There were no significant correlations between the $P_d$, the APVD, and the derived indexes of collateral and peripheral resistance (Table 2). The only weak correlation was observed with the antegrade APV after recanalization, measured at least 15 min after the final balloon dilatation, which was higher with a more severely reduced WMSI. The same was observed for the maximum hyperaemic APV, and thus, the CFVR as ratio of both was unrelated to WMSI (Table 2).

Table 1 Clinical data of 107 patients with CTOs without prior Q-wave infarction

<table>
<thead>
<tr>
<th></th>
<th>Normal LV function</th>
<th>Impaired LV function</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>66</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>$65.4 \pm 9.4$</td>
<td>$63.2 \pm 10.2$</td>
<td>0.26</td>
</tr>
<tr>
<td>Male gender</td>
<td>51 [77]</td>
<td>29 [71]</td>
<td>0.45</td>
</tr>
<tr>
<td>Number of diseased arteries</td>
<td>1.9 ± 0.8</td>
<td>1.9 ± 0.7</td>
<td>0.93</td>
</tr>
<tr>
<td>Occluded artery (LAD/right coronary)</td>
<td>22/44 [33/67]</td>
<td>23/18 [44/56]</td>
<td>0.27</td>
</tr>
<tr>
<td>Previous non-Q-wave infarction</td>
<td>12 [18]</td>
<td>23 [56]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CCS (1/2/3/4)</td>
<td>4/14/47/1 [6/21/71/2]</td>
<td>2/14/24/1 [5/34/59/2]</td>
<td>0.49</td>
</tr>
<tr>
<td>NYHA (0/1/2/3/4)</td>
<td>1/41/20/4/0 [2/62/32/6/0]</td>
<td>0/13/20/8 [0/32/49/19/0]</td>
<td>0.009</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26 [39]</td>
<td>14 [34]</td>
<td>0.59</td>
</tr>
<tr>
<td>Hypertension</td>
<td>59 [89]</td>
<td>31 [76]</td>
<td>0.06</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>48 [73]</td>
<td>35 [85]</td>
<td>0.13</td>
</tr>
<tr>
<td>History of smoking</td>
<td>27 [41]</td>
<td>24 [59]</td>
<td>0.08</td>
</tr>
<tr>
<td>EF</td>
<td>77.8 ± 10.6</td>
<td>55.7 ± 15.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WMSI (SD/chords)</td>
<td>$-0.15 \pm 0.31$</td>
<td>$-2.32 \pm 0.85$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>15.4 ± 6.6</td>
<td>16.9 ± 8.8</td>
<td>0.36</td>
</tr>
<tr>
<td>Rentrop grade (2/3)</td>
<td>7/59 [11/89]</td>
<td>6/35 [15/85]</td>
<td>0.54</td>
</tr>
<tr>
<td>Collateral connection grade (0/1/2)</td>
<td>7/32/27 [11/48/41]</td>
<td>8/17/16 [19/42/39]</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Data are mean ± SD or number of patients with percentage in brackets. CCS, classification of chest pain according to the Canadian Cardiovascular Society; LAD, left anterior descending coronary artery; NYHA, classification of heart failure according to the New York Heart Association.
The collateral function parameters based on pressure recordings (Pd and CPI) showed a Gaussian distribution (Figure 3). The minimum Pd in CTOs with normal LV function was 25 mmHg, and the minimum CPI was 0.18. Thresholds of collateral function parameters sufficient to prevent ischaemia during balloon occlusion were exceeded in CTOs for Pd in 58% of patients and for CPI in 78% of patients (Figure 3). The Doppler-derived CFI showed a non-Gaussian distribution in CTOs with a greater individual variability; the threshold for CFI of 0.3 was exceeded by only 65% of patients (Figure 3). In order to test whether the information provided by both CFI and CPI could be obtained by measuring only one parameter, we did a multivariable analysis with WMSI and LVEDP as covariates. However, there was only a weak correlation between CFI and CPI (r = 0.22; P = 0.03), which was not influenced by the covariates.

Collateral function and LV function

Both CPI and CFI showed no significant correlation with the impairment of regional LV function (Figure 4). Of the 41 patients with impaired LV function, LV function at follow-up...
was re-assessed in 34. Of these 34 patients, 50% showed a significant improvement in regional WMSI by more than 1 SD/chords. These patients were evenly distributed with regard to collateral function parameters showing no relation to the collateral function at the time of recanalization (Figure 4). This was similar among patients with single-vessel and multi-vessel disease.

Collateral function during pharmacological stress

In 62 patients, 39 with normal and 23 with impaired LV function, changes of the collateral haemodynamics during adenosine infusion were assessed (Table 3). They showed no difference in clinical characteristics when compared with those not undergoing stress testing. We observed a more pronounced reduction of $P_0$ than of $P_{\text{ao}}$ resulting in a decline of CPI in both groups. In contrast, the APV$_0$ increased slightly but not significantly. The $R_{\text{Coll}}$ tended to increase, whereas $R_0$ decreased, indicating a vasodilatory reserve of microcirculation in these CTOs, with no difference between patients with normal and impaired LV function.

The collateral CFVR was 1.15 ± 0.58 with a range from 0.37 to 2.61. Only 7% of patients had a collateral CFVR >2.0. In 36% of patients, the collateral CFVR even dropped below 0.85 during adenosine infusion, which indicated the presence of coronary steal (Figure 5). An angiographically significant lesion (>50% diameter stenosis) in the donor artery segment was observed in only seven patients with steal (32%). The FFR$_{\text{col}}$ was 0.32 ± 0.13 with a range from 0.03 to 0.78, and in only one patient, it was ≥0.75. The prevalence of coronary steal was independent of the extent of regional LV function (Figure 5).

Discussion

Direct assessment of collateral function shows that the functional competence of collaterals in CTOs is limited even in patients without a prior Q-wave MI. Less than 10% of collaterals provide a normal functional reserve during pharmacological stress. The high prevalence of coronary steal further reduces the collateral supply in at least one-third of patients. This observation applies to CTOs even with well-preserved LV function. Collateral function in CTOs >3 months duration is not related to the extent of preserved LV function and also not to LV recovery during follow-up.

Table 3  Collateral haemodynamics during pharmacological stress testing in patients with CTOs without prior Q-wave infarction

<table>
<thead>
<tr>
<th></th>
<th>Normal LV function (n = 39)</th>
<th>P-value</th>
<th>Impaired LV function (n = 23)</th>
<th>P-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heart rate (1 b.p.m.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>65 ± 14</td>
<td>&lt;0.001</td>
<td>69 ± 10</td>
<td>0.02</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>APV$_0$ (cm/s)</td>
<td>10.9 ± 4.7</td>
<td>12.7 ± 8.0</td>
<td>0.08</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>$P_0$ (mmHg)</td>
<td>50 ± 11</td>
<td>38 ± 15</td>
<td>&lt;0.001</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>$P_{\text{ao}}$ (mmHg)</td>
<td>105 ± 15</td>
<td>96 ± 17</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>CPI (no unit)</td>
<td>0.43 ± 0.11</td>
<td>0.32 ± 0.13</td>
<td>&lt;0.001</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>$R_{\text{Coll}}$ (mmHg/cm/s)</td>
<td>5.96 ± 3.19</td>
<td>7.03 ± 5.94</td>
<td>0.11</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>$R_{p}$ (mmHg/cm/s)</td>
<td>5.37 ± 2.28</td>
<td>4.22 ± 2.99</td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Collateral CFVR (no unit)</td>
<td>1.20 ± 0.58</td>
<td></td>
<td></td>
<td>0.36</td>
</tr>
</tbody>
</table>

Data are mean ± SD. For abbreviations, see Table 2. The P-values next to the data columns represent the changes within each group, whereas the P-value in the column to the right represents the comparison of changes between the groups.

Figure 5  Correlation of the collateral flow velocity reserve in patients with CTO with the impairment of regional LV dysfunction assessed by the WMSI (Figure 4). The horizontal line indicates 0.85 as the threshold below which patients had haemodynamic evidence of coronary steal.

Functional assessment of collaterals in CTOs

For the present study, we chose a direct approach to evaluate the competence of collateral supply in CTOs by measuring pressure and flow velocity in the collateralized epicardial segment distal to the occlusion. The validity and technical requisites of this approach, especially to ensure the absence of antegrade flow leakage after wire passage, had been described and discussed in detail before. We compared the functional measurements in CTOs with those obtained in studies during percutaneous balloon angioplasty of coronary lesions, about 20% of CTOs were in a low range of supposedly insufficient collateral supply. It is noteworthy that collateral supply even in some CTOs with normal regional LV function was observed below the above-mentioned thresholds. The CFI shows a
wider range of values when compared with CPI, probably due to the influence of microvascular dysfunction on the measurement of APV before and after recanalization,\textsuperscript{23,24} and therefore, CFI may be a less reliable index in CTOs. But neither CPI nor CFI could discriminate a collateral supply sufficient to uphold contractile function. Other factors such as a low peripheral microvascular resistance and metabolic adaptations to the lower blood supply during a gradually developing occlusion will be as important as collateral function for LV function.\textsuperscript{25} These additional factors may explain why collateral function in CTOs of $>3$ months duration is not related to the extent of regional LV impairment and is also not predictive of LV recovery.

The functional reserve of collaterals in CTOs

In a subset of patients, we applied a standard stress protocol with adenosine.\textsuperscript{26} As cutoff values we chose those accepted for assessing the functional reserve in non-occlusive coronary obstructions, i.e. a CFVR $\geq 2.0$ and an FFR $\geq 0.75$.\textsuperscript{21} These values are not validated for CTOs, but we assumed that the blood supply distal to an occlusion should reach the same minimum levels valid for an open artery in order to consider a CTO sufficiently collateralized, as collaterals are the only source for myocardial perfusion.\textsuperscript{20,27} In our study, only one patient had a collateral FFR $\geq 0.75$ considered non-critical for an epicardial lesion.\textsuperscript{28} The CFVR via collaterals reached a level $\geq 2.0$ in only 7%. The low CFVR could be also partly due to the high prevalence of microvascular dysfunction which may add to the functional limitation of collaterals.\textsuperscript{23,24} The functional reserve was even further limited by the occurrence of coronary steal in one-third of patients.

LV regional function and collateral functional reserve

When we divided the patients according to the extent of regional LV dysfunction, we observed similar collateral function at baseline. The prevalence of coronary steal was equal among the subgroups with normal and with impaired regional function. Thus, the presence of coronary steal did not explain an impaired regional LV function in patients without a prior Q-wave MI. In patients with CTOs of $>3$ months duration, collaterals had developed independent of the preserved LV function supporting experimental evidence that the major stimulus for collateral development is a pressure gradient along preformed arterioles.\textsuperscript{29}

Congenital large interarterial connections

In our study, none of the patients with successful recanalization of a CTO had large interarterial connections. These can be occasionally observed even in patients without a significant coronary artery disease\textsuperscript{30} and may fully substitute the blood supply of an occluded artery. The indication for PCI in these cases would be based on prognostic considerations regarding the extent and possible progression of atherosclerosis in a collateral donor artery.

Limitations of study

Limitations of the invasive assessment of collateral function in CTOs by Doppler and pressure wires had been discussed in detail before.\textsuperscript{9,10} Specific care was taken for exact positioning of the pressure and Doppler wires under fluoroscopic control using angiographic landmarks. It should be avoided to place the Doppler wire within a stenotic segment distal to the occlusion, but this cannot be always controlled. If the Doppler wire was positioned in a stenotic segment, the flow velocity signal would be higher than expected. This would explain the presence of a small number of particularly high velocity values in the frequency distribution (Figure 3), but it would not influence the interpretation of the functional results during hyperaemia, as these were relative measures.

In non-occlusive lesions, it is suggested that Doppler- and pressure-derived function indexes (CFI and CPI) are closely related and exchangeable.\textsuperscript{14} In CTOs, such a close correlation cannot be confirmed. This is also not explained by differences in haemodynamic parameters such as the LVEDP. On the basis of the recording of both indexes, a close correlation is unlikely, as the CPI is obtained by pressure measurements at the same time point ($P_D$ and $P_{Ao}$) whereas the CFI is a ratio of the APVO measured before dilatation and of the antegrade APV measured after stenting of the occluded artery. The high prevalence of microvascular dysfunction in CTOs, which improves only after several months after recanlization,\textsuperscript{23,24,31} affects the value of the antegrade APV and thus, the resulting ratio of CFI.

Clinical implications

In patients with a CTO, angiographically well-developed collaterals do not provide a sufficient functional supply to the occluded arterial segment. Even in patients with normal regional LV function, collaterals provide a normal coronary flow reserve in less than 10%. The high prevalence of coronary steal in CTOs indicates that patients with even well-collateralized CTOs may benefit from a revascularization.

Conflict of interest: none declared.

References