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van Liebergen, R.A.M.

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Chapter 6

Clinical, angiographical and hemodynamic predictors of recruitable collateral flow assessed during balloon angioplasty coronary occlusion

Jan J. Piek, MD, Rob A.M. van Liebergen, MD, Karel T. Koch, MD, Ron J.G. Peters, MD, George K. David, MD.

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CHAPTER 6

ABSTRACT

Objectives. To determine the predictive value of factors influencing coronary collateral vascular responses in humans.

Background. There is limited information on the factors responsible for coronary collateral vascular development despite the protective effect of collateral vessels in ischemic syndromes.

Methods. Angiography of the contralateral artery was performed during balloon coronary occlusion in 105 patients with 1-vessel disease (left anterior descending coronary artery in 69 patients; left circumflex coronary artery in 4 patients; right coronary artery in 32 patients) and a normal left ventricular function. Collateral vessels were graded according to Rentrop's classification. The relative collateral vascular resistance was calculated in a subgroup of 34 patients by means of aortic pressure, coronary wedge pressure and collateral flow, defined as the transient increase of coronary blood flow velocity of the contralateral artery during balloon coronary occlusion. Ischemia during coronary occlusion was evaluated by the ST-segment shift (mV) in a 12-lead electrocardiogram.

Results. A multivariate logistic analysis of clinical and angiographical variables revealed duration of angina (≥ 3 months, \( P<0.0001 \)), lesion severity (≥ 75 % diameter stenosis, \( P<0.0001 \)) and proximal lesion location (\( P=0.02 \)) as independent factors positively associated with recruitability of collateral vessels, while the use of nitrates exerted an independent negative effect (\( P=0.01 \)). The regression equation yielded an overall predictive accuracy of 80%. Presence of recruitable collateral vessels during coronary occlusion resulted in a higher coronary wedge/aortic pressure ratio (mean ± SD; 0.35 ± 0.13 versus 0.27 ± 0.12, \( P<0.005 \)), a lower relative collateral vascular resistance (6.7 ± 7.4 versus 21.3 ± 10, \( P<0.001 \)) and a reduction of electrocardiographic signs of ischemia (0.14 ± 0.19 mV versus 0.38 ± 0.33 mV, \( P<0.001 \)). The relative collateral vascular resistance was the best predictor for recruitability of collateral vessels compared to the other variables related to collateral vascular growth (\( P<0.05 \)).

Conclusions. Clinical and angiographical variables predict recruitability of collateral vessels with a 80% overall accuracy. These findings are important for risk stratification of patients undergoing interventions for ischemic coronary syndromes.

Abbreviations

CI = confidence interval
L = logit of the probability
NYHA = New York Heart Association
Pa0 = mean aortic pressure
Pw = mean coronary wedge pressure
Rcla = resistance contralateral artery
Rcoll = resistance collateral vascular bed
SE = standard error
\( V_{c, def} \) = maximal diastolic blood flow velocity contralateral artery during balloon deflation
\( V_{c, inf} \) = maximal diastolic blood flow velocity contralateral artery during balloon inflation
Numerous clinical studies have identified the functional significance of the collateral circulation in ischemic coronary syndromes (1). Despite these important observations, there is limited information on the factors associated with collateral vascular responses in humans. Coronary angioplasty serves as a model to study the collateral circulation in a controlled fashion during abrupt coronary balloon occlusion (2-5). This model allows documentation of recruitable collateral vessels which are probably associated with long-term collateral vascular development. Furthermore, this model enables quantification of collateral flow indices by means of coronary blood flow velocity analysis of the contralateral artery and assessment of the coronary wedge pressure (6,7). Our initial experience indicated that duration of angina and coronary lesion severity showed a weak, although statistically significant, correlation with recruitability of collateral vessels assessed during acute balloon coronary occlusion (5). These preliminary observations were extended in a larger cohort of patients in order to determine clinical and angiographical variables related to collateral vascular development. These clinical and angiographic variables were used to develop a model that allows prediction of recruitability of collateral vessels during acute coronary occlusion. Finally, the result of coronary collateral vessel growth on hemodynamic variables was evaluated in a subgroup of patients.

**METHODS**

One hundred and five patients (80 men and 25 women, age 57 ± 9 years) with one-vessel disease, referred to our Institution for PTCA, were studied. Inclusion criteria were [1] angina pectoris refractory to medical therapy, [2] right dominant coronary circulation and [3] normal left ventricular function with an ejection fraction > 50%. Exclusion criteria were [1] previous myocardial infarction, thrombolytic therapy or cardiac surgery, [2] electrocardiographic evidence of left ventricular hypertrophy or conduction abnormalities, [3] multilesion one-vessel disease or total coronary occlusion [4] peripheral vascular disease limiting arterial access. Clinical parameters, electrocardiographic and laboratory findings were recorded on admission. The medical history was recorded independently by two observers. A third interview followed if there was disagreement on the clinical information and a consensus was reached. The clinical variables of a total of 58 patients were reported in a previous study (5); the hemodynamic variables of 16 patients were included in another study (6). Informed consent was given according to the rules of the Institutional Ethics Committee who approved the study.

**Cardiac Catheterization**

Therapy with all anti-anginal medication was continued until cardiac catheterization. All patients received aspirin (100 mg) orally the night before PTCA. Lorazepam (1 mg) was orally administered before the procedure. At the beginning of the catheterization all patients received heparin intravenously (5000-7,500 IU) as a bolus. Nitroglycerin (0.1 mg i.c.) was only given for the occurrence of coronary artery spasm. Cardiac catheterization was performed in all patients by the percutaneous femoral approach. A 7Fr sheath was inserted in both femoral arteries. One guiding catheter was used for balloon angioplasty and another guiding catheter was used for angiography of the contralateral artery and insertion of the Doppler catheter or Doppler wire.
Study Protocol

Angiography. Angiography of the contralateral artery was performed before angioplasty by automatic contrast injection (Angiomat 3000, Liebel-Flarsheim Co.; right coronary artery 4 to 6 ml, 7 ml/s; left coronary artery 6 to 8 ml, 9 ml/s). Cineangiography was continued until there was no further opacification of the injected vascular bed. A repeat arteriogram of the contralateral artery was obtained after 30 seconds during the first balloon inflation. Angiography of the contralateral artery was again obtained after PTCA had been performed.

Coronary wedge pressure. Aortic pressure was measured from the guiding catheter. The distal coronary occlusion pressure was measured in 50 consecutive patients through the fluid-filled lumen of the balloon catheter during balloon inflation.

Collateral flow velocity. Coronary flow alterations in the contralateral artery were assessed in a subgroup of 34 consecutive patients in order to determine the relative collateral vascular resistance in relation to presence or absence of collateral vessels. A 3 Fr Doppler catheter, with a tip-mounted crystal (model DC-201, Millar Instruments, Houston, Texas) or a 0.014-inch Doppler guide-wire, equipped with a Doppler crystal at its tip (Cardiometrics, Mountain View, California) was inserted in the contralateral coronary artery after the first balloon inflation to obtain optimal and stable Doppler signals, avoiding side branches. Coronary blood flow velocity of the contralateral artery was assessed before, during and after the second and subsequent balloon inflations. Doppler signals of the Doppler catheter were generated by a 20 MHz pulsed Doppler flow velocity meter (Crystal Biotech Inc. Holliston, Massachusetts). The pulse stream output of the zero crossing counter was low-pass filtered with a cut-off frequency of either 60 or 0.25 Hz, offering respectively "phasic" and "mean" output signals. The spectral analysis unit of a Diasonics DRF-400 flow velocimeter (Santa Clara, California) was used to obtain an analysis of the frequency spectrum by fast Fourier transformation (FFT). The Doppler signals of the Doppler guide-wire were generated by 12-MHz pulse Doppler velocimeter and were processed by a real time spectral analyzer using fast Fourier transformation (Flowmap, Cardiometrics, Mountain View, California).

Electrocardiographic signs of ischemia during coronary occlusion of 1 minute duration were evaluated by the maximal ST-segment changes in a 12-lead electrocardiogram.

Quantitative Coronary Angiography

The severity of the coronary narrowings was determined by an automated contour detection algorithm (ARTREK, ADAC Laboratories) in two orthogonal projections, using the guiding catheter as a reference, to obtain the percentage of the diameter stenosis and the minimal luminal diameter. Definitions. A stenosis was considered 95% if there was an interruption of contrast medium but complete and brisk filling of the distal part of the stenosed artery, and 99% if there was a slow filling of the distal part. A coronary lesion was considered proximal when it was located in the right coronary artery before the acute marginal branch, in the left anterior descending coronary artery before the first septal perforator and in the left circumflex coronary artery before the first marginal branch. Collateral vessels were graded according to the Rentrop's classification: 0 = no filling of collateral vessels; 1 = filling of collateral vessels...
without any epicardial filling of the artery to be dilated; 2 = partial epicardial filling of the artery to be dilated by collateral vessels and 3 = complete epicardial filling of the artery to be dilated by collateral vessels. The grading of the collateral vessels was performed independently by 2 angiographers and a consensus was reached where they differed. Collateral vessels were considered absent during coronary occlusion when they were graded 0 or 1 and present when they were graded 2 or 3.

Quantitative Coronary Blood Velocity Analysis
Collateral flow was determined by the transient increase of coronary blood flow velocity of the contralateral artery during balloon inflation. The resistance of the collateral vascular bed was expressed as a relative value of the resistance of the contralateral vascular bed, according to a method described previously (6):

\[
\frac{P_a - P_w}{V_c,\text{def}} = R_{\text{coll}} = R_{\text{cl}} = \frac{V_c,\text{inf} - V_c,\text{def}}{P_a} 
\]

\( R_{\text{coll}} \) = resistance collateral vascular bed, \( R_{\text{cl}} \) = resistance contralateral artery, \( P_a \) = mean aortic pressure; \( P_w \) = coronary wedge pressure; \( V_c,\text{def} \) = maximal diastolic blood flow velocity contralateral artery during balloon deflation; \( V_c,\text{inf} \) = maximal diastolic blood flow velocity contralateral artery during balloon inflation.

Statistics
The relationship between the continuous variables age, duration of angina, mean aortic pressure, coronary wedge pressure, coronary lesion severity and the relative collateral vascular resistance, expressed as mean ± standard deviation, and the presence of collateral vessels during coronary occlusion was evaluated using the unpaired Student's t-test. The exact test for 2 x 2 tables was used to compare dichotomous variables. The predictive value of the continuous variables for absence or presence of collateral vessels during coronary occlusion were compared by means of the areas under the receiver operating characteristics curves. The best cut-off values of these curves were used as a substitute for the continuous variable in an univariate analysis. The variables with a p-value < 0.1 after univariate analysis were entered in a multivariate analysis. This multivariate analysis was performed by means of forward stepwise logistic regression using an analytical software program (Statistix 4.1). The coefficients of the independent predictors were used to calculate the probability of collateral vessels being present during coronary occlusion. The 95 % confidence interval was calculated by means of the variance-covariance matrix for coefficients. The coefficients of predictors for recruitable collateral vessels, multiplied by a factor 10 and rounded to a whole number, were used in a scoring system. A p-value <0.05 was considered statistically significant.

RESULTS

Coronary angioplasty procedure was successfully (<50% diameter stenosis) completed in all patients and adequate coronary angiograms for quantitative coronary angiography and
grading of the collateral vessels were obtained in all patients. Stable coronary blood flow velocity signals of the contralateral artery were in general obtained in the distal part of the coronary artery and were adequate for analysis in all 34 patients. Aortic pressure and distal coronary occlusion pressure were obtained in all 50 patients. Electrocardiographic tracings were adequate for analysis in 98 patients. There were no significant differences in heart rate and mean aortic pressure before, during and after balloon coronary occlusion of approximately 1 minute duration.

**Figure 1.** Grading of collateral vessels according to Rentrop's classification before, during and after balloon inflation in 105 patients with 1-vessel disease (grade 0-1 = absence of collateral vessels; grade 2-3 = presence of collateral vessels).

**Angiography of the Collateral Vessels**

Before the first balloon inflation, collateral vessels were graded 0 in 72 patients; graded 1 in 24; graded 2 in 6 and graded 3 in 3 patients (Fig. 1). During balloon occlusion collateral vessels remained absent (grade 0 or 1) in 54 patients and were present (grade 2 or 3) in 51 patients of whom 9 patients had collateral vessels before occlusion. Thus, recruitable collateral vessels were present in 42 patients. Collateral vessels were absent in all patients after successful completion of the procedure.
### Table 1. Clinical, angiographical and hemodynamic correlates of collateral vessels during coronary occlusion

<table>
<thead>
<tr>
<th></th>
<th>Collateral Vessels</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>absent</td>
<td>present</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=54</td>
<td>n=51</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>57 ± 9</td>
<td>57 ± 9</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39 (72%)</td>
<td>41 (80%)</td>
<td></td>
</tr>
<tr>
<td>Functional class NYHA</td>
<td>II-III</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 (44%)</td>
<td>29 (57%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 (56%)</td>
<td>22 (43%)</td>
<td></td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>6 (11%)</td>
<td>12 (24%)</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>31 (57%)</td>
<td>27 (53%)</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol &gt;6.5 mmol/l</td>
<td>15 (28%)</td>
<td>16 (31%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>beta-blocker</td>
<td>45 (83%)</td>
<td>43 (84%)</td>
<td></td>
</tr>
<tr>
<td>nitrates</td>
<td>40 (74%)</td>
<td>30 (59%)</td>
<td></td>
</tr>
<tr>
<td>calcium-antagonist</td>
<td>48 (89%)</td>
<td>41 (80%)</td>
<td></td>
</tr>
<tr>
<td>Duration of angina (months)</td>
<td>3 ± 4</td>
<td>6 ± 7</td>
<td></td>
</tr>
<tr>
<td>Left Anterior Descending coronary artery</td>
<td>47 (87%)</td>
<td>36 (71%)</td>
<td></td>
</tr>
<tr>
<td>Proximal coronary narrowing</td>
<td>22 (41%)</td>
<td>31 (61%)</td>
<td></td>
</tr>
<tr>
<td>Quantitative angiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter (%)</td>
<td>74 ± 12</td>
<td>82 ± 10</td>
<td></td>
</tr>
<tr>
<td>Minimal luminal diameter (mm)</td>
<td>0.75 ± 0.38</td>
<td>0.53 ± 0.32</td>
<td></td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>100 ± 9</td>
<td>100 ± 13</td>
<td></td>
</tr>
<tr>
<td>Pw/Pao</td>
<td>0.27 ± 0.12</td>
<td>0.35 ± 0.13</td>
<td></td>
</tr>
<tr>
<td>Rcoll/Rcla</td>
<td>21.3 ± 10</td>
<td>6.7 ± 7.4</td>
<td></td>
</tr>
<tr>
<td>ST-segment shift (mV)</td>
<td>0.38 ± 0.33</td>
<td>0.14 ± 0.19</td>
<td></td>
</tr>
</tbody>
</table>

NYHA = New York Heart Association; Pw/Pao = mean coronary wedge pressure/mean aortic pressure; Rcoll/Rcla = collateral resistance/resistance of the contralateral artery.

### Clinical and Hemodynamic Correlates of Presence of Collateral Vessels During Balloon Coronary Occlusion

The clinical and hemodynamic factors in relation to absence or presence of collateral vessels during coronary occlusion are summarized in Table 1. Collateral vessels during balloon coronary occlusion were related to the duration of angina and coronary lesion severity. Furthermore, a greater percentage of transient increase of coronary blood flow velocity of the contralateral artery was documented in the presence of collateral vessels during balloon coronary occlusion (19 ± 12% versus 4 ± 6%, P<0.001, Fig. 2). This resulted, in conjunction with an increased coronary wedge pressure, in a reduction of the relative collateral vascular resistance (Rcoll/Rcla; P<0.001, Table 1). Finally, electrocardiographic signs of ischemia were significantly reduced when collateral vessels were present (P<0.001, Table 1).
Figure 2. The upper panel shows contrast injection of the left anterior descending coronary artery (left anterior oblique view) before (left) and during (right) balloon occlusion of the right coronary artery, displaying opacification of the distal part of the right coronary artery by collateral vessels (grade 2 according to Rentrop's classification).

The left lower panel shows aortic pressure and distal coronary lesion pressure recordings before, during and after balloon inflation, as well as simultaneously obtained blood flow velocity alterations of the left anterior descending coronary artery. The right lower panel shows the electrocardiogram before balloon inflation and at 1 minute coronary occlusion of the right coronary artery. Recruitability of collateral vessels coincides with a high coronary wedge/aortic pressure ratio (0.69), a 18% transient increase of the maximal diastolic blood flow velocity of the left anterior descending coronary artery and absence of ST-segment changes at 1 minute coronary occlusion.
The predictive values of continuous variables, related to the presence of collateral vessels during coronary occlusion, were compared by the areas under the receiver operating characteristics curves (table 2). The relative collateral vascular resistance was a better predictor for presence of collateral vessels than the other continuous variables ($P<0.05$).

**Table 2. Receiver Operating Characteristic Curves**

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Area</th>
<th>SE</th>
<th>Cut-off value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of angina (months)</td>
<td>105</td>
<td>0.770</td>
<td>0.05</td>
<td>3</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>105</td>
<td>0.698</td>
<td>0.05</td>
<td>75</td>
</tr>
<tr>
<td>Minimal Luminal Diameter (mm)</td>
<td>105</td>
<td>0.679</td>
<td>0.05</td>
<td>0.45</td>
</tr>
<tr>
<td>ST-segment shift (mV)</td>
<td>98</td>
<td>0.762</td>
<td>0.05</td>
<td>0.2</td>
</tr>
<tr>
<td>Pw/Pao</td>
<td>50</td>
<td>0.703</td>
<td>0.07</td>
<td>0.3</td>
</tr>
<tr>
<td>Rcoll/Rcla</td>
<td>34</td>
<td>0.897 *</td>
<td>0.05</td>
<td>6</td>
</tr>
</tbody>
</table>

* $P<0.05$ compared to the other areas under the curve. SE = standard error; Pw/Pao = mean coronary wedge pressure/mean aortic pressure; Rcoll/Rcla = collateral resistance/ resistance of the contralateral artery

The variables duration of angina and the use of nitrates were the only independent clinical predictors for the presence of spontaneously visible and recruitable collateral vessels after stepwise logistic regression analysis (odds ratio 11.7; 95% confidence interval 4.4-31; $P<0.001$ and odds ratio 0.29; 95% confidence 0.1-0.8: $P<0.05$ respectively). The overall predictive accuracy of the regression equation was 0.75. Table 3 demonstrates the calculated probability of the presence of spontaneously visible and recruitable collateral vessels using these two variables.

The duration of angina, the use of nitrates, coronary lesion location and coronary lesion severity were the only independent predictors of recruitable collateral vessels after stepwise logistic regression analysis (table 4). The regression equation for the model using these variables is: logit ($p$) = $-4.5 + 2.6$ (duration $\geq$ 3 months) + 1.7 (no use of nitrates) + 1.5 (proximal lesion location) + 2.3 (diameter stenosis $\geq$ 75%). The overall accuracy of this regression equation was 0.80.

**Table 3. Predicted Probability of Recruitable and Spontaneously Visible Collateral Vessels and 95% Confidence Interval**

<table>
<thead>
<tr>
<th>Duration of angina</th>
<th>Nitrates</th>
<th>L</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 months</td>
<td>Use</td>
<td>-1.71</td>
<td>0.15</td>
<td>0.1-0.21</td>
</tr>
<tr>
<td>&lt; 3 months</td>
<td>No use</td>
<td>-0.51</td>
<td>0.38</td>
<td>0.28-0.48</td>
</tr>
<tr>
<td>$\geq$ 3 months</td>
<td>Use</td>
<td>0.79</td>
<td>0.67</td>
<td>0.59-0.74</td>
</tr>
<tr>
<td>$\geq$ 3 months</td>
<td>No use</td>
<td>1.99</td>
<td>0.88</td>
<td>0.81-0.92</td>
</tr>
</tbody>
</table>

CI = confidence interval; L = logit of the probability; p = probability
The coefficients of the independent predictors were used in a scoring system to calculate the probability of the presence of recruitable collateral vessels (table 4). The relationship between this calculated score, based on the aforementioned variables, and the probability of presence of recruitable collateral vessels is shown in figure 3.

**Table 4.** Independent Clinical and Angiographical Predictors of Recruitable Collateral Vessels After Multivariate Analysis and Scoring System for the Presence of Recruitable Collateral Vessels

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio</th>
<th>95% C</th>
<th>P-value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of angina ≥ 3 months</td>
<td>14.0</td>
<td>4.1-48</td>
<td>&lt;0.0001</td>
<td>26</td>
</tr>
<tr>
<td>No use of nitrates</td>
<td>5.3</td>
<td>1.5-19</td>
<td>0.0102</td>
<td>17</td>
</tr>
<tr>
<td>Proximal lesion location</td>
<td>4.7</td>
<td>1.4-16</td>
<td>0.0130</td>
<td>15</td>
</tr>
<tr>
<td>Diameter stenosis ≥ 75%</td>
<td>9.8</td>
<td>2.7-36</td>
<td>0.0006</td>
<td>23</td>
</tr>
</tbody>
</table>

Individual score is the sum of points for all above mentioned characteristics present: these scores can be used to predict the presence of recruitable collateral vessels (see Fig. 3).

**Figure 3.** The relationship between clinical and angiographical predictors, expressed in a scoring system, and the probability of the presence of recruitable collateral vessels. The grey zone represents the 95% confidence interval.
The results of the present study indicate that duration of angina, coronary lesion severity and a proximal coronary lesion location are independent factors positively associated with the presence of recruitable collateral vessels, while the use of nitrates exerts an independent negative effect. The angiographical appearance of collateral vessels during coronary occlusion relates to a lower relative collateral vascular resistance, that is the best predictor for recruitability of collateral vessels.

Clinical and Angiographical Predictors of Recruitable Collateral Vessels

Coronary angioplasty serves as a model for studying the collateral circulation in a controlled fashion. In their elegant study, Rentrop et al. demonstrated for the first time that the marked differences in angiographic appearance of collateral vessels before and during balloon coronary occlusion related to the pressure gradient across the collateral vascular bed (2). The present study confirms their angiographic findings showing that spontaneously visible collateral vessels are present in approximately 10% of the patients with 1-vessel disease, while recruitability of collateral vessels was documented in approximately 40% of these patients (fig. 1). The functional significance of these recruitable collateral vessels has been demonstrated in several clinical studies (3-6,8). This indicates that angiographical assessment of recruitable collateral vessels is important for appropriate classification of collateral vascular development.

Duration of angina and coronary lesion severity. The study of Cohen et al., which also included patients with 1-vessel disease and a normal left ventricular function, showed that the collateral vascular development is predominantly related to coronary lesion severity as determined by visual assessment (9). The results of the present study, that employed quantitative coronary angiography using an automated contour detection algorithm, is in accordance with their observations. An increase in coronary lesion severity yields a larger pressure gradient on the collateral vascular bed which is considered as one of the factors responsible for collateral vascular development (10,11). In their study the duration of angina did not correlate with angiographical appearance of collateral vessels. Their patients had experienced a longer period of angina (mean duration 7.5, range 0.25 to 36 months versus 3.3, range 0.25 to 12 months). Nevertheless, collateral vessels were present in 21 of 32 (66%) patients with a duration of angina of less than 3 months compared to 13 of the 52 (25%) patients in our study. This raises the possibility that some patients in their study may have experienced silent ischemia, known to occur frequently in patients with coronary artery disease, which was sufficient to stimulate collateral vascular development (12).

Recent insights from experimental studies have indicated that myocardial ischemia is the crucial factor that initiates a cascade of events resulting in growth of collateral vessels (12). The present investigation is the first study in a large cohort of patients showing the relationship between the duration of symptomatic coronary artery disease and the angiographical presence of recruitable collateral vessels. A period of three months duration of angina represents the best cut-off value indicating that this time period seems to be the threshold for maturation of preexisting collateral vessels before they become functionally important.

Coronary lesion location. A proximal coronary lesion location exerts a additional
stimulating effect. It is conceivable that, for a given coronary lesion severity, a proximal location will result in a lower threshold for the development of myocardial ischemia due to the larger size of the myocardium "at risk" and, hence, to the stimulation of collateral vascular development.

**Nitrates.** The negative effect of the use of nitrates on collateral vascular development was unexpected. A dichotomous analysis did not reveal a significant influence of the use of nitrates. The negative effect of nitrates was unveiled after multivariate analysis. The anti-anginal effects of nitrates are related to the peripheral vasodilating properties reducing myocardial oxygen consumption, as well as to direct coronary vasodilation, resulting in improved flow to the ischemic myocardium (13). The pharmacological responsiveness of collateral vessels may be related to the presence of smooth muscle cell proliferation, which develops in time in response to myocardial ischemia (14). It can be postulated that the use of nitrates diminishes the myocardial ischemic burden and, hence, the stimulation of collateral vascular development. On the other hand, nitrates are often added as a second or third step in medical treatment after beta-blockers and/or calcium-antagonist have failed to reduce symptoms. Consequently, it is possible that nitrates are associated with a patient cohort with more severe complaints, partly due to inadequate collateral blood flow to ischemic myocardium.

The results of the logistic regression analysis demonstrate that the presence or absence of recruitable collateral vessels can be correctly predicted in 80% of the cases using these aforementioned determinants of collateral vessels. In fact, the clinical variables duration of angina and use of nitrates already yield an overall correct classification of spontaneous visible and recruitable collateral vessels in 75% of the cases. These results demonstrate that the clinical and angiographical information provides important information relevant to risk stratification of patients with ischemic coronary syndromes.

**Hemodynamic Predictors of Recruitable Collateral Vessels**

Previous clinical studies showed that the coronary wedge pressure is increased in the presence of collateral vessels, presumably as a consequence of a reduced collateral vascular resistance, resulting in a reduction of signs of ischemia during brief coronary occlusion (3,4,6). Our current understanding of the collateral circulation is limited, partly due to the lack of methods capable of expressing the development of the collateral vascular bed in terms of flow and resistance. The dynamic behaviour in angiographic appearance of collateral vessels before and during balloon coronary occlusion can be examined by blood flow velocity analysis in the contralateral donor coronary artery (6,7). These studies demonstrated that a balloon coronary occlusion results in a transient 10-70 % increase in coronary blood flow velocity in the contralateral artery when collateral vessels are present, while this phenomenon is markedly in the absence of collateral vessels. Blood flow velocity changes in the contralateral artery during brief coronary occlusion may also be induced by alterations in preload due to akinesia of the occluded vascular bed (15). In the current investigation we did not assess alterations in preload during coronary occlusion. It can be expected however, that an increase in preload is more pronounced when collateral vessels are absent (4), while in the present study a transient increase of flow velocity during coronary occlusion was noted in those patients with collateral
vessels. Furthermore, hyperkinesia of the non-ischemic myocardium during coronary occlusion is a potential mechanism that may also explain the observed increase of blood flow velocity in the donor coronary artery. However, both experimental and human studies have indicated that this phenomenon is not operative during brief coronary occlusion (16,17,18,19). Consequently, these considerations support the contention that the observed flow velocity changes in the contralateral artery are related to collateral flow.

A recent study of Pijls et al. indicated that the fractional collateral flow reserve, i.e. the coronary wedge pressure related to aortic pressure after correction for the central venous pressure, serves as an alternative for assessment of collateral flow (20). They selected patients with stable angina of more than 3 months duration and did not document angiographic recruitability of collateral vessels. The patients in the present study had 1-vessel disease and a normal left ventricular function and, hence, the aortic pressure minus the central venous pressure approximates the aortic pressure. Consequently, the fractional collateral flow reserve reflects the coronary wedge/aortic pressure ratio in our study. Our results indicate that the relative collateral vascular resistance is a better predictor for the angiographic presence of collateral vessels during coronary occlusion than the coronary wedge pressure/aortic pressure ratio of ischemia as determined by the receiver operating characteristic curves (table 3). This may be related to the fact that the blood flow velocity alterations, used to calculate the relative collateral vascular resistance, are measured in the contralateral donor coronary artery, while the coronary wedge pressure assessed in the recipient coronary artery is determined by collateral flow arising from both non-diseased coronary arteries and hemodynamic factors such as central venous pressure and left ventricular pressure (11).

Coronary blood flow analysis of the contralateral artery allows the expression of the development of collateral vascular bed in terms of the relative vascular resistance. This offers the possibility of studying the pharmacological responsiveness of the collateral vascular resistance and provides insight into intrapatient variability of this resistance. The present study demonstrates that the angiographic presence of collateral vessels results in a 3-fold reduction of the relative collateral vascular resistance. The large interpatient variability of the collateral vascular resistance (Rcoll/Rcla, table 2) remains unclear and may be related to variations in stimulating factors such as the duration of angina, medication, coronary lesion severity, lesion location or other unknown contributing factors.

Finally, electrocardiographic signs of ischemia were reduced in the presence of collateral vessels, although absence of ischemia (< 0.1 mV ST-segment shift) was noted in only 45% of the patients with collateral vessels during balloon coronary occlusion. This illustrates that collateral vessels are capable to reduce rather than to abolish myocardial ischemia during brief coronary occlusion.

Limitations

The collateral vascular development was related to the period of symptomatic disease, while the contribution of silent ischemia to the development of collateral vessels is unknown. This subjective factor may be an explanation for the overlap between patients with and without collateral vessels during coronary occlusion. The results of the study are only applicable to patients with 1-vessel disease and normal left ventricular function, which represents only a
small proportion of patients with coronary artery disease. The medical therapy of the patients studied was not uniform and this may have contributed to observed variations between patients.

The angiographic grading of collateral vessels is sensitive to variations in the applied technique and is subject to intra- and inter-observer variability. Furthermore, intracoronary blood flow velocity assessment is a sensitive technique for the detection of alterations in blood flow, but this method it also prone to technical failures. The functional significance of collateral vessels during coronary occlusion were judged by electrocardiographic monitoring and were not expanded to hemodynamic monitoring or assessment of global or regional ejection fraction. The study provides only information on the function of collateral vessels during brief coronary occlusion.

Clinical Implications

The establishment of the time period required for maturation of pre-existing collateral vessels in humans has important clinical implications. Experimental studies have indicated that myocardial infarct size is determined by the size of the myocardium at risk, the duration of coronary occlusion and collateral flow to the jeopardized myocardium (21,22). Recent clinical studies have demonstrated that a short period of preceding angina (24-48 hours) exerts a protective effect as documented by an approximately 25-30 % reduction in myocardial infarct size (23,24). The present study demonstrates that such a time period is too short for effective collateral vascular development. The protective effect does not seem to be exerted by collateral flow but is most likely due to ischemic preconditioning, presumably related to stimulation of adenosine-A1 receptors and opening of ATP-dependent potassium channels (25,26). The present study illustrates that a patient without preceding angina runs a high risk of developing a large myocardial infarction following abrupt coronary occlusion due to the fact that collateral vessels are absent and a protective effect related to ischemic preconditioning is lacking. Furthermore, clinical studies have demonstrated that the time window for reperfusion therapy can be increased in the presence of collateral flow to the jeopardized myocardium (27-29). Finally, clinical studies using myocardial contrast echocardiography following the acute phase of myocardial infarction have demonstrated that collateral vascular supply to the occluded vascular bed is associated with an improved left ventricular function after revascularization (30,31).

The present study indicates that the clinical information on the duration of angina and the use of nitrates allows the prediction of spontaneously visible and recruitable vessels with a 75% overall accuracy. Furthermore, the clinical and angiographical variables predict recruitability of collateral vessels with an 80% overall accuracy. These findings are important for risk stratification of patients undergoing interventions for ischemic coronary syndromes.
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