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Clinical, Angiographic and Hemodynamic Predictors of Recruitable Collateral Flow Assessed During Balloon Angioplasty Coronary Occlusion

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Objectives. **We sought 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 single-vessel disease (left anterior descending coronary artery in 69 patients, left circumflex coronary artery in 4 patients, right coronary artery in 32 patients) and normal left ventricular function. Collateral vessels were graded according to the classification of Rentrop. 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 (ECG).**

Results. **A multivariate logistic analysis of clinical and angiographic 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, whereas the use of nitrates exerted an independent negative effect ($p = 0.01$). The regression equation yielded an overall predictive accuracy of 80%. The presence of recruitable collateral vessels during coronary occlusion resulted in a higher coronary wedge/aortic pressure ratio (mean [±SD] 0.35 ± 0.13 vs. 0.27 ± 0.12, $p < 0.005$), a lower relative collateral vascular resistance (6.7 ± 7.4 vs. 21.3 ± 10, $p < 0.001$) and a reduction of ECG signs of ischemia (0.14 ± 0.19 vs. 0.38 ± 0.33 mV, $p < 0.001$). The relative collateral vascular resistance was the best predictor for recruitability of collateral vessels compared with the other variables related to collateral vascular growth ($p < 0.05$).**

Conclusions. **Clinical and angiographic 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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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 to determine clinical and angiographic 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

A total of 105 patients (80 men and 25 women, age 57 ± 9 years) with single-vessel disease, referred to our institution for

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Abbreviations and Acronyms

CI = confidence interval
ECG = electrocardiogram, electrocardiographic
OR = odds ratio

percutaneous transluminal coronary angioplasty, 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 (ECG) evidence of left ventricular hypertrophy or conduction abnormalities, 3) multilesion single-vessel disease or total coronary occlusion; and 4) peripheral vascular disease limiting arterial access. Clinical variables and ECG 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 for a total of 58 patients were reported in a previous study (5); the hemodynamic variables for 16 patients were included in another study (6). Written informed consent was given according to the rules of the Institutional Ethics Committee, who approved the study.

Cardiac catheterization. Therapy with all antianginal medications was continued until cardiac catheterization. All patients received aspirin (100 mg) orally the night before coronary angioplasty. Lorazepam (1 mg) was orally administered before the procedure. At the beginning of the catheterization all patients received 5,000 to 7,500 IU of heparin intravenously as a bolus. Nitroglycerin (0.1 mg intracoronary) was only given for the occurrence of coronary artery spasm. Cardiac catheterization was performed in all patients by the percutaneous femoral approach. A 7F 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 s during the first balloon inflation. Angiography of the contralateral artery was again obtained after coronary angioplasty 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 to determine the relative collateral vascular resistance in relation to the presence or absence of collateral vessels. A 3F Doppler catheter, with a tip-mounted crystal (model DC-201, Millar Instruments) or a 0.014-in. (0.035 cm) Doppler guide wire, equipped with a Doppler crystal at its tip (Cardiometrics) was inserted into 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.). The pulse stream output of the zero crossing counter was low pass filtered with a cutoff frequency of either 60 or 0.25 Hz, offering "phasic" and "mean" output signals, respectively. The spectral analysis unit of a Diasonics DRF-400 flow velocimeter was used to obtain an analysis of the frequency spectrum by fast Fourier transformation. The Doppler signals of the Doppler guide wire were generated by a 12-MHz pulsed Doppler velocimeter and were processed by a real-time spectral analyzer using fast Fourier transformation (Flowmap, Cardiometrics).

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

Quantitative coronary angiography. The severity of the coronary narrowings was determined using an automated contour detection algorithm (ARTREK, ADAC Laboratories) in two orthogonal projections, using the guiding catheter as a reference, to obtain the percent diameter stenosis and the minimal lumen 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 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; 3 = complete epicardial filling of the artery to be dilated by collateral vessels. Grading of the collateral vessels was performed independently by two 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):

$$\frac{\text{Rcoll}}{\text{Rcla}} = \frac{\text{Pao} - \text{Pw}}{\text{Pao}} \times \frac{V_{c,def}}{V_{c,inf} - V_{c,def}},$$

where Rcoll = resistance collateral vascular bed; Rcla = resistance contralateral artery; Pao = mean aortic pressure; Pw = coronary wedge pressure; $V_{c,def}$ = maximal diastolic blood flow velocity of the contralateral artery during balloon deflation; $V_{c,inf}$ = maximal diastolic blood flow velocity of the contralateral artery during balloon inflation.

Statistics. The relation between the continuous variables—age, duration of angina, mean aortic pressure, coronary wedge pressure, coronary lesion severity and relative collateral vascular resistance, expressed as mean ±SD—and the presence of collateral vessels during coronary occlusion was evaluated using the unpaired Student *t* test. The exact test for 2 × 2 tables was used to compare dichotomous variables. The predictive value of the continuous variables for the absence or presence of collateral vessels during coronary occlusion was compared by means of the areas under the receiver operating characteristic curves. The best cutoff values of these curves were used as a substitute for the continuous variable in an univariate analysis. The variables with $p < 0.1$ 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 (CI) was calculated by means of the variance–covariance matrix for coefficients. The coefficients of predictors for recruitable collateral vessels, multiplied by a factor of 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 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 ~1 min duration.

Angiography of the collateral vessels. Before the first balloon inflation, collateral vessels were graded 0 in 72 patients; graded 1 in 24 patients; graded 2 in 6 patients; 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, 9 of whom 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.

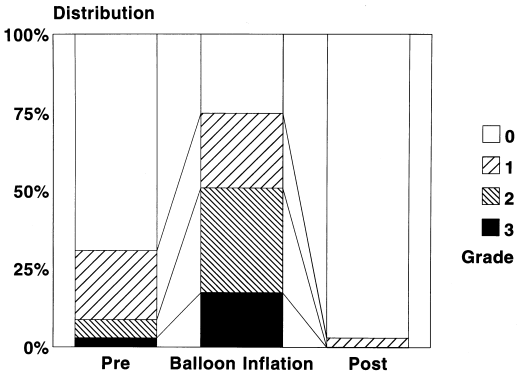

Figure 1. Grading of collateral vessels according to the Rentrop classification before, during and after balloon inflation in 105 patients with single-vessel disease (grade 0 or 1 = absence of collateral vessels; grade 2 or 3 = presence of collateral vessels).

Clinical and hemodynamic correlates of the presence of collateral vessels during balloon coronary occlusion. The clinical and hemodynamic factors in relation to the 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% vs. 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 ($p < 0.001$) (Table 1). Finally, ECG signs of ischemia were significantly reduced when collateral vessels were present ($p < 0.001$, Table 1).

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 characteristic curves (Table 2). The relative collateral vascular resistance was a better predictor of the presence of collateral vessels than the other continuous variables ($p < 0.05$).

The variables duration of angina and use of nitrates were the only independent clinical predictors of the presence of spontaneously visible and recruitable collateral vessels after stepwise logistic regression analysis (odds ratio [OR] 11.7, 95% CI 4.4 to 31, $p < 0.001$; and OR 0.29, 95% CI 0.1 to 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, use of nitrates, coronary lesion location and coronary lesion severity were the only independent predictors of recruitable collateral vessels after stepwise

Table 1. Clinical, Angiographic and Hemodynamic Correlates of Collateral Vessels During Coronary Occlusion

	Collateral Vessels		
	Absent (n = 54)	Present (n = 51)	p Value
Age (yr)	57 ± 9	57 ± 9	0.71
Male	39 (72%)	41 (80%)	0.33
NYHA functional class			
II–III	24 (44%)	29 (57%)	0.39
IV	30 (56%)	22 (43%)	0.28
Systemic hypertension	6 (11%)	12 (24%)	0.10
Cigarette smoking	31 (57%)	27 (53%)	0.65
Total cholesterol >6.5 mmol/liter	15 (28%)	16 (31%)	0.69
Diabetes mellitus	3 (6%)	2 (4%)	0.70
Medication			
Beta-blocker	45 (83%)	43 (84%)	0.89
Nitrates	40 (74%)	30 (59%)	0.07
Calcium antagonist	48 (89%)	41 (80%)	0.23
Duration of angina (mo)	3 ± 4	6 ± 7	0.01
LAD	47 (87%)	36 (71%)	0.08
Proximal coronary narrowing	22 (41%)	31 (61%)	0.06
Quantitative angiography			
Diameter (%)	74 ± 12	82 ± 10	0.001
MLD (mm)	0.75 ± 0.38	0.53 ± 0.32	0.001
Pao (mm Hg)	100 ± 9	100 ± 13	1.0
Pw/Pao	0.27 ± 0.12	0.35 ± 0.13	0.005
Rcoll/Rcla	21.3 ± 10	6.7 ± 7.4	0.001
ST segment shift (mV)	0.38 ± 0.33	0.14 ± 0.19	0.001

Data are presented as number (%) of patients or mean value ± SD. LAD = left anterior descending coronary artery; MLD = minimal lumen diameter; NYHA = New York Heart Association; Pw/Pao = mean coronary wedge pressure/mean aortic pressure; Rcoll/Rcla = collateral resistance/resistance of contralateral artery.

logistic regression analysis (Table 4). The regression equation for the model using these variables is: logit (p) = −4.5 + 2.6 (duration ≥3 months) + 1.7 (no use of nitrates) + 1.5 (proximal lesion location) + 2.3 (diameter stenosis ≥75%). The overall accuracy of this regression equation was 0.80.

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 relation between this calculated score, based on the aforementioned variables, and the probability of the presence of recruitable collateral vessels is shown in Figure 3.

Discussion

The results of the present study indicate that duration of angina, coronary lesion severity and proximal coronary lesion location are independent factors positively associated with the presence of recruitable collateral vessels, whereas the use of nitrates exerts an independent negative effect. The angiographic appearance of collateral vessels during coronary occlusion relates to a lower relative collateral vascular resistance, which is the best predictor of recruitability of collateral vessels.

Clinical and angiographic 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. (2) demonstrated for the first time that the marked differences in angiographic appearance of collateral vessels before and during balloon coronary occlusion was related to the pressure gradient across the collateral vascular bed. The present study confirms their angiographic findings, showing that spontaneously visible collateral vessels are present in ~10% of the patients with single-vessel disease; the 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 angiographic 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. (9), which also included patients with single-vessel disease and normal left ventricular function, showed that the collateral vascular development is predominantly related to coronary lesion severity as determined by visual assessment. The results of the present study, which 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 one of the factors responsible for collateral vascular development (10,11). In the study by Cohen et al. (9), the duration of angina did not correlate with the angiographic appearance of collateral vessels. Their patients had experienced a longer period of angina (mean duration 7.5 months, range 0.25 to 36; vs. 3.3 months, range 0.25 to 12). Nevertheless, collateral vessels were present in 21 (66%) of 32 patients with a duration of angina <3 months compared with 13 (25%) of the 52 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 relation between the duration of symptomatic coronary artery disease and the angiographic presence of recruitable collateral vessels. A period of 3 months' duration of angina represents the best cutoff 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 an 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 owing to the larger size of the myocardium "at

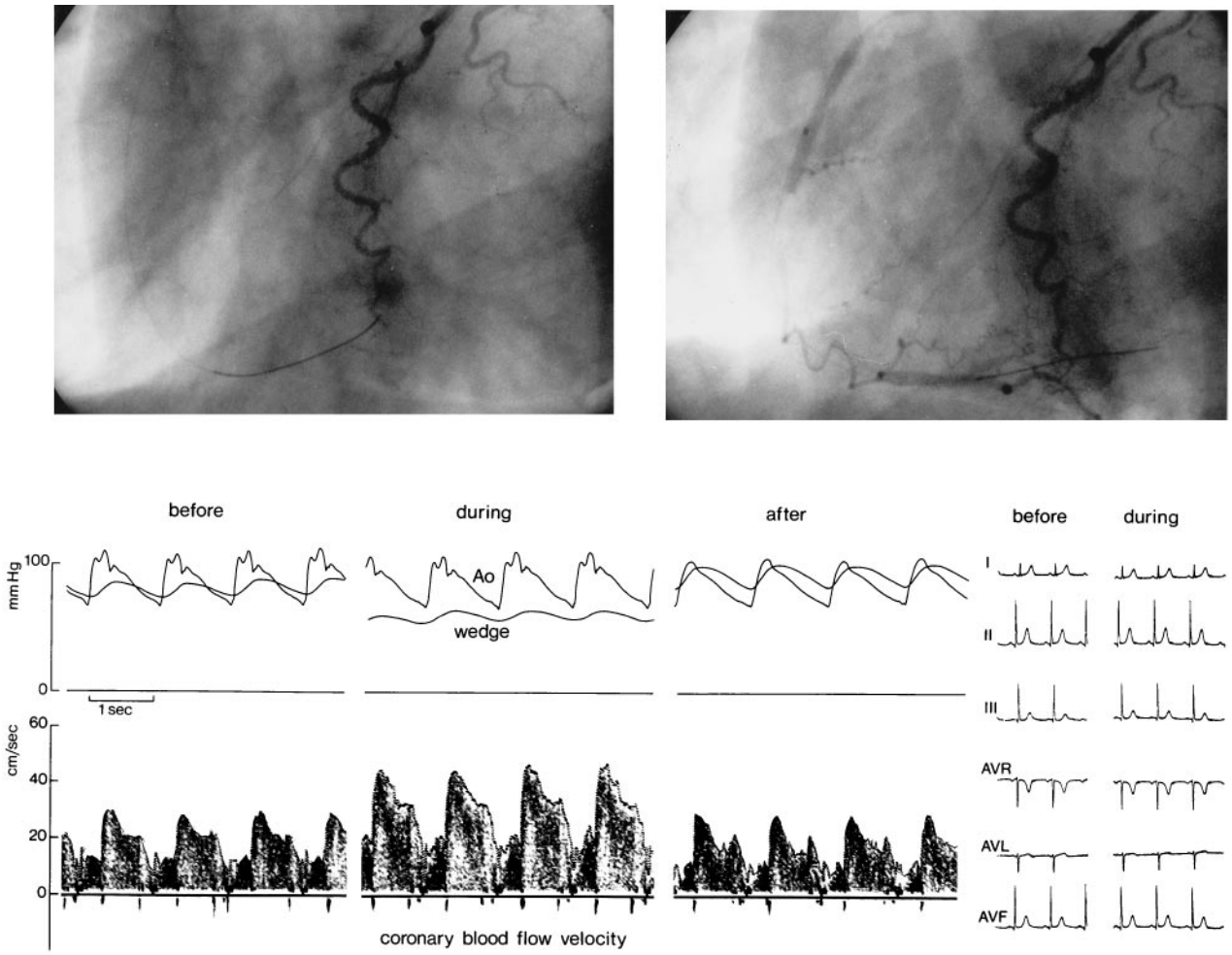

Figure 2. The **top** images show contrast injection of the left anterior descending coronary artery (left anterior oblique view) before **(left)** and during **(right)** balloon occlusion of the right coronary artery, displaying opacification of the distal part of the right coronary artery by collateral vessels (grade 2 according to the Rentrop classification). The **lower left** recordings show 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 **lower right** tracings show the ECG before balloon inflation and at 1 min of coronary occlusion of the right coronary artery. Recruitability of collateral vessels coincides with a high coronary wedge/aortic pressure ratio (0.69), an 18% transient increase in the maximal diastolic blood flow velocity of the left anterior descending coronary artery and absence of ST segment changes at 1 min of coronary occlusion.

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 antianginal 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 pharmacologic 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. In contrast, nitrates are often added as a second or third step in medical treatment after beta-blockers or calcium antagonists, or both, have failed to reduce symptoms. Consequently, it is possible

Table 2. Receiver Operating Characteristic Curves

	No. of Pts	Area	SE	Cutoff Value
Duration of angina (mo)	105	0.770	0.05	3
Diameter stenosis (%)	105	0.698	0.05	75
MLD (mm)	105	0.679	0.05	0.45
ST segment shift (mV)	98	0.762	0.05	0.2
Pw/Pao	50	0.703	0.07	0.3
Rcoll/Rcla	34	0.897*	0.05	6

*$p < 0.05$ versus other areas under the curve. Abbreviations as in Table 1.

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

Nitrates	L	p Value	95% CI
Angina <3 mo			
Used	−1.71	0.15	0.1–0.21
Not used	−0.51	0.38	0.28–0.48
Angina ≥3 mo			
Used	0.79	0.67	0.59–0.74
Not used	1.99	0.88	0.81–0.92

CI = confidence interval; L = logit of the probability.

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 the 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 angiographic data provide 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 behavior of collateral vessels as seen angiographically 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% to 70% increase in coronary blood flow velocity in the contralateral artery when collateral vessels are present, although this phenomenon is marked 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), whereas 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 nonischemic 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 (16–19). Consequently, these considerations support the contention that the observed flow velocity changes in the contralateral artery are related to collateral flow.

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

	OR (95% CI)	p Value	Points
Angina ≥3 mo	14.0 (4.1–48)	< 0.0001	26
Nitrates not used	5.3 (1.5–19)	0.0102	17
Proximal lesion location	4.7 (1.4–16)	0.0130	15
Diameter stenosis ≥75%	9.8 (2.7–36)	0.0006	23

*An individual score is the sum of points for all the listed characteristics present; these scores can be used to predict the presence of recruitable collateral vessels (see Fig. 3).

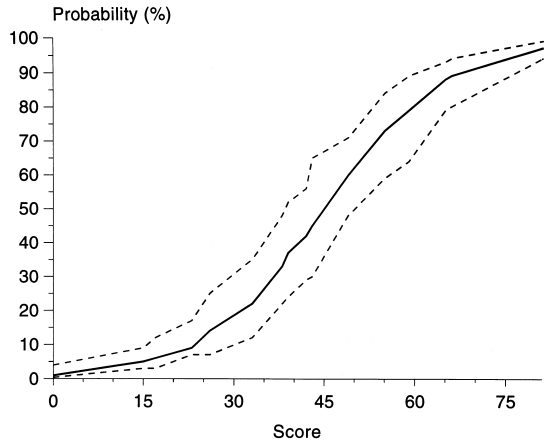

Figure 3. The relation between clinical and angiographic predictors, expressed in a scoring system, and the probability of the presence of recruitable collateral vessels. **Dashed lines** = 95% confidence interval.

A recent study by Pijls et al. (20) indicated that the fractional collateral flow reserve, that is, the coronary wedge pressure related to aortic pressure after correction for the central venous pressure, serves as an alternative for assessment of collateral flow. These investigators 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 single-vessel disease and normal left ventricular function; 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 of 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, whereas the coronary wedge pressure assessed in the recipient coronary artery is determined by collateral flow arising from both nondiseased 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 pharmacologic 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 threefold reduction of the relative collateral vascular resistance. The large interpatient variability of the collateral vascular resistance (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, ECG signs of ischemia were reduced in the presence of collateral vessels, although the 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 of reducing rather than abolishing myocardial ischemia during brief coronary occlusion.

Study limitations. The collateral vascular development was related to the period of symptomatic disease, although 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 single-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 intraobserver and interobserver viability. Furthermore, intracoronary blood flow velocity assessment is a sensitive technique for the detection of alterations in blood flow, but this method is also prone to technical failures. The functional significance of collateral vessels during coronary occlusion was determined by ECG monitoring and was 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 period required for maturation of preexisting 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 to 48 h) exerts a protective effect, as documented by an ~25% to 30% reduction in myocardial infarct size (23,24). The present study demonstrates that such a 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-A_1 receptors and opening of adenosine triphosphate–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 after abrupt coronary occlusion owing 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 after the acute phase of myocardial infarction have demonstrated that collateral vascular supply to the occluded vascular bed is associated with 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 angiographic 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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References

1. Cohen MV. Coronary Collaterals: Functional Significance of Coronary Collaterals in Man. Armonk (NY): Futura, 1985:93–114.
2. Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. J Am Coll Cardiol 1985;5:587–92.
3. Meier B, Luethy P, Finci L, Steffenino GD, Rutishauser W. Coronary wedge pressure in relation to spontaneously visible and recruitable collaterals. Circulation 1987;75:906–13.
4. Rentrop KP, Thornton JC, Feit F, Van Buskirk M. Determinants and protective potential of coronary arterial collaterals as assessed by an angioplasty model. Am J Cardiol 1988;61:677–84.
5. Piek JJ, Koolen JJ, Hoedemaker G, David GK, Visser CA, Dunning AJ. Severity of single-vessel coronary arterial stenosis and duration of angina as determinants of recruitable collateral vessels during balloon angioplasty occlusion. Am J Cardiol 1991;67:13–7.
6. Piek JJ, Koolen JJ, Metting van Rijn AC, et al. Spectral analysis of flow velocity in the contralateral artery during coronary angioplasty: a new method for assessing collateral flow. J Am Coll Cardiol 1993;21:1574–82.
7. Kyriakidis MK, Petropoulakis PN, Tentolouris CA, et al. Relation between changes in blood flow of the contralateral coronary artery and the angiographic extent and function of recruitable collateral vessels arising from this artery during balloon coronary occlusion. J Am Coll Cardiol 1994;23:869–78.
8. Cohen M, Rentrop KP. Limitation of myocardial ischemia by collateral

circulation during sudden controlled coronary artery occlusion in human subjects: a prospective study. Circulation. 1986;74:469–76.
9. Cohen M, Sherman W, Rentrop KP, Gorlin R. Determinants of collateral filling observed during sudden controlled coronary artery occlusion in human subjects. J Am Coll Cardiol 1989;13:297–303.
10. Elliot EC, Bloor CM, Jones EL, Mitchell WJ, Gregg DE. Effect of controlled coronary occlusion on collateral circulation in conscious dogs. Am J Physiol 1971;220:857–61.
11. Gregg DE. The natural history of coronary collateral development. Circ Res 1974;35:335–44.
12. Schaper W, Sharma HS, Quinkler W, Markert T, Wunsch M, Schaper J. Molecular biologic concepts of coronary anastomoses. J Am Coll Cardiol 1990;15:513–8.
13. Bassenge E, Zanzinger J. Nitrates in different vascular beds, nitrate tolerance, and interactions with endothelial function. Am J Cardiol 1992;70:23–9B.
14. Pasyk S, Schaper W, Schaper J, Pasyk K, Miskiewicz G, Steinseifer B. DNA synthesis in coronary collaterals after coronary artery occlusion in conscious dogs. Am J Physiol 1982;242:H1031–7.
15. McGinn AL, White CW, Wilson RF. Interstudy variability of coronary flow reserve: influence of heart rate, arterial pressure, and ventricular preload. Circulation 1990;81:1319–30.
16. Serruys PW, Wijns W, van den Brand M, et al. Left ventricular performance, regional blood flow, wall motion, and lactate metabolism during transluminal angioplasty. Circulation 1984;70:25–36.
17. Fujita M, McKown DP, McKown MD, Hartley JW, Franklin D. Evaluation of coronary collateral development by regional myocardial function and reactive hyperemia. Cardiovasc Res 1987;21:377–84.
18. Fujita M, McKown DP, McKown MD, Franklin D. Electrocardiographic evaluation of collateral development in conscious dogs. J Electrocardiol 1988;21:55–64.
19. Verani MS, Lacy JL, Guidry GW, et al. Quantification of left ventricular performance during transient coronary occlusion at various anatomic sites in humans: a study using tantalum-178 and a multiwire gamma camera. J Am Coll Cardiol 1992;19:297–306.
20. Pijls NHJ, Bech GJW, El Gamal MIH, et al. Quantification of recruitable coronary collateral blood flow in conscious humans and its potential to predict future ischemic events. J Am Coll Cardiol 1995;25:1522–8.
21. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation 1977;56:786–94.
22. Jugdutt BI, Hutchins GM, Bulkley BH, Becker LC. Myocardial infarction in the conscious dog: three-dimensional mapping of infarct, collateral flow and region at risk. Circulation 1979;60:1141–50.
23. Kloner RA, Shook T, Przyklenk K, et al. Previous angina alters in-hospital outcome in TIMI 4: a clinical correlate to preconditioning? Circulation 1995;91:37–47.
24. Ottani F, Galvani M, Ferrini D, et al. Prodromal angina limits infarct size: a role for ischemic preconditioning. Circulation 1995;91:291–7.
25. Thornton JD, Liu GS, Olsson RA, Downey JM. Intravenous pretreatment with A_1-selective adenosine analogues protects the heart against infarction. Circulation 1992;85:659–65.
26. Gross GJ, Auchampach JA. Blockade of ATP-sensitive potassium channels prevents myocardial preconditioning in dogs. Circ Res 1992;70:223–33.
27. Rogers WJ, Hood WPJ, Mantle JA, et al. Return of left ventricular function after reperfusion in patients with myocardial infarction: importance of subtotal stenoses or intact collaterals. Circulation 1984;69:338–49.
28. Blanke H, Cohen M, Karsch KR, Fagerstrom R, Rentrop KP. Prevalence and significance of residual flow to the infarct zone during the acute phase of myocardial infarction. J Am Coll Cardiol 1985;5:827–31.
29. Rentrop KP, Feit F, Sherman W, et al. Late thrombolytic therapy preserves left ventricular function in patients with collateralized total coronary occlusion: primary end point findings of the second Mount Sinai–New York University Reperfusion Trial. J Am Coll Cardiol 1989;14:58–64.
30. Sabia PJ, Powers ER, Jayaweera AR, Ragosta M, Kaul S. Functional significance of collateral blood flow in patients with recent acute myocardial infarction: a study using myocardial contrast echocardiography. Circulation 1992;85:2080–9.
31. Sabia PJ, Powers ER, Ragosta M, Sarembock IJ, Burwell LR, Kaul S. An association between collateral blood flow and myocardial viability in patients with recent myocardial infarction. N Engl J Med 1992;327:1825–31.