Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 38, No. 7, 2001
ISSN 0735-1097/01/$20.00
PII S0735-1097(01)01675-8

Frequency Distribution of Collateral Flow and Factors Influencing Collateral Channel Development

Functional Collateral Channel Measurement in 450 Patients With Coronary Artery Disease

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OBJECTIVES We sought to determine the pathogenetic predictors of collateral channels in a large cohort of patients with coronary artery disease (CAD).

BACKGROUND The frequency distribution of collateral flow in patients with CAD is unknown. Only small qualitative studies have investigated which factors influence the development of collateral channels.

METHODS In 450 patients with one- to three-vessel CAD undergoing percutaneous transluminal coronary angioplasty (PTCA), collateral flow was measured. A collateral flow index (CFI; no unit) expressing collateral flow relative to normal anterograde flow was determined using coronary wedge pressure or Doppler measurements through sensor-tipped PTCA guide wires. Frequency distribution analysis of CFI and univariate and multivariate analyses of 32 factors, including gender, age, patient history, cardiovascular risk factors, medication and coronary angiographic data, were performed.

RESULTS Two-thirds of the patients had a CFI <0.25 and ~40% of patients had a CFI <0.15, but only ~10% of the patients had a recruitable CFI ≥ 0.4. By univariate analysis, the following were predictors of CFI ≥ 0.25: high levels of high-density lipoprotein cholesterol, the absence of previous non–Q-wave myocardial infarction, angina pectoris during an exercise test, angiographic indicators of severe CAD and the left circumflex or right coronary artery as the collateral-receiving vessel. Percent diameter stenosis of the lesion undergoing PTCA was the only independent predictor of a high CFI.

CONCLUSIONS This large clinical study of patients with CAD in whom collateral flow was quantitatively assessed reveals that two-thirds of the patients do not have enough collateral flow to prevent myocardial ischemia during coronary occlusion, and that coronary lesion severity is the only independent pathogenetic variable related to collateral flow. (J Am Coll Cardiol 2001;38: 1872–8) © 2001 by the American College of Cardiology

The coronary collateral circulation is an alternative source of blood supply to myocardium jeopardized by stenosis or occlusion of a coronary vessel. A well-developed coronary collateral circulation may have a considerable impact on the prognosis of coronary artery disease (CAD) (1). So far, a few pathogenetic factors have been consistently described as influencing the development of coronary collateral channels. Well-established factors positively determining the extent of collateralization are the severity of coronary artery stenoses (2) and the duration of myocardial ischemic symptoms (3,4). In contrast, there has been discordant data on the influence of metabolic disorders on collateral channel development, such as diabetes mellitus (5–7). The possible relevance of cholesterol metabolism to the expansion of the collateral circulation has been indicated only experimentally (8). The presence of systemic hypertension has also been suggested to influence the development of well-grown collateral channels (9). Previous studies on the pathogenesis of collateral channels in humans often lack sufficient patient numbers or quantitative means for collateral channel assessment, or both. Several studies have shown that assessing the collateral circulation by intracoronary Doppler flow or pressure wires, or both, is a precise method to determine collateral blood flow in the clinical setting (10–12).

The purpose of this study of 450 patients with CAD was to determine how often different levels of collateral flow occur and to comprehensively elucidate the pathogenetic factors that independently influence the development of the coronary collateral network.

METHODS

Patients. In 450 patients (age 61 ± 11 years) with one- to three-vessel CAD and without Q-wave myocardial infarction, the coronary collateral circulation was measured quantitatively in one coronary artery undergoing percutaneous transluminal coronary angioplasty (PTCA) because of CAD-related symptoms. The patients included in this study have been described in part elsewhere (11,13–19). These

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Manuscript received June 5, 2001; revised manuscript received August 17, 2001, accepted August 29, 2001.

Abbreviations and Acronyms

CAD = coronary artery disease
CFI = collateral flow index
CVP = central venous pressure
LAD = left anterior descending coronary artery
LCx = left circumflex coronary artery
LVEDP = left ventricular end-diastolic pressure
P_{ao} = aortic pressure
P_{occl} = occlusive pressure (coronary wedge pressure)
PTCA = percutaneous transluminal coronary angioplasty
RCA = right coronary artery

studies were approved by the local Ethics Committee, and the patients gave written, informed consent to participate.

The patients were classified into two groups according to an intracoronary, sensor-derived collateral flow index (CFI; no unit) <0.25 or ≥ 0.25. The CFI expresses collateral flow during coronary balloon occlusion relative to normal anterograde flow during vessel patency. A CFI ≥ 0.25 has been demonstrated to be sufficient to prevent myocardial ischemia in a region supplied by an occluded coronary artery (11).

Coronary angiography. The patients underwent left heart catheterization, including biplane left ventricular angiography and coronary angiography, for diagnostic purposes. Coronary artery stenoses were assessed quantitatively as the percent diameter reduction, using the guiding catheter for calibration. The area at risk of myocardial infarction was measured quantitatively from coronary angiograms as the summed coronary artery branch lengths of the epicardial vascular tree distal to the stenosis to be dilated in relation to the branch lengths of the entire coronary artery tree (20). This ratio represents the amount of myocardium distal to a stenosis relative to the total amount of myocardium supplied by the entire vessel. Aortic pressure was measured using the guiding catheter during angioplasty.

Collateral channel assessment. Collateral channel assessment was performed by four different methods in all patients, whereby the principal end point of the study was the functional measurement obtained by sensor-tipped guide wires during vessel occlusion (i.e., recruitable collateral flow).

Either the 0.014-in. (0.035-cm), intracoronary pressure, sensor-tipped guide wire or the Doppler guide wire was used during PTCA. The fiberoptic pressure guide wire (WaveWire, Endosonics, Rancho Cordova, California; or PressureWire, Radi Medical, Uppsala, Sweden) was set at zero, calibrated, advanced through the guiding catheter, normalized for aortic pressure at the ostium of the coronary artery and positioned distal to the stenosis to be dilated. The pressure-derived collateral flow index (CFI_p; no unit) was determined (n = 328) by simultaneous measurement of mean aortic pressure (P_{ao}, mm Hg) and distal coronary pressure at the end of 1-min balloon occlusion (P_{occl}, or coronary wedge pressure, mm Hg). If not gauged simultaneously (n = 120), central venous pressure (CVP, mm Hg) was estimated at 5 mm Hg. The CFI was calculated as: $(P_{occl} - CVP)/(P_{ao} - CVP)$ (11,21). The CFI values computed by estimated CVP did not differ from those calculated by measured CVP: 0.22 ± 0.15 and 0.22 ± 0.15, respectively.

We have demonstrated that coronary wedge pressure is a reliable measure of collateral flow in patients with left ventricular end-diastolic pressure (LVEDP) <15 mm Hg before vessel occlusion (22). Therefore, in the presence of LVEDP ≥ 15 mm Hg, intracoronary flow velocity measurements were used to assess CFI. Velocity-derived CFI (CFI_v) measurements (n = 217) were performed using a 0.014-in. Doppler guide wire with a 12-MHz, piezoelectric crystal at its tip (FlowWire, Endosonics). In 192 patients, simultaneous pressure and Doppler-derived CFI measurements were performed. Validation of the Doppler wire has been described previously (23). Velocity-derived CFI was determined as the ratio of the flow velocity–time integral distal to the occluded stenosis divided by the baseline flow velocity–time integral obtained at the same site after PTCA and after reactive hyperemia (11). Bi-directional flow velocity signals were added to obtain the total collateral flow velocity. Pressure- and Doppler-derived methods for collateral channel assessment have been validated previously (11,12). If both pressure- and flow-derived CFIs were determined in one patient, the average between CFI_p and CFI_v was calculated to assess the CFI.

Myocardial ischemia during balloon occlusion was assessed by the occurrence of angina pectoris and by a simultaneously obtained intracoronary electrocardiogram (ECG) (24). In the absence of ST-segment changes >0.1 mV during 1-min balloon occlusion, coronary collateral channels were defined as sufficient or insufficient collateral channels.

The degree of angiographic collateral flow was determined according to the extent of epicardial coronary artery filling through collateral channels injected with a contrast agent from the contralateral side before PTCA: 0 = no filling of the distal vessel; 1 = small side branches filled; 2 = major side branches filled; and 3 = main vessel filled (2).

Statistical analysis. Univariate analysis of all 32 categorical and continuous variables, with regard to the two study groups or continuous CFI values, was performed using the chi-square test, unpaired Student *t* test and linear regression analysis, respectively. Multivariate analysis was performed by multiple regression, testing all demographic, clinical, hemodynamic and angiographic factors for their independence as a predictor of CFI. The variables tested included the following: age, gender, body mass index, mean blood pressure, heart rate, left ventricular ejection fraction, LVEDP, six cardiovascular risk factors (Table 1), seven cardiovascular drugs (Table 1), serum lipids, previous non–Q-wave myocardial infarction, treadmill exercise test results obtained before invasive examination and six coronary

JACC Vol. 38, No. 7, 2001
December 2001:1872–8

Table 1. Univariate Analysis: Clinical Characteristics

	CFI <0.25 (n = 307)	CFI ≥0.25 (n = 143)	p Value
Men	236 (77%)	109 (76%)	NS
Age (years)	61 ± 10	61 ± 11	NS
Body mass index (kg/m^2)	27 ± 4	27 ± 4	NS
Mean blood pressure, P_{ao} (mm Hg)	95 ± 15	96 ± 16	NS
Heart rate (beats/min)	73 ± 12	72 ± 12	NS
LVEF (%)	65 ± 11	66 ± 11	NS
LVEDP (mm Hg)	14 ± 7	13 ± 6	NS
Cardiovascular risk factors			
Diabetes mellitus	46 (15%)	24 (17%)	NS
Systemic hypertension	157 (51%)	69 (48%)	NS
Smoking	117 (38%)	69 (48%)	NS
Obesity	61 (20%)	27 (19%)	NS
Untreated hypercholesterolemia	55 (18%)	31 (22%)	NS
Family history for CAD	101 (33%)	50 (35%)	NS
Cardiovascular medication			
ASA	252 (82%)	124 (87%)	NS
Beta-blockers	178 (58%)	90 (63%)	NS
Nitrates	117 (38%)	57 (40%)	NS
Cholesterol-lowering drugs	101 (33%)	44 (31%)	NS
ACE inhibitors	80 (26%)	30 (21%)	NS
Calcium antagonists	52 (17%)	26 (18%)	NS
Diuretics	28 (9%)	27 (19%)	NS
Serum lipids			
Cholesterol (mmol/l)	5.7 ± 1.1	5.5 ± 1.0	NS
HDL cholesterol (mmol/l)	1.2 ± 0.3	1.3 ± 0.5	0.02
LDL cholesterol (mmol/l)	3.4 ± 1.0	3.3 ± 1.0	NS
Total cholesterol/HDL cholesterol	5.1 ± 1.8	4.8 ± 1.9	0.03
Triglycerides (mmol/l)	2.0 ± 1.5	1.9 ± 1.5	NS

Data are presented as the number (%) of patients or mean value ± SD.

ACE = angiotensin-converting enzyme; ASA = acetylsalicylic acid; CAD = coronary artery disease; CFI = collateral flow index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; NS = not significant.

angiographic variables. Statistical significance was set at $p < 0.05$. Data are presented as the mean value ± SD.

RESULTS

Univariate analysis: clinical data. There was no statistically significant difference between the groups in terms of gender, age, body mass index, mean blood pressure, heart rate or left ventricular systolic function and filling pressure (Table 1). Furthermore, there was no significant difference in the cardiovascular risk profile or cardiovascular medical therapy between patients with CFI <0.25 and those with CFI ≥0.25 (Table 1). Total serum cholesterol showed a trend toward higher values in the group with CFI <0.25 than in the group with CFI ≥0.25 ($p = 0.09$). High-density lipoprotein (HDL) cholesterol was significantly lower in the group with CFI <0.25 than in the group with CFI ≥0.25. The ratio between total cholesterol and HDL cholesterol was higher in patients with CFI <0.25 than in the patients with CFI ≥0.25. There was no difference in the serum low-density lipoprotein cholesterol and triglyceride levels between the groups (Table 1).

Patients with previous nontransmural infarctions had a lower CFI than did those without these infarctions, and patients without angina pectoris during the treadmill exercise test had a significantly lower CFI than did those with chest pain (Table 2).

Univariate analysis: coronary angiographic data. Individuals without chronic total coronary artery occlusions revealed a lower CFI than did those with occlusions (Table 2). Patients undergoing CFI measurement in the left anterior descending coronary artery (LAD) had a lower CFI than did those with left circumflex coronary artery (LCx) or right coronary artery (RCA) CFI measurements (Table 2). There were significant differences between the groups in percent diameter stenosis of the lesion undergoing PTCA, in the number of total coronary occlusions, in the number of vessels affected by CAD, in the total number of stenoses and in the area at risk of myocardial infarction (Table 3). Percent diameter stenosis correlated directly with the CFI (Fig. 1). Area at risk of myocardial infarction was directly and significantly associated with the CFI (Fig. 2). When the CFI was measured in the LAD, it occurred more frequently in the group with CFI <0.25 than in the group with CFI ≥0.25 (Table 3).

Frequency distribution of collateral flow and collateral channel assessment. The CFI distribution in our study group is shown in Figure 3. On average, CFI was 0.22 ± 0.15. The CFI was <0.25 in 307 patients (68%) and ≥0.25

Table 2. Univariate Analysis: Variables Related to Collateral Flow

Variable	CFI	p Value
Previous non–Q-wave myocardial infarction		
Yes (n = 50)	0.17 ± 0.12	
No (n = 400)	0.23 ± 0.15	0.01
Treadmill exercise test with angina pectoris		
Yes	0.27 ± 0.17	
No	0.20 ± 0.16	0.01
Presence of chronic total coronary occlusion		
Yes	0.30 ± 0.18	
No	0.19 ± 0.14	< 0.0001
Coronary arteries undergoing CFI measurement		
LAD (n = 255)	0.19 ± 0.13	
LCX (n = 90)	0.25 ± 0.16	0.0008*
RCA (n = 105)	0.25 ± 0.17	0.0003*

*Compared with LAD. Data are presented as the mean value ± SD.
CFI = collateral flow index; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

in 143 patients (32%) (Table 3, Fig. 3). The mean CFI in these groups was 0.14 ± 0.07 and 0.38 ± 0.14, respectively. This distribution was consistent, irrespective of the method of assessing CFI. The CFI_v was 0.16 ± 0.07 and 0.40 ± 0.18, whereas CFI_p was 0.13 ± 0.1 and 0.33 ± 0.14, respectively, in the two groups. Angina pectoris during balloon occlusion occurred in 67% of patients with insufficient collateral channels and in 42% of those with sufficient collateral channels ($p < 0.0001$). In the group of patients with insufficient collateral flow, 84% of the patients developed ST-segment elevations >1 mm on the intracoronary ECG during balloon occlusion of the artery, whereas only 26% did so in the group with sufficient collateral flow ($p < 0.0001$). The degree of angiographic collateral flow (grades 0 to 3) differed significantly between the two groups (Table 3).

Multivariate analysis. Multiple regression analysis with CFI as the dependent variable revealed that the 32 clinical and angiographic variables described in the Methods section accounted for 32% of the CFI variability ($p = 0.0048$). Introducing all of the variables for collateral channel assessment (Table 3), in addition to the clinical variables, into the model yielded 95% of the independent variables accounting for CFI variability. Using the clinical and angiographic variables in the model, percent diameter stenosis of the lesion undergoing CFI measurement (i.e., PTCA) was the only independent predictor of a high CFI ($p < 0.0001$).

Table 3. Univariate Analysis: Coronary Angiographic Data and Collateral Channel Assessment

	CFI <0.25 (n = 307)	CFI ≥0.25 (n = 143)	p Value
Coronary angiographic data			
Percent diameter narrowing of stenosis	76 ± 14	82 ± 15	< 0.0001
No. of chronic total occlusions	35 (16%)	50 (35%)	< 0.0001
No. of vessels diseased	1.8 ± 0.7	2.0 ± 0.8	0.04
No. of stenoses	2.9 ± 1.8	3.4 ± 2	0.01
Area at risk of myocardial infarction	0.46 ± 0.2	0.51 ± 0.2	0.04
Vessel undergoing CFI measurement (i.e., PTCA)			
LAD	185 (60%)	70 (49%)	0.03
LCx	61 (19%)	29 (20%)	NS
RCA	65 (21%)	40 (28%)	NS
Collateral assessment			
CFI*	0.14 ± 0.07	0.38 ± 0.14	< 0.0001
CFI_v (n = 217)	0.16 ± 0.07	0.40 ± 0.18	< 0.0001
CFI_p (n = 328)	0.13 ± 0.1	0.33 ± 0.14	< 0.0001
Angina pectoris during PTCA	206 (67%)	60 (42%)	< 0.0001
Intracoronary ECG			
Insufficient collateral flow	258 (84%)	37 (26%)	< 0.0001
Sufficient collateral flow	49 (16%)	106 (74%)	< 0.0001
Degree of angiographic collateral flow (0–3)	0.55 ± 0.73	1.45 ± 1.07	< 0.0001

*CF_v or CFI_p or average of both when measured simultaneously (n = 112). Data are presented as the mean value ± SD or number (%) of patients.
CFI_v = Doppler flow velocity-derived CFI; CFI_p = pressure-derived CFI; ECG = electrocardiogram; PTCA = percutaneous transluminal coronary angioplasty. Other abbreviations as in Table 2.

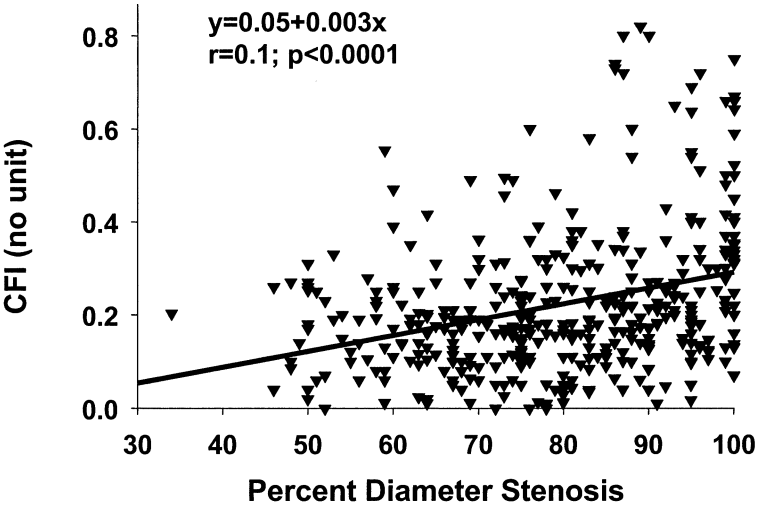

Figure 1. Collateral flow index (CFI; no unit) versus percent diameter narrowing of the stenosis to be dilated. The CFI is higher in patients with more severe coronary artery stenosis.

DISCUSSION

The present analysis in 450 patients with CAD revealed that a well-developed collateral circulation, as assessed quantitatively, is pathogenetically influenced only by the severity of coronary atherosclerosis. Collateral flow sufficient to prevent myocardial ischemia during coronary occlusion was found in only one-third of the patients.

Frequency distribution of collateral flow in humans. As shown by Vanoverschelde et al. (25), in selected patients with total coronary artery occlusions, in the absence of myocardial infarction, collateral flow to the myocardial region in need can be as high as 60% to 80% of normal perfusion. Recent investigations in rather small groups have revealed that well-developed collateral channels are present in one-fourth to one-half of patients with CAD, and such anastomoses have been defined to conduct ~25% of the normal blood flow to the occluded vascular area (10,26). Using the same cut-off value of 25% collateral flow relative to normal flow, the present study found that 32% of patients had collateral channels sufficient to prevent myocardial ischemia during brief coronary occlusions. This investigation is sufficiently powered to reliably document, for the first time, to the best of our knowledge, the Poisson distribution of collateral flow, with ~40% of the patients having a CFI <0.15 and, at the higher end of the range, only ~10% of the patients (n = 44) having a recruitable CFI ≥0.4 (Fig. 3).

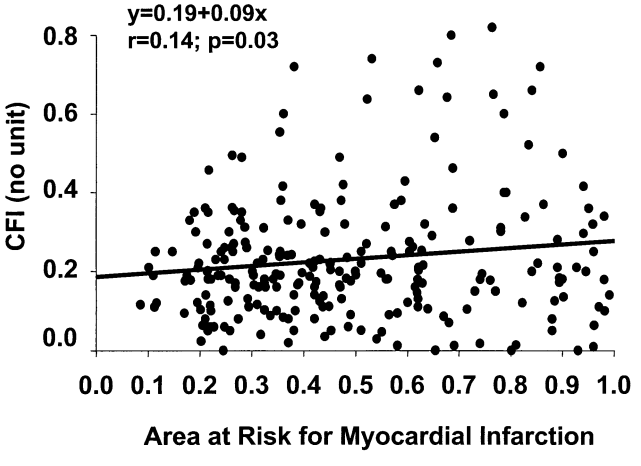

Figure 2. Collateral flow index (CFI; no unit) versus area at risk of myocardial infarction. The CFI is higher in patients with a larger area at risk of myocardial infarction distal to the stenosis to be dilated.

Protective potential of collateral channels in humans. The question may be raised as to whether the definition used for sufficient collateral flow (i.e., CFI ≥0.25) is reasonable. Pijls et al. (27) predicted absent ischemia correctly in all of 29 subjects with no ECG signs of ischemia induced by 1- to 2-min coronary balloon occlusions, and in our study, ischemia was predictable in 107 (75%) of 143 patients. Angina pectoris occurring during balloon occlusion could be predicted much less reliably (i.e., in only 42%) in patients with a CFI ≥0.25. Regarding the clinical end point of myocardial necrosis after revascularized acute coronary thrombotic occlusion, Lee et al. (26) demonstrated that patients with sufficient collateral flow were not free of it. However, they also made it clear that among patients with well-developed collateral channels, infarct size no longer depended on how long it took to open the vessel, but rather on how extensively the collateral channels were developed. These findings are consistent with the concept introduced 20 years ago by Reimer et al. (28), who stated that infarct size is a product of coronary occlusion time (in case of sufficient collateral flow being a constant >0), the ischemic area at risk of infarction and the inverse of collateral flow to it. Aside from the apparent relationship between occlusion duration and collateral flow, another relationship—that between area at risk and "natural bypasses" to it—becomes intuitively evident. Although the correctness of such a relationship in which there is a declining area at risk (as the

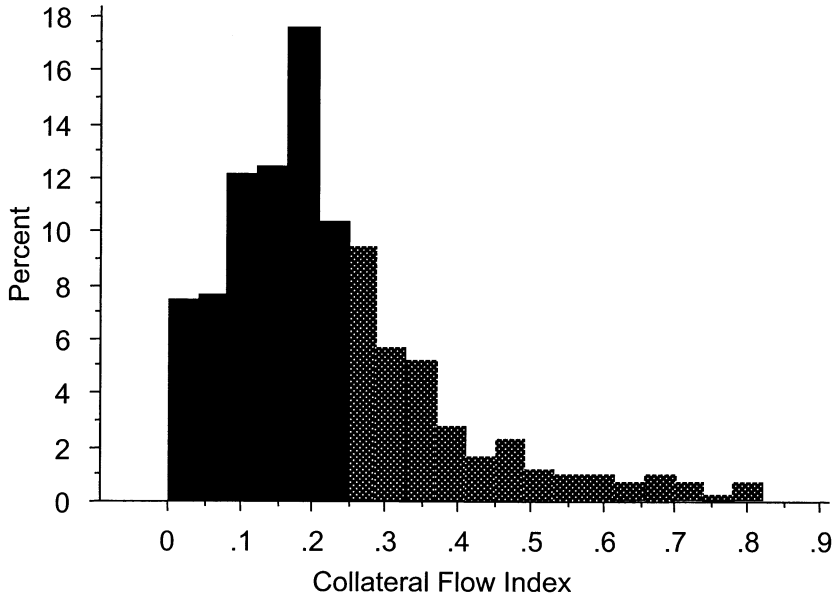

Figure 3. Frequency distribution (expressed as percentage of entire population) of pressure- and Doppler flow velocity-derived collateral flow index (CFI) (no unit) in 450 patients with coronary artery disease. Sixty-eight percent of the patients had a CFI <0.25 **(white-spotted columns)**, indicating collateral flow insufficient to protect the myocardium from ischemia during coronary occlusion. Patients with a CFI ≥0.25 are indicated by the **solid black columns**.

dependent variable), as influenced by augmented collateral flow, was not tested in our study, an additional hypothesis of improved collateral channel development (as the dependent variable), related to greater ischemic risk territories, was verified by univariate analysis (Fig. 2).

Factors influencing collateral channel development in humans. Closely related to the finding just discussed, proximal stenosis location (i.e., a nominal variable for area at risk of infarction) has been found to be an independent variable related to recruitable collateral channels, aside from stenosis severity and duration of angina pectoris (29). Although our categories of proximal, mid and distal stenosis location were perfectly associated ($p < 0.0001$; data not shown) with angiographically determined area at risk, the relationship documented by Piek et al. (29) could not be reproduced. This may be explained by the unexpected result of our investigation that collateral flow to the LAD was consistently lower than that to the LCx or RCA, although it was the LCx and not the LAD with the lowest number of proximally located stenoses (approximately one-third vs. one-half in LAD vs. RCA, respectively; results not shown). Percent diameter coronary artery narrowing—the only variable consistently described as an independent predictor of well-developed collateral channels (30,31)—was corroborated in our study. The fact that the presence of chronic total occlusion was also linked to improved collateral flow supports the finding of stenosis severity as a predictor of a high CFI, biologically. Pathophysiologically, it is reasonable that stenosis severity is *the* variable influencing preexisting, likely ischemia-induced, small collateral channels to become conductive anastomoses, because the perfusion pressure gradient directed toward the blocked vascular area leads to an increase in flow velocity and shear forces within the preformed collateral channels, thus causing their dilation and remodeling (32).

Inconsistently described pathogenetic factors related to impaired collateral development are old age (33), female gender (6), high heart rate (34), hypercholesterolemia (8), systemic hypertension (9) and cardiovascular drugs such as nitrates (29) and spironolactone (35). In our study, elevated HDL cholesterol showed an association with a high CFI, although it did not manifest itself as an independent predictor. Accordingly, a history of hypercholesterolemia was not related to impaired, recruitable collateral flow, nor was the presence of any other cardiovascular risk factors. This is reiterated here with regard to a recently published study in which a group of patients with diabetes mellitus had a worse degree of angiographic collateral flow than that in the nondiabetic control group (6). Unfortunately, this well-powered study did not angiographically measure the recruitable collateral score, and more importantly, the only variable constantly described to influence collateral channel development—coronary stenosis severity—was estimated visually, thus practically excluding it from suitable analysis.

Study limitations. Our study group is not representative of *all* patients with CAD, because of a selection bias. Excluded from the study were patients with myocardial infarction in the vascular territory undergoing collateral flow measurement. Patients with an extensively developed coronary collateral network, which prevents myocardial ischemia, even during exercise, do not suffer from angina pectoris and therefore do not need to undergo coronary angiography. Thus, the frequency of patients with CAD and extremely well-adapted collateral flow to a myocardial area in need may be underestimated.

Our study group consisted of a nonuniform group of

patients with variably severe CAD, ~10% of whom had a nontransmural myocardial infarction; these facts may have confounded the interpretation of the data.

The duration of angina pectoris was not determined, so this variable could not be used reliably for data analysis in our study. Thus, this factor may have theoretically been overlooked as predictor of well-developed collateral channels.

Conclusions. This large clinical study of patients with CAD and quantitatively assessed collateral flow reveals that two-thirds of the patients do not have enough collateral flow to prevent myocardial ischemia during coronary occlusion, and that coronary lesion severity is the only independent pathogenetic variable related to collateral flow.

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