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Coronary Collaterals during Single-Vessel Coronary Angioplasty: Effects of Nitroglycerin

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Summary

Background: Although the protective role of collaterals in coronary artery disease (CAD) is well known, the influence of drugs on collateral function remains controversial.

Hypothesis: We aimed to investigate prospectively the prevalence of spontaneously visible and recruitable coronary collaterals in consecutive patients with single-vessel CAD and the effect of systemic administration of nitroglycerin on these types of collaterals during percutaneous transluminal coronary angioplasty (PTCA).

Methods: Ipsi- and contralateral coronary artery contrast injections were performed before and during PTCA. Simultaneously with balloon occlusion, we measured coronary artery occlusion pressure via the balloon catheter. All measurements were repeated after administration of 0.5 mg of nitroglycerin intravenously.

Results: Of 101 consecutive patients, 24% had spontaneously visible and 30% had recruitable collaterals. Contralateral collaterals were five times more frequent than ipsilateral collaterals. Presence of collaterals was highly associated with the degree of coronary stenosis. Coronary occlusion pressure was higher in patients with than in those without collaterals. Collaterals prevented pain and ischemia during PTCA, and in this respect spontaneously visible collaterals were more effective than recruitable collaterals. There was no effect of systemic administration of nitroglycerin on appearance or occlusion pressure of coronary collaterals.

Conclusion: Coronary collaterals were found in more than half of patients with single-vessel CAD, as the prevalence of recruitable collaterals was slightly higher than that of spontaneously visible collaterals. Nitroglycerin did neither recruit nor augment coronary collaterals.

Key words: recruitable coronary collaterals, spontaneously visible coronary collaterals, coronary artery disease, nitroglycerin

Introduction

Coronary collaterals are thin-walled, nonfunctional conduits in healthy subjects. Once they are recruited secondary to failure of the native vessel to supply sufficient flow, collaterals undergo histologic and anatomic transformation.[1] The presence of collaterals may preserve function in myocardium supplied by diseased coronary arteries, limit infarct size, and prevent left ventricular aneurism formation following acute myocardial infarction.[2] The effectiveness of various drugs in the development and function of collaterals remains controversial. Although nitroglycerin has been suggested to dilate collateral vessels, most of this information comes from animal experiments or indirectly from perfusion studies in humans.[3–6] In this prospective study, we aimed to characterize patients with and without coronary collaterals and to evaluate the effects of systemic administration of nitroglycerin on both visible and recruitable coronary collaterals.

Methods

Patients

Consecutive patients with stable angina pectoris and single-vessel CAD (> 50% luminal diameter stenosis) undergoing elective percutaneous transluminal coronary angioplasty (PTCA) were studied. Antecedent angiograms were performed 3 days to 4 months (mean 1 month) before PTCA. Exclusion criteria comprised previous coronary artery bypass

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surgery or PTCA, multilesion single-vessel disease, valvular disease, overt heart failure, bundle-branch block in the electrocardiogram (ECG), peripheral artery disease limiting access to both femoral arteries, renal failure, severe hypertension, and inability to give informed consent.

Procedure

All patients took aspirin and were given an intravenous bolus of 10,000 U of heparin pre-PTCA. Angioplasty was performed with over-the-wire systems (Baxter Healthcare Corp., Irvine, Calif., USA; Scimed, Galway, Ireland; Medtronic, Inc., Minneapolis, Minn., USA, balloon sizes 3.0–3.5 mm). Ipsi- and contralateral coronary artery injections were performed pre-PTCA to demonstrate spontaneously visible collaterals. After PTCA, the balloon catheter was reintroduced to the site of the lesion. After more than 30 s of low pressure (2 bars) balloon inflation, repeated ipsi- and contralateral coronary artery contrast injections were performed simultaneously with measurements of coronary artery occlusion pressure and aortic pressure measured at the tip of the guiding catheter (no side holes). After removal of the guidewire, coronary artery occlusion pressure was measured via the fluid-filled catheter lumen during balloon inflation by means of a 59-UCAL Uniflow pressure transducer simulator/tester (Baxter Healthcare Corp.); the simulator incorporated a specially designed pressure cylinder and precision solid-state transducer for generating and measuring pressures in the range 0–300 mmHg, with a resolution of 1 mmHg. Accuracy with this equipment is ± 1% of readings and repeatability and hysteresis 0.15% of full scale output. All pressures were simultaneously recorded on a Siemens Elema Mingograph 7 multichannel recorder (sensitivity 1–2 mmHg) (Siemens plc., Hamburg, Germany). The coefficient of variation of 36 duplicate coronary artery occlusion pressure measurements was found to be 0.01. Interobserver variability tested in 10 patients was ± 1 mmHg. Per-procedure ST-segment depression ≥ 0.1 mV, 80 ms after the J point, in at least two leads (12-lead ECG) was considered significant. Pain intensity was recorded on a 0–10 scale. Recruitable collaterals were not visible on the routine angiogram, but visible during proximal occlusion of the recipient coronary artery. Spontaneously visible or recruitable collaterals ≥ grade 1 (range 0–3) in accordance with the Rentrop classification[7] were noted by three independent observers. After PTCA and all measurements had been performed, we gave nitroglycerin 0.5 mg intravenously and repeated the entire procedure and all measurements.

Statistics

Mean or median values are shown. Differences between continuous variables were evaluated using the Student's *t*-test or Mann Whitney U-test, while differences between categorical variables were tested using the chi-square test. Associations between continuous outcome variables and explanatory variables were tested using simple or logistic regression techniques. Independent determinants of collaterals, including univariate determinants with $p < 0.2$, were evaluated by stepwise multivariable elimination from the saturated model. The significance level was $p < 0.05$. All patients gave informed consent and the study was approved by the local ethics committee. The investigations were in accordance with the Declaration of Helsinki.

Results

Of 121 consecutive patients with single-vessel CAD, 101 patients fulfilled the inclusion/exclusion criteria. We found spontaneously visible collaterals in 24 patients, recruitable collaterals in 30, and no collaterals in 47. Of the 54 patients with collaterals, 45 had contralateral collaterals only, 3 had ipsilateral collaterals only, and 6 had both. There were no major baseline differences between patients with spontaneously visible, recruitable, or no collaterals, except that fewer women than men had collaterals (Table I). Presence of collaterals was not related to the type of diseased coronary arteries (Table II). However, the presence of collaterals was highly associated with the degree of coronary artery stenosis/occlusion (Fig. 1). Of 43 patients with previous myocardial infarction, 30% had spontaneously visible and 30% had recruitable collaterals.

One patient suffered a Q-wave myocardial infarction 18 h after PTCA. Successful PTCA was followed by the immediate disappearance of spontaneously visible collaterals. During renewed balloon occlusion, the collaterals were recruited to the same extent as before PTCA. Pain > grade 2 (range 0–10) during balloon occlusion occurred in 26% of patients with recruitable or spontaneously visible collaterals and in 72% of patients with no collaterals ($p = 0.00001$). Patients with recruitable collaterals had a higher incidence of chest pain during PTCA than did patients with spontaneously visible collaterals ($p = 0.048$) and a lower incidence than patients with no collaterals ($p = 0.001$). Ischemic ST-segment changes during PTCA were observed in 13% of patients with spontaneously visible, in 30% of patients with recruitable, and in 89% of patients with no collaterals (Fig. 2). Coronary artery occlusion pressure was stable 30 s after balloon occlusion and correlated with the grade of angiographic evidence of collateral circulation (Fig. 3). Mean occlusion pressure was 40 mmHg in the group with spontaneously visible collaterals, 31 mmHg in patients with recruitable, and 20 mmHg in patients with no collaterals ($p < 0.0001$). An occlusion pressure of ≥ 36 mmHg was found exclusively in patients with collaterals. The discriminatory occlusion pressure for no collaterals was ≤ 17 mmHg. Fifteen patients who developed spasms during PTCA and who received nitroglycerin for that reason were not included in the nitroglycerin part of the study. In the remaining 86 patients, mean base line occlusion pressures of 40, 32, and 21 mmHg did not differ from the values of 42, 30, and 19 mmHg after nitroglycerin administration in the groups with spontaneously visible, recruitable, and no collaterals, respectively. Furthermore, nitroglycerin did not recruit collaterals (ipsi- and contralateral angiograms). The gradient between simultaneously measured coronary occlusion pressure and mean aortic pres-

TABLE I Clinical characteristics of 101 patients with absent, recruitable, or spontaneously visible collaterals

	Absent	Recruitable	Spontaneously visible	p Value
Number of patients	47	30	24	
Age (years)	54 (39–71)	50 (28–64)	53 (40–68)	0.06
Female gender (n)	12	3	1	0.04
Family history (n)	41	28	24	0.16
Diabetes mellitus (n)	2	1	1	0.42
Smoking history (n)	42	27	23	0.64
Hypertension (n)	9	4	5	0.73
Cholesterol (mmol/l)	6.34	6.05	6.18	0.19
Heart failure (NYHA I+II) (n)	9	6	6	0.84
Myocardial infarct (n)	17	13	13	0.35
Q-wave (n)	9	7	8	0.37
Angina duration (months)	13.6 (0–60)	18.5 (1–96)	12.9 (1–60)	0.43
Angina at rest (n)	31	16	12	0.35
Angina episodes per week	20 (0–45)	7 (0–42)	4 (0–42)	0.53
Beta blockade (n)	26	17	12	0.88
Calcium antagonists (n)	31	21	14	0.67
Nitrates (n)	26	18	14	0.34

Data are expressed as mean (range) or n = number of patients. There was no intake of medicine the day of examination.
Abbreviation: NYHA = New York Heart Association functional class.

TABLE II Angiographic characteristics of 101 patients with absent, recruitable, or spontaneously visible collaterals

	Absent	Recruitable	Spontaneously visible	p Value
Number of patients	47	30	24	
Diseased artery				0.10
LAD (n)	32	18	10	
RCA (n)	8	6	9	
Cx (n)	6	5	3	
Obtuse marginal (n)	1	1	0	
Diagonal branch (n)	0	0	2	
EF (%)	69 (39–80)	65 (41–80)	64 (37–77)	0.10
LVSP mmHg	146 (90–200)	127 (92–200)	126 (93–185)	0.10
LVEDP mmHg	15 (6–28)	15 (10–26)	15 (8–28)	0.83
Occluded vessels (n)	2	10	17	0.0001
Stenosis pre PTCA (%)	81 (50–100)	87 (65–100)	94 (60–100)	0.0001
Stenosis post PTCA (%)	17 (0–35)	17 (0–40)	18 (0–35)	0.45

Abbreviations: n = number of patients, Cx = circumflex coronary artery, EF = ejection fraction, LAD = left anterior descending coronary artery, LVEDP = left ventricular end-diastolic pressure, LVSP = left ventricular systolic pressure, PTCA = percutaneous transluminal coronary angioplasty, RCA = right coronary artery.

sure was 61 mmHg in patients with spontaneously visible, 68 mmHg in patients with recruitable, and 77 mmHg in patients with no collaterals (Fig. 4); there was a significant difference between patients with spontaneously visible and no collaterals ($p = 0.0007$) and between patients with recruitable and no collaterals ($p = 0.02$), but not between patients with spontaneously visible and recruitable collaterals ($p = 0.13$). In the logistic regression analysis, only coronary occlusion pressure and pain during PTCA were independently associated with the presence of collaterals with odds ratios (95% confidence interval) of 1.87 (1.25–2.78) and 0.02 (0.00–0.78), respectively.

Discussion

In this consecutive series of patients with single-vessel coronary artery disease, we found spontaneously visible and recruitable collaterals in 24 and 30% of patients, respectively. The prevalence of contralateral collaterals was several times higher than that of ipsilateral collaterals. The study confirmed that collaterals are primarily seen in patients with severe coronary artery stenoses,[8,9] whereas we found no association between presence of collaterals and angina duration or severity. Coronary occlusion pressure was higher in arteries with spon-

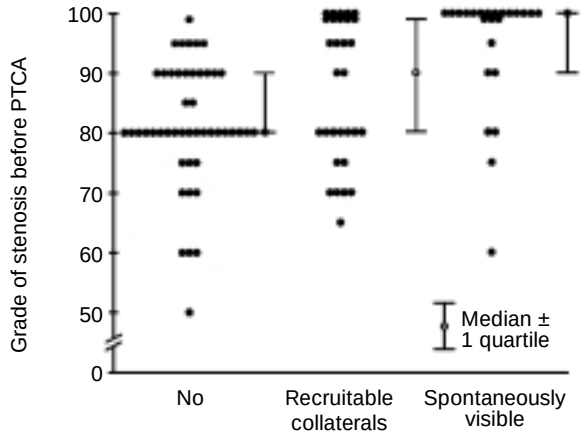

FIG. 1 Relationship between coronary collaterals and coronary artery stenosis severity in 101 patients ($p < 0.0001$). PTCA = percutaneous transluminal coronary angioplasty.

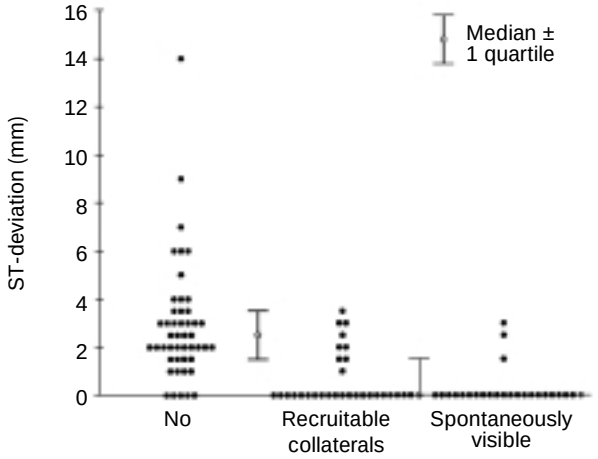

FIG. 2 Relationship between ischemic ST-segment changes and presence of coronary collaterals during percutaneous transluminal coronary angioplasty ($p < 0.0001$).

taneously visible and recruitable collaterals than in arteries without collaterals. There was, however, a considerable overlap of occlusion pressures among the three groups (Fig. 3). Meier *et al.*[9] found spontaneously visible collaterals to be four times as frequent as recruitable collaterals when they considered collateral filling ≥ grade 2 (Rentrop classification). In contrast, Piek *et al.*[10] found recruitable collaterals to be four times as frequent as spontaneously visible collaterals when using the same criteria of collateralization. By using Rentrop ≥ grade 1 criteria, Piek *et al.*[10] demonstrated spontaneously visible collaterals in 31% and recruitable collaterals in the majority of patients, a finding similar to ours. The ipsilateral contribution to collateral flow has been reported to range from 17% (our study) to 53%.[9] Presence of collaterals prevented chest pains and ST-segment changes during PTCA compared with patients without collaterals, as spontaneously visible collaterals are more effective than recruitable collaterals.

In humans, the effect of nitroglycerin on collateral function has mainly been assessed by means of scintigrams.[5,6] Scintigraphy, however, does not take into account improved myocardial perfusion secondary to nitroglycerin-induced cardiac unloading.[11–13] Piek *et al.* found increased coronary collateral flow (Doppler wire technique) after injection of nitroglycerin into the donor coronary artery in patients with spontaneously visible collaterals (n = 24), but not in patients with recruitable collaterals (n = 11).[14] There was no information whether patients with ipsi- and/or contralateral supply of collaterals had the trial drug injected in either or both donor arteries. If a study drug is given in only the contralateral artery, the ipsilateral arterial contribution (17–53% of cases) will be missed. Further-

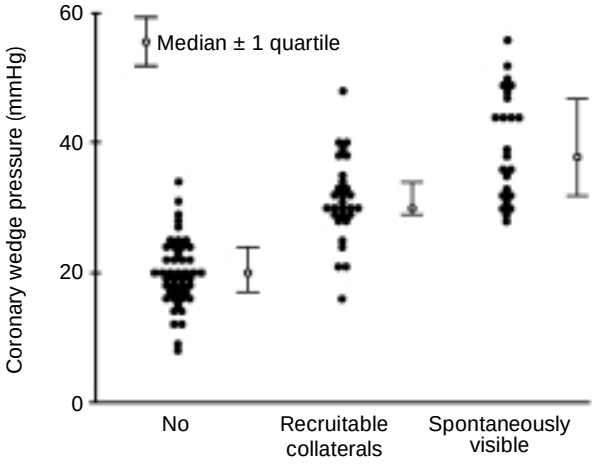

FIG. 3 Relationship between coronary artery wedge pressure during balloon occlusion and angiographic presence of collaterals ($p < 0.0001$).

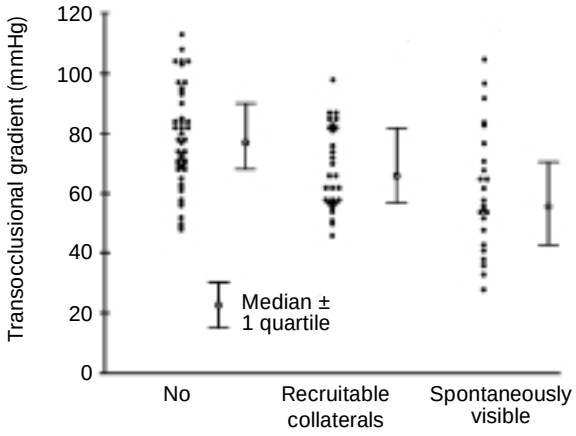

FIG. 4 Aortocoronary occlusion pressure gradients during percutaneous transluminal coronary angioplasty in relation to presence of coronary collaterals.

more, in patients with both ipsi- and contralateral collaterals (11–39%),[9] a simultaneous ante- and retrograd flow increase in the blocked artery may not be observed with the flow catheter in a watershed position, whereas the resultant increase in coronary occlusion pressure is likely to be detected. We found no effect of systemic administration of nitroglycerin on the angiographic presence of collaterals or of coronary occlusion pressure. We therefore speculate that improved myocardial perfusion after nitroglycerin is most likely secondary to cardiac unloading.

Conclusion

The prevalence of recruitable collaterals was slightly higher than that of spontaneously visible collaterals in this consecutive series of patients with single-vessel coronary artery disease. However, spontaneously visible collaterals were better than recruitable collaterals in the prevention of pain and ST-segment deviation during PTCA. Systemic administration of nitroglycerin did not augment or recruit coronary collaterals.

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