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Quantitatively assessed coronary collateral circulation and restenosis following percutaneous revascularization

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Aims A high degree of collateral supply to a vascular area where a percutaneous transluminal coronary angioplasty (PTCA) has been performed represents a haemodynamic force competing with the antegrade flow through the dilated lesion. Therefore, our purpose was to determine whether patients with restenosis following PTCA have a higher collateral flow to the recipient vessel than patients without restenosis.

Methods and Results In 200 consecutive PTCA patients, an intracoronary pressure-derived collateral flow index (CFI) was determined quantitatively during balloon occlusion, using simultaneous measurements of the mean aortic pressure (P_{ao}) and of the intracoronary pressure distal to the occluded stenosis (P_{occl}), as well as the estimated central venous pressure (CVP=5 mmHg): $CFI=(P_{occl}-CVP)/(P_{ao}-CVP)$. Sixty-four patients had an angiographic follow-up examination after at least 2 months, and were subdivided into patients with restenosis (>50% diameter stenosis, n=34) and patients without restenosis (n=30). Patients with restenosis had a significantly higher collateral flow index at the initial coronary angiography than patients without restenosis ($0{\cdot}26 \pm 0{\cdot}14$ vs $0{\cdot}12 \pm 0{\cdot}09$; $P<0{\cdot}0001$).

Conclusions Patients with restenosis after PTCA show a more extended collateral supply to this recipient area than patients without restenosis. Well developed collaterals to a revascularized region are a risk factor for restenosis of the treated lesion.
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Key Words: Coronary artery disease, coronary collateral circulation, intracoronary pressure measurements, angiography, percutaneous transluminal coronary angioplasty, restenosis.

See page 1731 for the Editorial comment on this article

Introduction

Restenosis, the Achilles heel of percutaneous transluminal coronary angioplasty (PTCA), is of multifactorial origin[1] and remains difficult to predict[2]. In accordance with observations from coronary bypass surgery[3] and reports from previous studies using qualitative collateral assessment[4–6], it is conceivable that a high degree of collateral supply to a vascular area where a PTCA has been performed may represent a haemodynamic force competing with the antegrade flow through the dilated lesion. Therefore, well-developed collaterals seem to represent a risk factor for restenosis. The purpose of the present prospective study was to test the hypothesis that patients with restenosis following PTCA have a higher, quantitatively assessed collateral flow to the recipient vessel than patients without restenosis.

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Methods

Patients

Two hundred consecutive patients (age 61 ± 10 years (range 33–85), 160 men, 40 women) with single or multivessel coronary artery disease were included in this prospective study. All of them underwent PTCA of at least one stenotic lesion because of symptoms related to coronary artery disease. Sixty-four of these 200 patients had an angiographic follow-up examination after at least 2 months, and were subdivided into two study groups according to the presence (restenosis group) or absence (no restenosis group) of a restenosis of the coronary artery.

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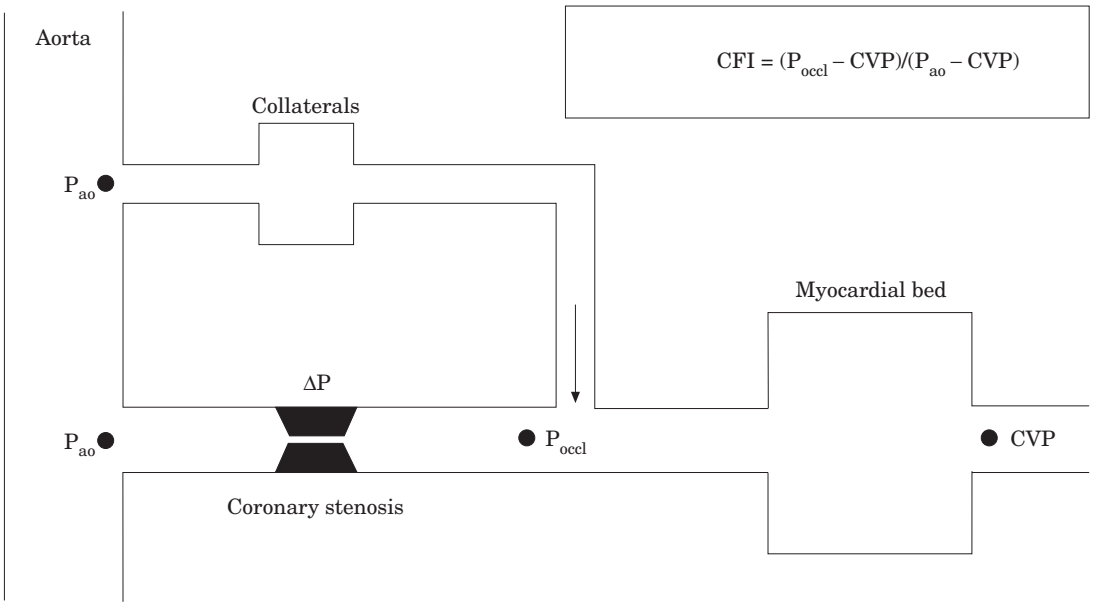

Figure 1 **Schematic representation of a coronary artery stenosis bypassed by collaterals. During balloon occlusion, there is no antegrade flow through the stenosis. Therefore, pressure signals (greater than the central venous pressure, CVP) obtained distal to the occluded stenosis originate from collaterals. They allow the determination of a collateral flow index, which expresses collateral flow as a fraction of normal flow through the patent vessel. This intracoronary pressure-derived collateral flow index (CFI, no unit) can be determined during balloon occlusion of the coronary stenosis, using simultaneous measurements of mean aortic pressure (P_{ao}) and of intracoronary pressure distal to the occluded stenosis (P_{occl}), as well as the estimated central venous pressure.**

This investigation was approved by the institutional ethics committee, and the patients gave informed consent to participate in the study.

Cardiac catheterization and coronary angiography

All patients underwent left heart catheterization for diagnostic purposes. Aortic pressure was measured using the PTCA guiding catheter. Biplane coronary angiography was performed followed by biplane left ventriculography. Coronary artery stenoses were determined by quantitative coronary angiography, using the guiding catheter for calibration. Angiographic collateral degrees (0–3) were determined independently by two observers according to the extent of epicardial coronary artery filling via collaterals with contrast medium from the contralateral side before PTCA: 0=no filling of the distal vessel via collaterals, 1=small side branches filled, 2=major side branches of the main epicardial vessel filled, 3=main epicardial vessel filled by collaterals[7,8].

Collateral assessment

A 0·014 inch (1/3 mm in diameter) fibreoptic pressure monitoring guidewire (Pressureguide®, Radi Medical Systems, Uppsala, Sweden) was set at zero, calibrated, advanced through the guiding catheter and positioned distal to the stenosis to be dilated[9,10]. This pressure wire has been previously validated[11].

The intracoronary pressure-derived collateral flow index (CFI, no unit) was determined by simultaneous measurements of the mean aortic pressure (P_{ao}, mmHg, obtained from the angioplasty guiding catheter) and of the coronary wedge pressure, defined as mean distal coronary artery pressure[12] during balloon occlusion (P_{occl}, mmHg; Fig. 1). The central venous pressure (CVP) was estimated to be equal to 5 mmHg. The collateral flow index was calculated as (P_{occl} − CVP) divided by (P_{ao} − CVP)[11,13] (Fig. 2). Thus, the collateral flow index expresses collateral flow relative to normal flow through the patent vessel.

Study protocol

Following diagnostic coronary angiography, an interval of at least 10 min was allowed for dissipation of the effect of the non-ionic contrast medium on coronary vasomotion. An intracoronary bolus of 0·2 mg of nitroglycerin was given in order to maintain epicardial coronary artery calibres constant. The pressure wire was positioned distal to the stenosis to be dilated. During the entire protocol, an intracoronary ECG obtained from a guidewire[14] and a 3-lead surface ECG were recorded. Mean aortic pressure and distal intracoronary occlusive or wedge pressure were recorded simultaneously during

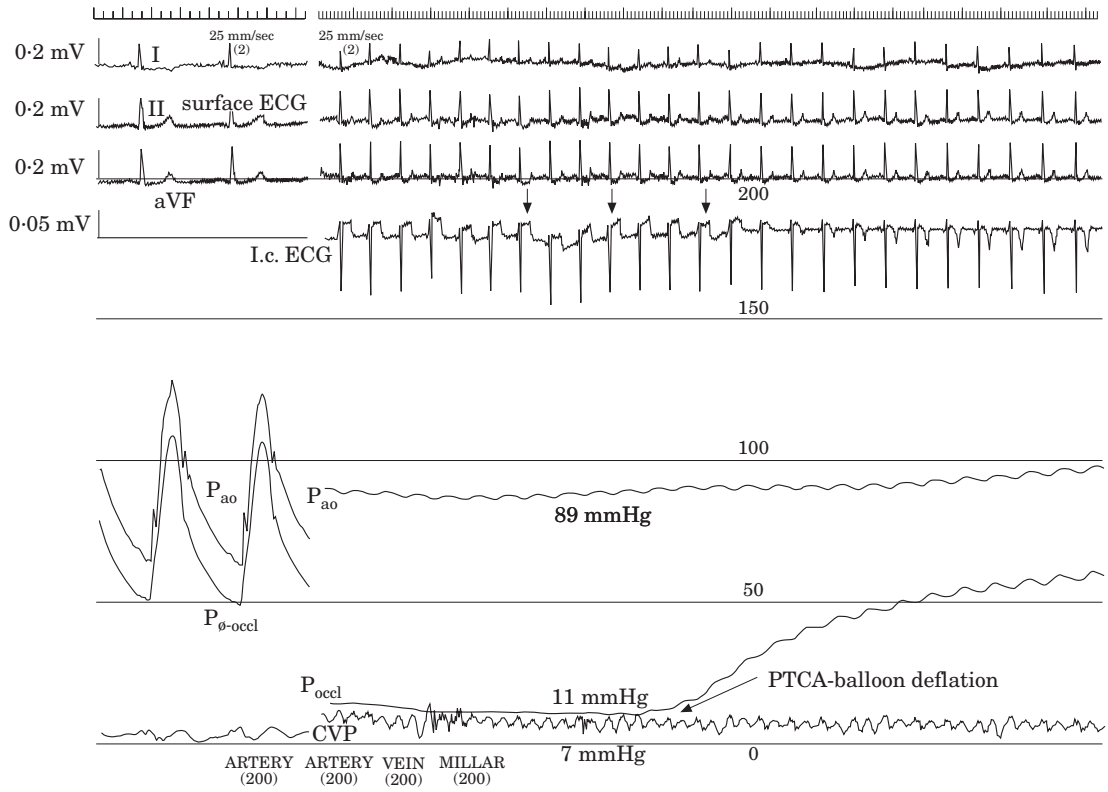

Figure 2 **Simultaneous tracings of mean aortic pressure (P_{ao}), distal coronary artery pressure (P_{occl}), central venous pressure (CVP) and of an intracoronary ECG lead obtained from the pressure guidewire during and after balloon occlusion in a patient with poor collateralization. During balloon occlusion, the distal coronary artery pressure is low, and the intracoronary ECG lead shows marked ST-segment elevations, which regress after balloon deflation. The collateral flow index (CFI, no unit), expressing collateral flow relative to normal flow through the patent vessel, is defined as (P_{occl} − CVP)/(P_{ao} − CVP).**

balloon occlusion. During PTCA, an intracoronary stent was implanted in 43% of cases, at the discretion of the operator.

Follow-up

Only patients with signs or symptoms of myocardial ischaemia, or those scheduled for PTCA of a second lesion underwent a second angiography. In order to be certain that the patients not submitted to re-angiography were free of symptoms, and that no re-angiography had been performed in another centre, a questionnaire was sent to the primary care physicians and cardiologists in charge of the patients, and the patients were also contacted by telephone. Follow-up information was available for all 200 patients, and the length of clinical follow-up was 17 ± 8 months (range 4–32). Ninety-nine re-angiographies were performed in 74 patients, and the previously dilated sites were re-examined by quantitative coronary angiography. A restenosis was defined as a more than 50% diameter reduction of the lumen at the site of the previous PTCA. Sixty-four of 200 patients had a follow-up angiogram at least 2 months after the initial PTCA (mean 8 ± 5 months). These patients were subdivided into patients with restenosis (n=34) and patients without restenosis (n=30).

Statistical analysis

Results are presented as mean value ± 1 SD, or as percentage of patients. Between-group comparison of continuous data were performed by an unpaired two-sided Student's t-test or, where appropriate, by a paired two-sided Student's t-test. A chi-squared test was used for comparison of categorical variables among the two study groups. A *P*-value <0·05 was considered to be statistically significant.

Results

Patient characteristics

The baseline clinical and angiographic characteristics of all 200 consecutive patients as well as of the 64 patients with an angiographic follow-up of at least 2 months are shown in Tables 1 and 2. There were no significant

Table 1 Baseline characteristics

	All patients	Patients with angiographic follow-up	*P*
Number of patients	200	64	
Age, years	61 ± 10 (33–85)	60 ± 10 (33–79)	ns
Male sex (%)	80	73	ns
Smoking (%)	50	45	ns
Hypertension (%)	51	59	ns
Diabetes mellitus (%)	15	14	ns
Hypercholesterolaemia (%)	49	47	ns
Family history of coronary artery disease (%)	37	38	ns
Aspirin (%)	89	88	ns
Beta-blockers (%)	65	60	ns
Calcium antagonists (%)	18	15	ns
Nitrates (%)	38	35	ns
ACE inhibitors (%)	28	32	ns
Lipid-lowering agents (%)	31	24	ns
Diuretics (%)	11	15	ns

ACE=angiotensin-converting enzyme.

Table 2 Baseline angiographic data

	All patients	Patients with angiographic follow-up	*P*
Number of patients	200	64	
Heart rate (beats . min^{-1})	73 ± 12	75 ± 13	ns
Blood pressure (mmHg)	133 ± 25/72 ± 12	135 ± 26/74 ± 12	ns
Left ventricular ejection fraction (%)	66 ± 10	65 ± 10	ns
Number of diseased vessels (%)			ns
One	47	44	
Two	40	39	
Three	13	17	
PTCA vessel (%)			ns
LAD	46	55	
Obtuse marginal branch	3	5	
LCX	17	12	
RCA	34	28	
Stenosis location (%)			ns
Proximal	52	51	
Mid	42	44	
Distal	6	5	
% Diameter stenosis	83 ± 11	83 ± 11	ns
Stent implantation (%)	43	47	ns
Angiographic collateral degree (score 0–3)	1·0 ± 0·9	1·2 ± 1·0	ns
Coronary collateral flow index	0·17 ± 0·12	0·19 ± 0·14	0·044

LAD=left anterior descending coronary artery; LCX=left circumflex coronary artery; PTCA=percutaneous transluminal coronary angioplasty; RCA=right coronary artery.

differences between patients submitted and patients not submitted to re-angiography, with the exception that patients submitted to re-angiography had a higher collateral flow index at baseline angiography. Thirty-four of the 64 patients with angiographic follow-up presented with a restenosis. The interval between the initial PTCA and the angiographic diagnosis of restenosis was 6 ± 4 months.

There were no statistically significant differences among the two groups with (n=34) and without restenosis (n=30) regarding length of angiographic follow-up, age of the patients, gender, haemodynamic variables during baseline cardiac catheterization such as heart rate and blood pressure, and cardiovascular risk factors such as smoking, arterial hypertension, diabetes mellitus, hypercholesterolaemia and family history of coronary artery disease (Table 3). Of the drugs used (Table 3), no differences were observed with respect to beta-blockers, nitrates, ACE inhibitors, diuretics and lipid-lowering agents. Calcium antagonists were administered more

Table 3 Baseline characteristics among patients with and without restenosis

	Restenosis	No restenosis	*P*
Number of patients	34	30	
Age, years	62 ± 10	59 ± 11	ns
Male sex (%)	74	73	ns
Length of clinical follow-up (months)	17 ± 8	17 ± 8	ns
Smoking (%)	44	47	ns
Hypertension (%)	59	60	ns
Diabetes mellitus (%)	18	10	ns
Hypercholesterolaemia (%)	47	47	ns
Family history of coronary artery disease (%)	29	47	ns
Aspirin (%)	97	77	0.01
Beta-blockers (%)	62	57	ns
Calcium antagonists (%)	6	25	0.03
Nitrates (%)	38	32	ns
ACE inhibitors (%)	32	32	ns
Lipid-lowering agents (%)	18	32	ns
Diuretics (%)	10	21	ns

ACE=angiotension-converting enzyme; ns=not significant.

often before the initial PTCA among patients free of restenosis of the dilated lesion. Acetylsalicylic acid was administered more often before the initial PTCA among patients suffering a restenosis during follow-up, but patients on acetylsalicylic acid had a higher collateral flow index at baseline coronary angiography than patients not receiving this drug (0·20 ± 0·14 vs 0·10 ± 0·08; P=0·05).

Baseline angiographic and collateral flow data

For the 64 patients with an angiographic follow-up of at least 2 months, the study groups with and without restenosis did not differ regarding baseline angiographic left ventricular ejection fraction, number of diseased vessels, stenosis location and severity, and frequency of stent implantation (Table 4). Patients with restenosis showed a significantly higher angiographic collateral degree and collateral flow index to this recipient area at baseline coronary angiography than patients without restenosis, respectively 1·6 ± 1·0 vs 0·7 ± 0·7; P<0·0001 (Fig. 3) and 0·26 ± 0·14 vs 0·12 ± 0·09; P<0·0001 (Fig. 4), respectively.

The collateral flow index was similar in patients with single and multivessel disease, did not differ by PTCA vessel and was also not significantly influenced by patient gender or the presence of cardiovascular risk factors (data not shown).

Follow-up angiographic data

In the 34 patients with a restenosis, the severity of the restenosis was not significantly different from the severity of the initial stenosis (84 ± 12% vs 80 ± 16%; P=ns).

Information about the entire study population

Among all our 200 consecutive PTCA patients, there were no statistically significant differences between the patients with angiographically proven restenosis (n=34) and those angiographically or clinically free of restenosis (n=166) regarding age, gender, heart rate and blood pressure, and cardiovascular risk factors. Of the drugs used, only calcium antagonists were administered more often before the initial PTCA among patients free of restenosis of the dilated lesion. The patients with angiographically proven restenosis and those angiographically or clinically free of restenosis also did not differ regarding baseline angiographic left ventricular ejection fraction, number of diseased vessels, frequency of stent implantation and severity of the stenosis before the initial PTCA. Patients with left anterior descending stenoses showed significantly more restenoses. Patients with restenosis also had a significantly higher angiographic collateral degree and collateral flow index at baseline coronary angiography than patients without restenosis, 1·6 ± 1·0 vs 0·9 ± 0·9; P<0·0001 and 0·26 ± 0·14 vs 0·15 ± 0·11; P<0·0001, respectively.

Discussion

This prospective study in patients with coronary artery disease documents that patients with restenosis after PTCA have a significantly higher, quantitatively determined collateral supply to the recipient area than patients without restenosis.

In patients who underwent successful PTCA, the recurrence of the initial lesion constitutes the most important draw-back to long-term event-free survival. Restenosis affects about one third-of patients in whom a narrowed artery has been dilated[15–17], and about 60%

Table 4 Angiographic data among patients with and without restenosis

	Restenosis	No restenosis	*P*
Number of patients	34	30	
Heart rate (beats . min^{-1})	75 ± 14	74 ± 11	ns
Blood pressure (mmHg)			
Systolic	139 ± 28	130 ± 23	ns
Diastolic	74 ± 12	73 ± 12	ns
Left ventricular ejection fraction (%)	66 ± 10	64 ± 11	ns
Number of diseased vessels (%)			ns
One	50	37	
Two	38	40	
Three	12	23	
PTCA vessel (%)			ns
LAD	65	44	
Obtuse marginal branch	6	3	
LCX	6	20	
RCA	23	33	
Stenosis location (%)			ns
Proximal	53	50	
Mid	41	47	
Distal	6	3	
% Diameter stenosis	84 ± 12	82 ± 11	ns
Stent implantation (%)	47	47	ns
Angiographic collateral degree (score 0–3)	1·6 ± 1·0	0·7 ± 0·7	<0·0001
Coronary collateral flow index	0·26 ± 0·14	0·12 ± 0·09	<0·0001

LAD=left anterior descending coronary artery; LCX=left circumflex coronary artery; ns=not significant; PTCA=percutaneous transluminal coronary angioplasty; RCA=right coronary artery.

of those in whom a chronically occluded artery has been recanalized[18,19]. These figures are usually expressed per patient with control angiography and are higher with incomplete follow-up angiographies because of the selection of symptomatic patients. In our study, which did not include a systematic follow-up re-angiography, only patients with signs or symptoms of myocardial ischaemia, or those scheduled for PTCA of a second lesion underwent re-angiography. Our rate of documented restenosis over all PTCA patients was therefore only 17%, and thus only about half the restenosis rate reported in studies restricted to patients with control angiography. However, although many patients with documented restenosis have recurrence of their symptoms, asymptomatic coronary restenosis is known to be a frequent phenomenon, since up to 34%[20] or even 48%[21] of angiographic restenoses were reported to be clinically silent. Therefore, our low overall restenosis rate is probably primarily due to the lack of a systematic re-angiography. Additionally, the restenosis rate is reduced after stent implantation, both for new coronary artery stenoses[22,23], and for restenotic lesions[24]. Therefore, intracoronary stenting (43% overall in our study) might have further reduced the restenosis rate. Restenosis typically occurs 1–3 months after PTCA[25], and in 95% of patients it occurs within 6 months after the procedure. In our study, the minimal clinical follow-up time was only 4 months, a factor which also presumably reduced the restenosis rate.

In our study, 74 of 200 patients underwent a total of 99 re-angiographies. Sixty-four of these patients had a follow-up angiogram after at least 2 months. In this group, the selection bias of symptomatic patients led to a high restenosis rate of 53%.

After surgical coronary artery bypass grafting, an accelerated progression of native vessel disease has been well documented, both in vessels in which the pre-operative diameter stenosis was greater than 50%[26–28], and also in normal segments that lie between a significant stenosis and the bypass graft anasthomosis[29]. This phenomenon has been attributed to increased distal pressure induced by the graft, decreasing transtenotic flow[26,30]. Cashin *et al.*[3] reported that placement of grafts to coronary arteries with less than 50% diameter stenoses produced a major acceleration of atherosclerosis in these vessels. In 85 men who had undergone coronary artery bypass surgery, bypass grafts were placed on 37 arteries with only minimal atherosclerosis. In this group, there were also 93 vessels with only minimal atherosclerosis which were not bypassed. Progression of atherosclerosis was more than 10 times as frequent in bypassed arteries with minimal atherosclerosis than in comparable arteries that were not bypassed.

A few previous studies[4–6] had suggested a negative influence of competitive collateral flow on the long-term results of angioplasty. Urban *et al.*[4] re-evaluated angiographically 100 vessels in 91 patients for which the mean

Table 5 Angiographic data for patients with collaterals sufficient and insufficient to prevent ECG signs of ischaemia during balloon occlusion

	Sufficient collaterals	Insufficient collaterals	*P*
Number of patients	13	51	
Left ventricular ejection fraction (%)	63 ± 12	66 ± 10	ns
Number of diseased vessels (%)			ns
One	46	43	
Two	39	39	
Three	15	18	
PTCA vessel (%)			ns
LAD	69	51	
Obtuse marginal branch	8	4	
LCX	8	14	
RCA	15	31	
Stenosis location (%)			ns
Proximal	69	47	
Mid	31	47	
Distal	0	6	
% Diameter stenosis	83 ± 13	83 ± 11	ns
Angiographic collateral degree (score 0–3)	2·3 ± 0·90	0·9 ± 0·8	<0·0001
Coronary collateral flow index	0·34 ± 0·18	0·15 ± 0·10	<0·0001
Angina pectoris during PTCA (%)	22	89	<0·0001
Stent implantation (%)	38	49	ns
Restenosis (%)	85	45	0·01

LAD=left anterior descending coronary artery; LCX=left circumflex coronary artery; ns=not significant; PTCA=percutaneous transluminal coronary angioplasty; RCA=right coronary artery.

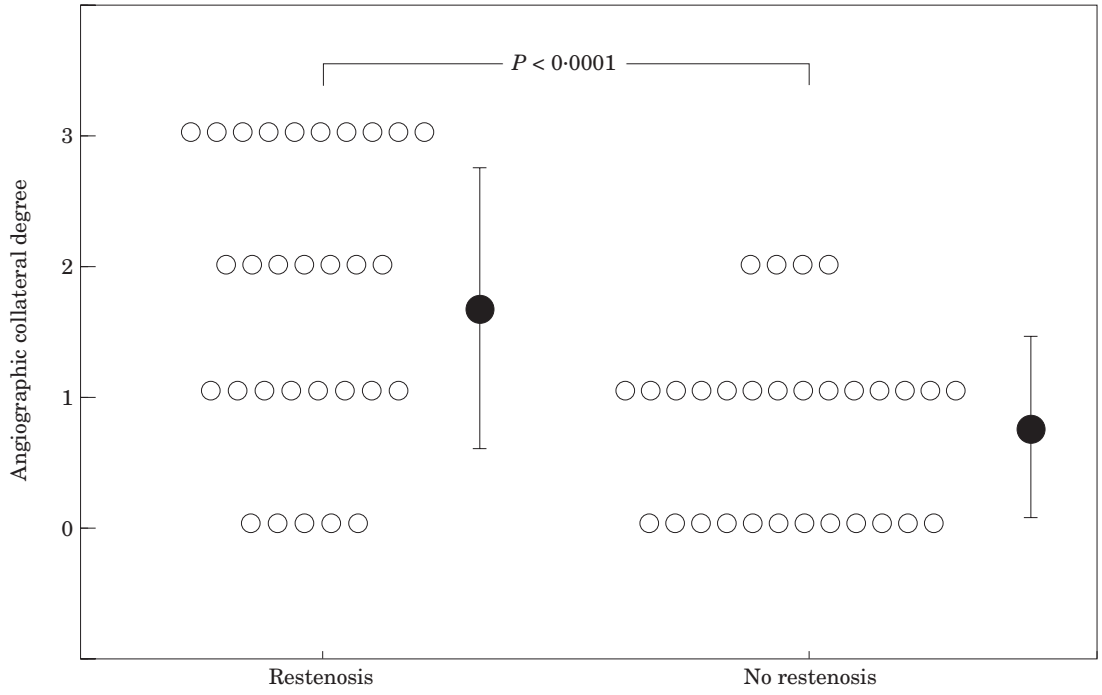

Figure 3 **Plot of the angiographic collateral degree (vertical axis) in patients with and without restenosis. There was a significant difference between both groups. Mean value ± 1 SD is also shown.**

coronary wedge pressure (rounded to the next value divisible by 5) had been measured at the time of the first angioplasty. Restenosis rate was 52% in arteries with a coronary wedge pressure ≥30 mmHg, compared with 23% in those with a coronary wedge pressure <30 mmHg (P<0·01). The mean coronary wedge

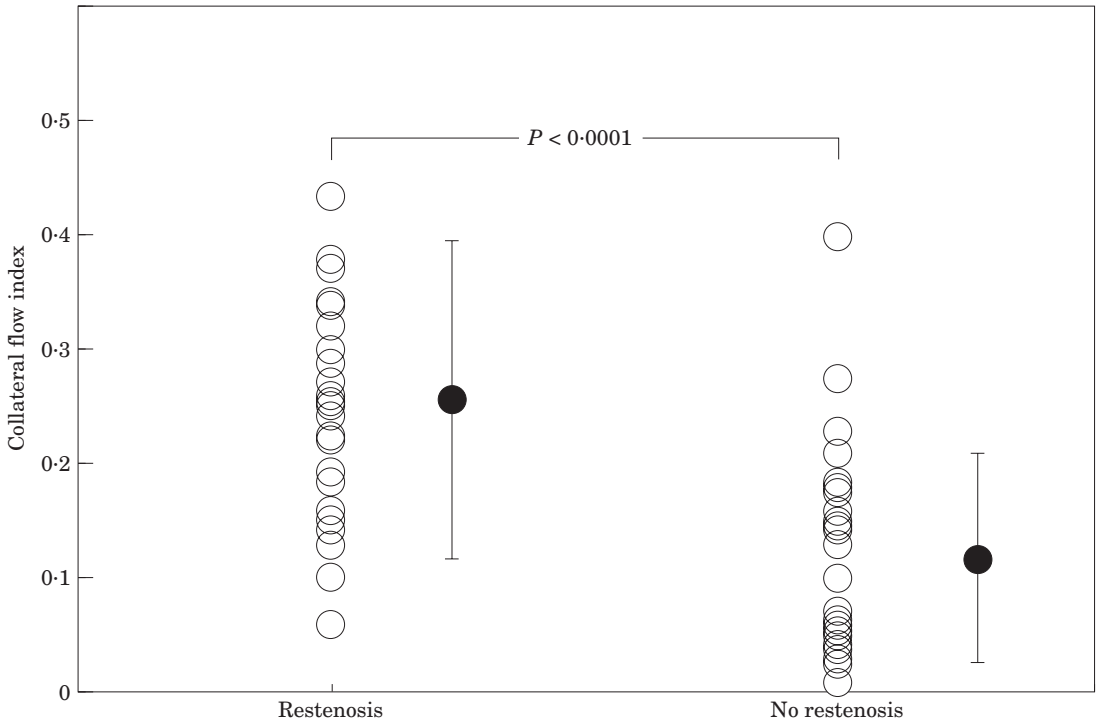

Figure 4 **Plot of the collateral flow index data (vertical axis) in patients with and without restenosis. There was a significant difference between both groups. Mean value ± 1 SD is also shown.**

pressure was significantly higher for the 37 vessels with restenosis (30 ± 10 mmHg) than for the 63 vessels without restenosis (26 ± 9; $P<0·01$).

Probst *et al.*[5] angiographically estimated the collaterals at the time of PTCA in 104 patients. In a subset of 49 patients, systolic coronary pressure was also determined, and used as coronary wedge pressure. Patients with angiographically visible collaterals had a significantly higher incidence of restenosis after 4 to 7 months than those without visible collaterals (46% vs 26%; $P<0·05$). Patients with a systolic coronary pressure ≤45 mmHg had a significantly lower restenosis rate than those with a coronary wedge pressure >45 mmHg (23% vs 53%; $P<0·05$). The estimation of collateral flow using the coronary wedge pressure alone is, however, substantially influenced by the systemic perfusion pressure, which has been accounted for in the present study. Nakae *et al.*[6] angiographically examined 124 patients undergoing primary coronary angioplasty within 12 h of the onset of a first acute myocardial infarction. Restenosis occurred in 38% of 69 patients with angiographically poor or no collateral circulation, in contrast to 64% of 55 patients with angiographically good collateral circulation ($P<0·005$).

It is noteworthy that, according to a previous study from this laboratory[11], a collateral flow index threshold of 0·30 very accurately distinguished collaterals sufficient to prevent ECG signs of ischaemia during PTCA from those insufficient to prevent ECG signs of ischaemia. Sufficient collaterals could be diagnosed with 75% sensitivity and 92% specificity by intracoronary pressure measurements. In this study, patients with collaterals sufficient to prevent ECG signs of ischaemia during balloon occlusion had a significantly higher collateral flow index and angiographic collateral degree than patients with insufficient collaterals, and presented less angina pectoris during balloon occlusion (Table 5). Among our 64 patients with an angiographic follow-up of at least 2 months, patients with sufficient collaterals (n=13) had a restenosis rate of 85%, compared with a restenosis rate of 45% in patients with insufficient collaterals (n=51; $P=0·01$). Among all our 200 patients, of whom 44 had sufficient and 156 insufficient collaterals, this difference did however not reach statistical significance (25% vs 15%, $P=0·11$).

Therefore, the presence of collaterals sufficient to prevent ECG signs of ischaemia during PTCA appears to be a risk factor for restenosis of the dilated lesion.

Study limitations

The most serious limitation of our study is the lack of systematic re-angiography. Only 99 re-angiographies were performed in 74 patients, and only 64 of the initial 200 patients had an angiographic follow-up of at least 2 months. The number of analysable patients was thus reduced to around one-third of the initial cohort, and the selection bias of symptomatic patients led to a restenosis rate per follow-up angiography of 53%.

In conclusion, this study confirms previous qualitative observations that patients showing a restenosis

following PTCA have a superior quantitatively assessed collateral supply to the recipient vessel than patients without restenosis. Thus, well-developed collaterals to a revascularized region are a risk factor for restenosis of the treated lesion.

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