

Coronary flow reserve in the contralateral artery increases after successful coronary angioplasty in patients with spontaneously visible collateral vessels

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Abstract

Objective—To test the hypothesis that coronary flow reserve could increase in the angiographically normal contralateral artery after successful coronary angioplasty of an ipsilateral coronary artery.

Design—Coronary flow reserve was estimated using a Doppler flow guide wire, by giving intracoronary adenosine in the contralateral artery, before and 15 minutes after the end of angioplasty.

Setting—Tertiary referral centre.

Patients—31 patients, mean (SD) age 56 (11) years, with stable angina and single vessel disease, undergoing angioplasty of the right coronary or the left anterior descending artery.

Results—In the contralateral artery baseline average peak velocity was 21 (9) cm/s before angioplasty and decreased to 12 (6) cm/s after ($p < 0.005$), while hyperaemic average peak velocity was 47 (19) cm/s before and decreased to 34 (15) cm/s after ($p < 0.005$). However, coronary flow reserve in the contralateral artery was 2.4 (0.7) before angioplasty and increased to 2.9 (0.6) after ($p < 0.05$). The contralateral coronary flow reserve after angioplasty increased by 0.8 (0.4) in 11 patients with visible collaterals before angioplasty and by 0.3 (0.6) in the remaining patients without visible collaterals ($p < 0.05$). Blood pressure and heart rate were unchanged after the procedure.

Conclusions—Coronary flow reserve in an angiographically normal contralateral artery increases after successful coronary angioplasty of the ipsilateral artery in patients with spontaneously visible collateral vessels before the procedure.

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Keywords: coronary flow reserve; contralateral coronary artery; angioplasty

A reduced coronary flow reserve after the administration of dipyridamole has been reported in regions supplied by angiographically normal arteries in patients with atherosclerosis without previous infarction.^{1 2} The impairment of vasodilator reserve may be an early manifestation of microvascular endothelial dysfunction in the presence of angiographically undetectable coronary atherosclerosis.^{3 4} A possible explanation for decreased coronary and myocardial flow reserve in patients with atherosclerosis in areas without significant artery stenosis is the provision of collateral vessels to other diseased segments. Under these circumstances one would expect that removing the burden of the collateral blood flow from the normal contralateral arteries by angioplasty to the stenotic arteries would increase the coronary flow reserve in the contralateral arteries.

Our aim in this study was to test the hypothesis that coronary flow reserve could increase in the angiographically normal contralateral artery after successful coronary angioplasty of a remote artery.

Methods

This was a prospective study of 31 patients who underwent coronary angioplasty for the treatment of single vessel disease, either of the left anterior descending or of the right coronary artery, with a stenosis $> 70\%$, normal left ventricular ejection fraction, and dominant right coronary artery (table 1). All patients had objective evidence of myocardial ischemia on non-invasive testing. The protocol was approved by the hospital ethics committee and the patients gave informed consent.

Exclusion criteria were previous myocardial infarction, arterial hypertension, diabetes mellitus, cardiomyopathy, valvar disease, tortuous coronary vessels, history suggestive of variant angina pectoris, stenosis of the contralateral artery $\geq 50\%$, and severe non-cardiac disease.

We analysed the diagnostic coronary angiogram performed before the coronary angioplasty. Coronary artery stenosis severity was measured with callipers.⁵ The left ventricular ejection fraction was determined. Collateral filling of the dilated vessel was classified as follows⁶: class 0, no epicardial filling; class I, filling of side branches only; class II, partial filling of the epicardial segment; class III, complete filling of

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Table 1 Clinical characteristics of the patients studied

	No visible collaterals	Visible collaterals	All patients
Number	20	11	31
Age (years)	56 (11)	55 (10)	56 (11)
Left ventricular ejection fraction (%)	58 (7)	55 (4)	57 (6)
RCA, LAD disease (n)	6, 14	3, 8	9, 22
Balloon size (mm)	3.5 (0.4)	3.4 (0.4)	3.5 (0.4)
Atmospheres	14 (5)	14 (3)	14 (3)
Stent (number of patients)	13	6	19
% Stenosis before angioplasty	84 (7)	87 (7)	85 (7)
% Stenosis after angioplasty	8 (5)	8 (7)	8 (6)

Values are mean (SD) unless otherwise specified.

LAD, left anterior descending artery; RCA, right coronary artery. The clinical characteristics of the 2 subgroups were similar.

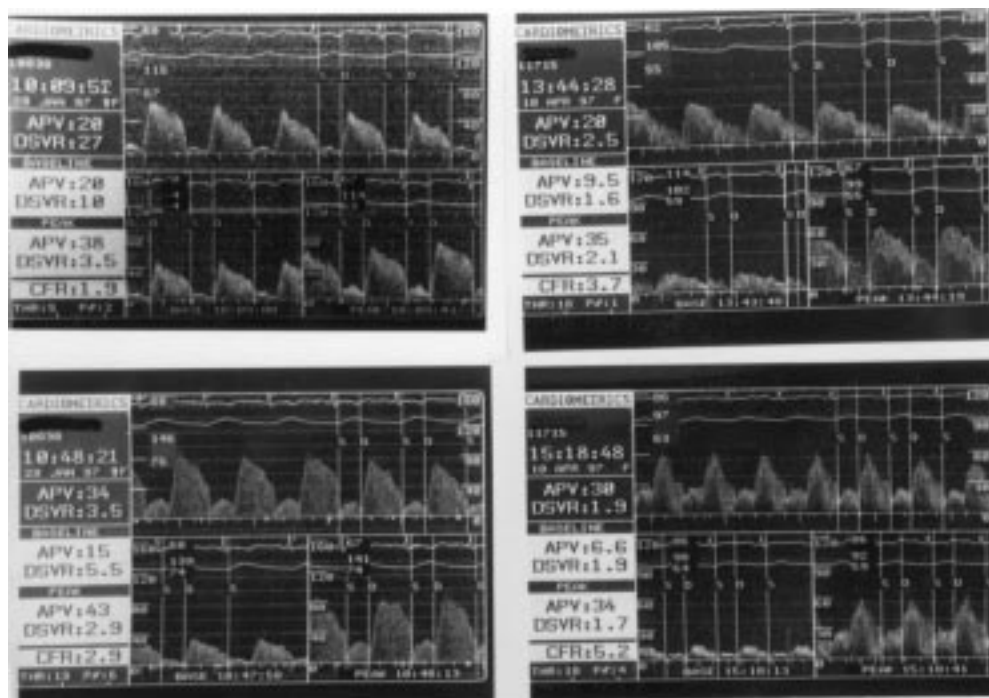


Figure 1 Coronary flow reserve in the contralateral right coronary (left) and left anterior descending coronary artery (right) in two patients, before (top) and after (bottom) angioplasty. Baseline average peak velocity decreased and coronary flow reserve increased after angioplasty.

the epicardial segment. In this study spontaneously visible collaterals were determined as class I–III in Rentrop's classification, while the absence of such collaterals was graded as class 0. Eleven patients had visible coronary collaterals before angioplasty. Of these 11 patients, two had grade I, seven had grade II, and two had grade III collaterals according to Rentrop's classification.

The patients were divided into two subgroups: those with and those without visible collaterals.

CATHETERISATION PROTOCOL

Patients were brought to the cardiac catheterisation laboratory in a fasting state. Drugs were withheld on the day of the procedure. Intrarterial heparin (7000 IU) was given immediately after sheath placement. All patients received aspirin orally before the procedure. Additional heparin was given throughout the procedure to maintain the activated clotting time between 200 and 300 seconds. All patients received intracoronary glyceryl trinitrate before, throughout, and at the end of the procedure. Coronary flow reserve was measured five minutes after glyceryl trinitrate administration.

First the contralateral artery was catheterised with a diagnostic catheter. A 0.014 inch Doppler flow guidewire was inserted into the proximal segment of the contralateral artery. This flow guidewire position was recorded on videotape so that Doppler measurements could be made at the same site after balloon angioplasty. Blood pressure and the ECG were displayed on the multichannel recorder and on the screen of the Flowmap (Cardiometrics Inc, Mountain View, California, USA), while the

coronary blood flow velocity was displayed only on the screen of the Flowmap.

The Doppler guidewire is a 0.014 inch, 175 cm long flexible and steerable guidewire having a floppy, shapeable distal end with a 12 MHz piezoelectric transducer mounted at the tip. The Doppler system calculates and displays several spectral variables on-line, including the instantaneous peak velocity and the time averaged peak velocity (mean of two beats). The flow velocity measurements obtained with this system have been validated in vitro and in an animal model using simultaneous electromagnetic flow measurements for comparison.⁷ The Doppler system calculates and displays on-line average peak velocity.

Coronary artery velocity signals and catheter pressures were recorded only after obtaining stable baseline signals. Contralateral coronary flow velocity, mean arterial pressure, and heart rate were recorded at baseline and following intracoronary administration of adenosine (12 µg in the right coronary artery and 18 µg in the left).

After measurements of coronary flow reserve from the contralateral artery, the diseased artery was catheterised with a standard 8F coronary guiding catheter. Coronary angioplasty was performed using standard techniques.⁸

DOPPLER MEASUREMENTS AFTER ANGIOPLASTY

Fifteen minutes after the termination of coronary angioplasty the coronary flow reserve in the ipsilateral and the contralateral arteries was recorded. In the treated artery coronary flow reserve was measured after placing the Doppler flow guidewire distal to the dilated lesion. Ipsilateral coronary flow velocity, mean arterial pressure, and heart rate were recorded at

Table 2 Average peak velocity and coronary flow velocity reserve according to the presence or absence of collaterals

Variable	Patient group	Before angioplasty	After angioplasty	p Value
Mean blood pressure (mm Hg)	All patients (n = 31)	98 (16)	95 (16)	NS
	Patients with visible collaterals (n = 11)	96 (14)	95 (15)	NS
	Patients without visible collaterals (n = 20)	99 (19)	96 (18)	NS
Heart rate (beats/min)	All patients (n = 31)	74 (6)	75 (10)	NS
	Patients with visible collaterals (n = 11)	71 (6)	74 (7)	NS
	Patients without visible collaterals (n = 20)	75 (6)	76 (11)	NS
Contralateral baseline APV (cm/s)	All patients (n = 31)	21 (9)	12 (6)	0.000000
	Patients with visible collaterals (n = 11)	20 (6)	11 (4)	0.0008
	Patients without visible collaterals (n = 20)	22 (10)	13 (7)	0.00007
Contralateral hyperaemic APV (cm/s)	All patients (n = 31)	47 (19)	34 (15)	0.00004
	Patients with visible collaterals (n = 11)	42 (11)	30 (10)	0.03
	Patients without visible collaterals (n = 20)	50 (23)	36 (17)	0.0006
Contralateral coronary flow reserve	All patients (n = 31)	2.4 (0.7)	2.9 (0.6)	0.0003
	Patients with visible collaterals (n = 11)	2.2 (0.8)	3.0 (0.8)	0.00006
	Patients without visible collaterals (n = 20)	2.5 (0.6)	2.8 (0.4)	NS
Ipsilateral baseline APV (cm/s)	All patients (n = 31)	—	14 (6)	—
	Patients with visible collaterals (n = 11)	—	17 (7)	—
	Patients without visible collaterals (n = 20)	—	12 (5)	—
Ipsilateral hyperaemic APV (cm/s)	All patients (n = 31)	—	30 (17)	—
	Patients with visible collaterals (n = 11)	—	36 (23)	—
	Patients without visible collaterals (n = 20)	—	26 (12)	—
Ipsilateral coronary flow reserve	All patients (n = 31)	—	2.2 (0.4)	—
	Patients with visible collaterals (n = 11)	—	2.1 (0.7)	—
	Patients without visible collaterals (n = 20)	—	2.2 (0.3)	—

Values are mean (SD).

The variables studied were not statistically different in the two subgroups.

APV, average peak velocity.

baseline and following intracoronary administration of adenosine (12 µg in the right coronary artery and 18 µg in the left).

The coronary flow reserve in the contralateral artery was then measured. The Doppler flow guidewire was positioned at the same site as before angioplasty. After a stable signal was obtained, the same measurements as before angioplasty were repeated at baseline and after hyperaemia.

ASSESSMENT OF CORONARY FLOW RESERVE

The Doppler flow guidewire was connected to a 12 MHz pulsed Doppler velocimeter, which analysed on-line Doppler velocity spectra and calculated the temporal average of the instantaneous peak velocity waveform, both during baseline conditions and during maximum hyperaemia. Coronary flow reserve was then computed as the ratio of hyperaemic to baseline average peak velocity (fig 1). Coronary flow reserve was estimated after duplicate measurements. Although the Doppler guidewire measures only relative velocity changes and not the absolute volumetric flow, flow velocity measurements can be used as an accurate indicator of coronary flow reserve, provided that the vessel cross sectional area is constant during hyperaemia. Intracoronary bolus injection of adenosine does not modify coronary lumen diameter⁹; therefore coronary flow reserve should closely reflect volumetric coronary flow reserve. On the basis of previous studies^{10 11} a coronary flow reserve of ≤ 2.0 was considered abnormal.

STATISTICAL ANALYSIS

All data are expressed as mean (SD). The Student's paired *t* test was used to compare the data before and after coronary angioplasty. Linear regression analysis using the least squares difference and analysis of variance were employed to examine possible relations between the changes in coronary flow reserve in the con-

tralateral artery and the coronary artery stenosis severity before and after angioplasty, the use of intravascular stents, the coronary artery studied, the presence or absence of coronary collaterals, and the coronary flow reserve of the treated artery. A probability (p) value of < 0.05 was considered statistically significant.

Results

The majority of the patients had left anterior descending artery disease; thus the right coronary artery was the one most studied (table 1). All the procedures were successful and the postangioplasty stenosis rate was very low because of the use of intravascular stents.

Table 2 shows the blood pressure, heart rate, and coronary flow reserve in the treated and the contralateral artery before and after angioplasty. Blood pressure had a tendency to decrease after angioplasty but the change did not reach statistical significance. Heart rate remained unchanged after angioplasty. Baseline average peak velocity decreased by 9 (7) cm/s (34%) after angioplasty, and hyperaemic average peak velocity decreased by 13 (15) cm/s (20%) in the contralateral artery. Thus coronary flow reserve in the contralateral artery increased after angioplasty because the baseline average peak velocity decreased more after angioplasty than did the hyperaemic average peak velocity ($p < 0.05$).

The increase in coronary flow reserve had no relation to the severity of coronary artery stenosis before or after angioplasty, to the artery studied, to the ipsilateral coronary flow reserve after angioplasty, to whether stents were placed, or to the heart rate and blood pressure changes after angioplasty. The increase in contralateral artery coronary flow reserve had no relation to the subclassification of the 11 patients with visible collaterals into three grades (I–III) according to Rentrop's classification, possibly because of the low statistical power after this classification (two patients had grade I, seven patients grade II, and

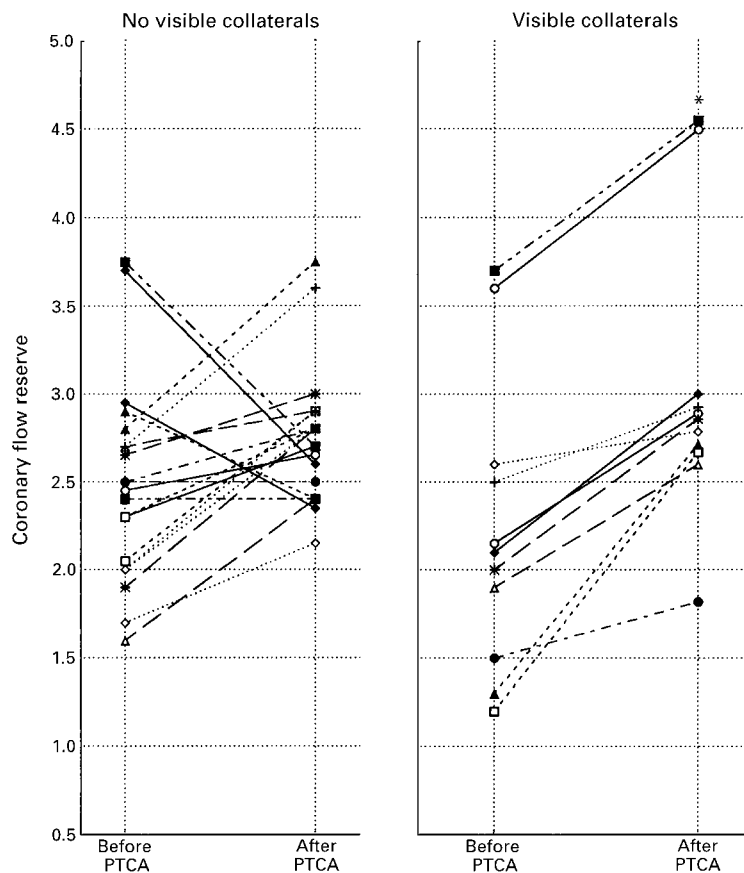


Figure 2 Line plots of the coronary flow reserve of the contralateral artery, before and after angioplasty (PTCA) in the two subgroups with and without visible collaterals.

* $p < 0.05$ v before PTCA.

two patients grade III preangioplasty collaterals). The flow reserve of the contralateral coronary artery before angioplasty was abnormal in 10 of the 31 patients (32%) (fig 2). The contralateral coronary flow reserve in the patients with visible collaterals before and after angioplasty was not significantly different from that of the patients without visible collaterals. Contralateral coronary flow reserve increased after angioplasty by 0.8 (0.4) in the patients with visible collaterals and by 0.3 (0.6) in the rest of the patients ($p < 0.05$). In four patients, all in the subgroup without visible collaterals, contralateral coronary flow reserve decreased after angioplasty (fig 2). In these four patients no decrease or significant change in heart rate occurred that could explain the decrease in coronary flow reserve.

Coronary flow reserve in the ipsilateral artery remained abnormal (≤ 2.0) in 13 of the 31 patients (42%) after successful angioplasty. Coronary flow reserve of the treated artery after angioplasty in the patients with visible collaterals was not different from that of patients without visible collaterals. However, ipsilateral coronary flow reserve after angioplasty was 2.3 (0.4) in the 19 patients with stent placement and 1.9 (0.5) in the 12 patients without stent placement ($p < 0.05$).

Discussion

In this study we tested the hypothesis that the coronary flow reserve of the angiographically normal contralateral artery could increase after

successful angioplasty and showed it to be correct. This increase in the coronary flow reserve resulted from the average peak velocity decreasing after angioplasty to a greater degree in the baseline than in the hyperaemic phase. The increase in the coronary flow reserve in the contralateral artery was only significant in patients with visible collateral vessels before angioplasty.

The decrease in the baseline and hyperaemic average peak velocity could be attributed in some degree to the non-significant decrease in the blood pressure that occurred after angioplasty. Heart rate remained unchanged by the procedure, so the increase in coronary flow reserve cannot be attributed to possible changes in this variable.¹² The excretion of different vasoactive substances—such as endothelins and atrial natriuretic peptides—during angioplasty^{8,13} can provoke vasodilatation or vasoconstriction and could thus affect baseline and hyperaemic blood velocity. One could therefore hypothesise that they might affect coronary flow reserve in the contralateral artery. We attempted to prevent changes in vasomotor tone, however, by inducing constant maximal epicardial coronary vasodilatation with glyceryl trinitrate. Furthermore, coronary flow reserve measurements after angioplasty were obtained 15 minutes after the last inflation, allowing enough time for the return of baseline average peak velocity to the steady state.

A reduced coronary flow reserve after the administration of dipyridamole has previously been reported in regions supplied by angiographically normal arteries in atherosclerotic patients without previous infarction.¹ Our data agree with these findings—10 of our 31 patients (32%) had abnormal coronary flow reserve in their grossly normal contralateral arteries before angioplasty. The impairment in vasodilator reserve may be an early manifestation of microvascular endothelial dysfunction in the presence of angiographically undetectable coronary atherosclerosis.^{3,4} Uren *et al* showed that coronary vasodilator reserve is reduced in regions subtended by normal arteries remote from ischaemic but non-infarcted myocardium.² They showed that the reduction in coronary vasodilator reserve in the remote regions was caused by a combination of a higher baseline myocardial blood flow and reduced vasodilator response after dipyridamole compared with values in the control group. In our study, however, the increase in the contralateral coronary flow reserve after angioplasty was caused by a decrease in the baseline average peak velocity rather than an increase in the hyperaemic average peak velocity.

The mechanism of the increase in coronary flow reserve after angioplasty is not known. In part it could be as follows. In the contralateral arteries the need to provide blood flow, through collateral vessels, to more than one vascular zone places an added burden of blood flow on the supply vessel at rest. As a result, blood flow in the contralateral artery at rest is increased after release of smooth muscle tone in the resistance vessels and, given that the hyperaemic blood

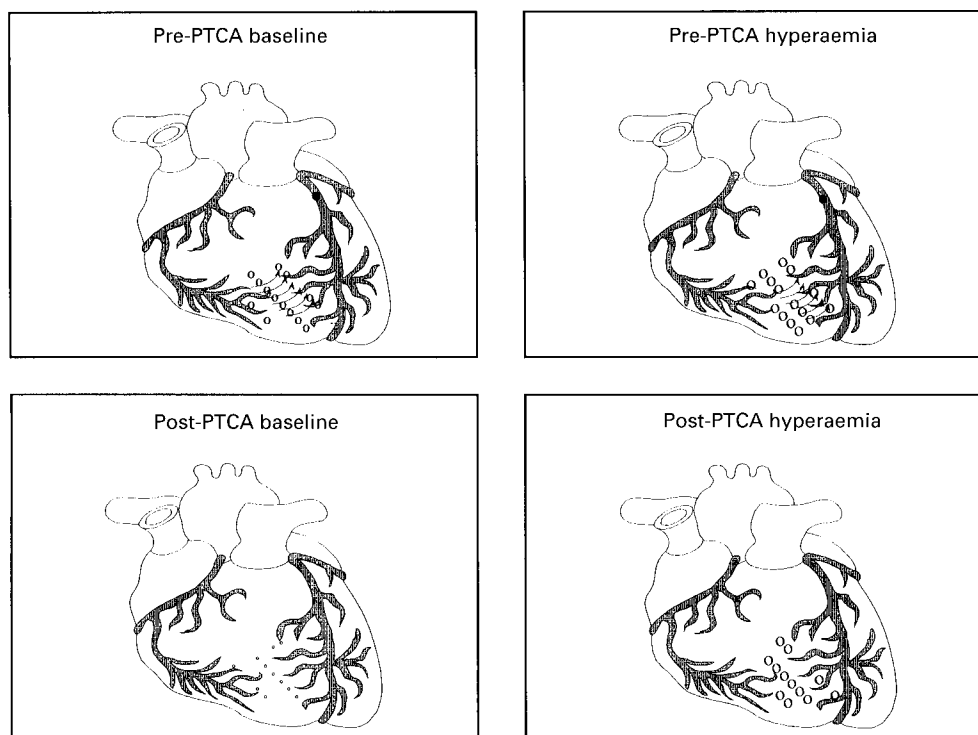


Figure 3 The possible mechanism whereby coronary flow reserve in the contralateral artery increases after angioplasty. Smooth muscle tone release in the resistance vessels (circles) occurs before angioplasty (PTCA) so that the contralateral artery may provide blood flow, through collateral vessels, to the stenotic artery (pre-PTCA baseline). Given that the hyperaemic blood flow (pre-PTCA hyperaemia) is fixed, coronary flow reserve is reduced pre-angioplasty. After successful angioplasty the collateral blood flow disappears, the smooth muscle tone in the resistance vessels returns to approximately normal, and chronic vasodilatation of the resistance vessels disappears (post-PTCA baseline). Subsequently baseline average peak velocity decreases while hyperaemic blood flow does not change significantly (post-PTCA hyperaemia). In this way, coronary flow reserve after angioplasty increases in comparison with the situation before angioplasty.

flow is fixed, coronary flow reserve is reduced. After successful angioplasty collateral blood flow ceases, smooth muscle tone in the resistance vessels returns to approximately normal values leading to a decrease in baseline average peak velocity, and the chronic vasodilatation of the resistance vessels disappears, while hyperaemic blood flow does not change significantly. In this way, coronary flow reserve increases (fig 3). Therefore, it seems that the coronary flow reserve of the contralateral artery in patients with spontaneously visible collateral vessels may be reduced before angioplasty, because the contralateral artery provides blood flow to ischaemic vascular regions with a potential loss of autoregulation, resulting in a reduced coronary flow reserve.

After successful coronary angioplasty, the coronary flow reserve is determined by the vascular integrity of the contralateral artery only, and as a result the coronary flow reserve increases. The decrease in baseline flow velocity after angioplasty remains to be elucidated, although it is not related to haemodynamic changes such as blood pressure or heart rate. Nevertheless, it is conceivable that this decrease in baseline blood flow velocity may be related to other haemodynamic changes, such as a reduction in preload after successful angioplasty. In the group without visible collaterals, 14 patients showed an increase in coronary flow reserve. The observed increase in coronary flow reserve in these patients suggests that this phenomenon may not be related only to

the presence of collateral vessels; alternatively, it may indicate the limitations of angiography for documenting collateral vascular development. Our study did not show that the coronary flow reserve was decreased to a greater extent in arteries which supplied more collaterals to the diseased vessels; however, the increase in coronary flow reserve in the contralateral artery after angioplasty was related to the presence of collateral flow that this artery provided to the diseased artery.

Coronary flow reserve of the ipsilateral artery has been shown to remain abnormal in many patients after successful coronary angioplasty.^{14 15} Flow reserve in the treated artery remained abnormal in 42% of our patients after angioplasty, a similar proportion to that found in other studies.^{14 15} Persistence of residual material after balloon angioplasty despite an adequate angiographic result may account for impaired coronary flow reserve, and stenting can normalise this in many cases.¹⁶ It has been suggested that prolonged ischaemia during balloon inflation causes a decrease in microvascular resistance which interferes with the measurement of coronary flow reserve. Another possible mechanism which could interfere with coronary flow reserve after coronary interventions could be the effects of the administration of drugs, the change in blood pressure and heart rate, and the excretion of different vasoactive substances.^{8 12} The finding of abnormal coronary flow reserve after successful angioplasty cannot be attributed to changes in heart

rate or blood pressure because we observed no such changes. Neither can it be attributed to the drugs that were given or the effects of excreted vasoactive substances, since all these would have adversely affected the coronary flow reserve in the contralateral artery, which, instead of decreasing, showed a marked increase.

LIMITATIONS OF THE STUDY

The major limitation of the study is that the data suggest that the increase in the coronary flow reserve in the contralateral artery is related to collateral vessel growth before coronary angioplasty, although an increase in coronary flow reserve was—as mentioned above—also noted in patients without spontaneously visible collateral vessels. Furthermore, the mechanism responsible for the reduction in baseline blood flow velocity in the contralateral artery after coronary angioplasty remains obscure and requires further analysis. Angiographic grading of coronary collateral vessels was not performed using automatic contrast injection, while assessment of recruitable collateral vessels was not attempted in our study. The random classification for absence or presence of collateral vessels is different from the classification used by other investigators, but this was done in order to achieve a clear cut classification. Another limitation is the relatively small number of patients studied. The haemodynamic variables measured did not include an analysis of regional wall motion or left ventricular pressure measurements before and after angioplasty.

We did not measure preload indices, such as the pulmonary wedge pressure, that could change after coronary angioplasty. As we know,¹⁷ an increase in preload decreases coronary flow reserve. The technical limitations of obtaining satisfactory flow velocity signals have been described in detail elsewhere.¹⁵ We tried to avoid these limitations by careful patient selection (for example, patients with tortuous vessels or multiple serial distal lesions were excluded) and by appropriate positioning of the Doppler guidewire away from regions of non-laminar flow.

CLINICAL IMPLICATIONS

With this study we show for the first time that coronary flow reserve in the contralateral artery increases after successful angioplasty and that this increase is only significant in patients with spontaneously visible collateral vessels. This finding indicates that collateral vessels play an important role in the physiology of patients undergoing coronary angioplasty. Recent data suggest that the relative coronary

flow reserve—that is, the ratio of the coronary flow reserve of the ipsilateral artery and that of a reference artery—may be of potential value in evaluating the results of angioplasty. Our study suggests that the relative coronary flow reserve may be influenced by changes in flow reserve in the contralateral artery before and after angioplasty, suggesting that it might be appropriate to use the coronary flow reserve after angioplasty for reference, instead of measuring this value before angioplasty.

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