Inability of coronary blood flow reserve measurements to assess the efficacy of coronary angioplasty in the first 24 hours in unselected patients

To determine functional and anatomic changes in the first 24 hours after coronary angioplasty, we studied at random 15 patients (9 men, mean age 60 years) who underwent coronary angioplasty of 16 coronary arteries. Quantitative coronary angiography and coronary flow reserve measurements from digitized coronary angiograms were performed before, immediately after, and 24 hours after coronary angioplasty. Calculated were the minimal luminal diameter, obstruction area, and percentage diameter stenosis from two preferably orthogonal projections. Prior myocardial infarction in the myocardial region of interest was present in four patients. Seven patients had multivessel disease. Collateral vessels supplying the compromised flow region were observed in three patients. Six patients had refractory unstable angina pectoris. After coronary angioplasty, angiographically visible dissection was noted in six patients, whereas side branch occlusion was observed in one. Minimal luminal diameter before, immediately after, and 24 hours after was 0.93 ± 0.18 mm, 1.53 ± 28 mm, and 1.53 ± 0.21 mm, respectively; obstruction area was 0.70 ± 0.26 mm^2, 1.92 ± 0.69 mm^2, and 1.87 ± 0.51 mm^2, respectively; diameter stenosis was 60.4 ± 8.0%, 36.8 ± 11.4%, and 37.6 ± 5.3%, respectively. The coronary flow reserve (lower limit of normal with this technique 3.4) was essentially the same before and immediately after coronary angioplasty (1.26 ± 0.59 vs 1.30 ± 0.42, p = NS) with a slight improvement to 1.78 ± 0.90 ($p < 0.05$) 1 day later. Coronary artery dimensions correlated poorly with coronary blood flow reserve before and after angioplasty. We conclude that on average no changes in minimal luminal diameter, obstruction area, and percentage diameter stenosis occurred in the first 24 hours after coronary angioplasty, although there were individual variations, and coronary flow reserve measurements from digitized coronary angiograms were only minimally improved 1 day after coronary angioplasty and correlated poorly with quantitative measurements of coronary artery dimensions. Therefore it is suggested that coronary flow reserve measurements from digitized coronary angiograms in the setting of coronary angioplasty have little value in unselected patients with conditions known to disturb coronary flow reserve.
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The immediate result of coronary angioplasty is routinely assessed by visual analysis of the radiographic appearance of the residual stenosis. Successful coronary angioplasty is commonly defined as a residual stenosis of less than 50% luminal narrowing assessed by visual analysis, but alternative criteria such as a 20% increase in luminal diameter have also been used. Factors such as dissection, haziness, and intraluminal defects are often noted, but their significance remains uncertain if the patient does not show signs of ischemia. Quantitative coronary angiography with automated border definition in multiple views, currently not on line in most laboratories, is helpful as an objective reproducible anatomic measurement, but the translation to functional information is hampered by several limitations, especially after coronary angioplasty.[1-3] It has been shown that after balloon dilatation, with resulting complex asymmetric lesion morphology, the use of videodensitometry seems

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Table I. Clinical characteristics

Characteristics	
No. of patients	15
Sex	
Male	9
Female	6
Age (yr)	60 (48-68)
Dilated vessels (16)	
RCA	4
LAD	8
LCX	4
Unstable angina pectoris	6 (40%)
Multivessel coronary artery disease	7 (47%)
Left ventricular hypertrophy (ECG)	—
Previous myocardial infarction	4 (27%)
Collateral vessels	3 (20%)

RCA, right coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery.

more useful than estimation of the severity of stenosis by edge-detection methods.[4] Measurement of the translesional pressure gradient is helpful in assessing postdilatation results, but this technique is associated with a wide variability, since measurements are dependent on flow and perfusion pressure and are influenced by the catheter itself.[5-7]

Recently sequential coronary flow reserve measurements in the setting of coronary angioplasty by various methods has been proposed as a desirable means to establish the functional result of the intervention. The initial results indicated that coronary flow reserve did not normalize in many patients immediately after successful coronary angioplasty but did so late (several months) after the procedure.[2, 8] These results were obtained from carefully selected patient subgroups,[2, 8-11] which are not representative of a normal clinical coronary angioplasty patient population. The purpose of the present study was to study quantitatively the anatomic and functional changes in the first 24 hours after clinically successful coronary angioplasty in an unselected patient population by means of quantitative coronary angiography and digital subtraction angiography.

METHODS

Patients. Fifteen patients (nine men and six women) with a mean age of 60 (48 to 68) years, undergoing coronary angioplasty of 16 coronary artery lesions, constituted the study group (Table I). Informed consent was obtained before the angioplasty procedure. Although our intention was to study a consecutive series of patients, this could not be accomplished because of logistic restraints (e.g., cardiac catheterization after 24 hours, patient refusal) and technically inadequate recordings (respiration artifacts, atrial fibrillation, and frequent ectopic beats). Nevertheless, the patient group represented a random, unselected clinical coronary angioplasty population. Patients were not excluded for factors known to disturb coronary flow reserve. None of the patients had ECG evidence of left ventricular hypertrophy, but this could not be ruled out since no additional imaging techniques were performed to study this aspect. Seven patients (47%) had multivessel coronary artery disease. A previous myocardial infarction in the region under study was present in four patients (27%). Six patients (40%) had refractory unstable angina pectoris. In three patients (20%) the myocardial region under study was supplied by angiographically visible collateral vessels.

Coronary angioplasty procedure. Coronary angioplasty was performed according to the technique of Gruentzig et al.[12] through a femoral route. Details regarding the procedure used in our laboratory have been described previously.[13, 14] Patients received maintenance therapy of salicylic acid, 500 mg/day. All antianginal medication was continued until the 24-hour follow-up investigations and was then stopped, but beta-blocking agents for hypertension were continued. Successful coronary angioplasty was defined as less than 50% diameter stenosis on visual inspection of the postangioplasty coronary angiogram and no in-hospital complications such as recurrence of angina pectoris, repeat angioplasty, coronary bypass grafting, myocardial infarction, or death. Angiographic evidence of intimal disruption was defined according to the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry.[15] No additional investigations such as measurements of translesional pressure gradient or exercise tests to confirm the functional results of coronary angioplasty were performed.

Quantitative analysis of the coronary artery. Quantitative analysis of the coronary angiogram was performed with a computer-based Cardiovascular Angiography Analysis System, previously described in detail.[1, 16, 17] In essence boundaries of a selected segment of coronary artery are detected automatically from optically magnified and video-digitized regions of interest of a cineframe. The absolute diameter of the stenosis in millimeters is determined with the use of the guiding catheter as a scaling device. This involves automatic edge detection of the boundaries of the catheter in situ and the comparison of this value with the actual diameter measurement of the catheter determined by means of a micrometer. Calibration of the diameter in absolute values (in millimeters) is achieved by comparing the mean diameter of the guiding catheter in pixels with the measured size in millimeters. Each catheter is measured individually.[18] To correct the detected contour of the arterial and catheter segments for pincushion distortion, a correction vector is computed for each pixel based on a computer-processed cineframe with a centimeter grid placed against the input screen of the image intensifer.[17] Because the functional significance of a stenosis is related to the expected normal cross-sectional area of the vessel at the point of obstruction, we use a computer estimation of the original arterial dimension at the site of the obstruction to define the interpolated reference diameter and, assuming a

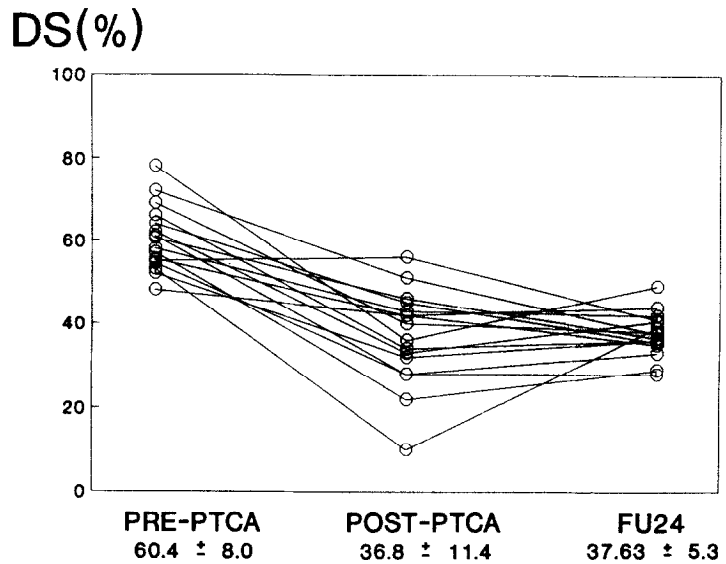

Fig. 1. Percentage diameter stenosis *(DS, %)* before *(PRE-PTCA)*, immediately after *(POST-PTCA)*, and 24 hours after *(FU24)* coronary angioplasty.

circular model, the reference area.[17] The percentage diameter stenosis, minimal lumen diameter in millimeters, and cross-sectional obstruction area (in millimeters squared) are then calculated.

Coronary flow reserve measurements with digital subtraction cineangiography. Angiographic acquisition for coronary flow reserve analysis was performed at least 10 minutes after the final balloon inflation. The coronary flow reserve measurement from the 35 mm cinefilm has been implemented on the Cardiovascular Angiography Analysis System.[1] Voltage (kilovolts) and current (milliamperes) of the x-ray generator are adjusted automatically in our catheterization laboratory by a microprocessor system.[19] Identical x-ray settings, voltage, and current of the x-ray generator at different times, as well as stable cinefilm development, were obtained as previously described.[19] The heart was atrially paced at a rate just above the spontaneous heart rate. An ECG-triggered injection into the coronary artery was made with iopamidol at 37° C through a Medrad Mark IV infusion pump (Medrad Inc., Pittsburgh, Pa.). The angiography was repeated during papaverine-induced hyperemia.[20, 21] The injection rate of the contrast medium was judged to be adequate if backflow of contrast medium into the aorta occurred. Five or six consecutive end-diastolic cineframes were selected for analysis. Logarithmic nonmagnified mask-mode background subtraction was applied to the image subset to eliminate noncontrast medium densities. The last end-diastolic frame before the administration of contrast medium was chosen as the mask. From the sequence of background-subtracted images, a contrast arrival time image was determined with an emperically derived fixed-density threshold.[1] Each pixel was labeled with the sequence number of the cardiac cycle numbered from the cycle in which the pixel intensity level first exceeded the threshold. In addition to the contrast arrival time image, a density image was computed, with the intensity of each pixel representative of the maximal accumulation of local contrast medium. The coronary flow reserve was defined as the ratio of the regional flow computed from a hyperemic image divided by the regional flow of the corresponding baseline image. Regional flow values were quantitatively determined by means of the following videodensitometric principle: regional blood flow (Q) = regional vascular volume/transit time.[1] Regional vascular volume was assessed from logarithmic mask-mode subtraction images by means of the Lambert-Beer relationship. Coronary flow reserve was then calculated as: CFR = Qh/Qb = Dh/Th:Db/Tb, where D is the mean contrast density and T is the mean appearance time at baseline (b) and hyperemia (h). Mean contrast medium appearance time and density were computed within a user-defined region of interest, which was chosen so that the epicardial coronary arteries visible on the coronary angiogram, the coronary sinus, and the great cardiac vein were all excluded from the analysis.[1] Normal values for coronary flow reserve measured with this technique have previously been established.[1, 8] As a result a coronary flow reserve value less than 3.4 is considered abnormal.

Statistical analysis. Comparisons were made with the Student's *t* test for paired and unpaired observations. A *p* value of less than 0.05 was considered significant. Values are expressed as mean ± standard deviation. Least-squares regression analyses were used to find the "best fit" relationship between coronary flow reserve and quantitatively assessed coronary artery dimensions.

RESULTS

Coronary angioplasty. In each instance the immediate result of angioplasty was considered successful by the operator. In six vessels angiographic evidence of dissection at the dilatation site was observed accom-

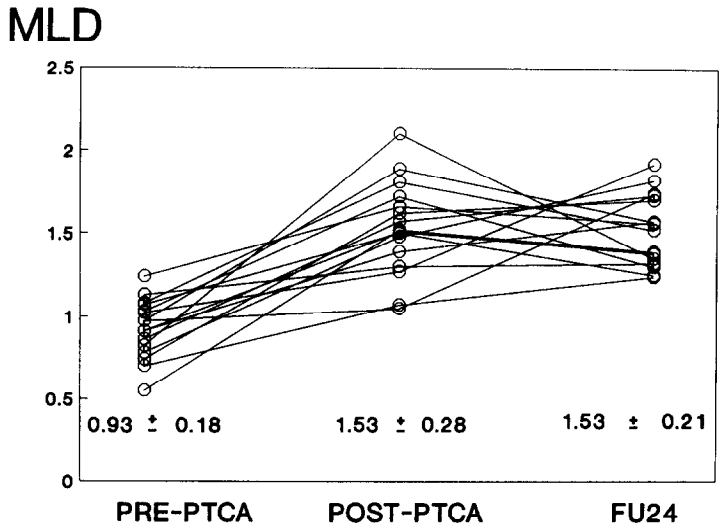

Fig. 2. Minimal luminal diameter (*MLD*, mm) before *(PRE-PTCA)*, immediately after *(POST-PTCA)*, and 24 hours after *(FU24)* coronary angioplasty.

panied by a "hazy" aspect in four instances and contrast staining in one. A filling defect without visible dissection was noted in one patient, whereas side branch occlusion occurred in another patient. These circumstances did not cause ischemic symptoms, and creatine phosphokinase measurements after the procedure were in the normal range (less than 110 U/L).

Quantitative coronary angiography. Before coronary angioplasty the mean percentage diameter stenosis was 60.4 ± 8.0%. Immediately after angioplasty this value was 36.8 ± 11.4% ($p < 0.05$). After 24 hours the mean percentage diameter stenosis remained unchanged with a much smaller standard deviation (37.6 ± 5.3%, p = NS) (Fig. 1). In two patients the residual stenosis was more than 50% (51% and 56%), but 24 hours later the percentage diameter stenosis was less than 50% in all instances. On the other hand, the lowest percentage diameter stenosis (10%) immediately after angioplasty increased to an intermediate value (39%) after 24 hours. In each instance reference diameters remained unchanged. The mean minimal luminal diameter before angioplasty was 0.93 ± 0.18 mm and increased significantly to 1.53 ± 0.28 mm after angioplasty ($p < 0.05$; Fig. 2). At 24 hours' follow-up the mean minimal luminal diameter was unchanged (1.53 ± 0.21, p = NS), although some individual variation was observed (Fig. 2). The same trends were observed for measurements of the obstruction area (Fig. 3).

Coronary flow reserve measurements. The mean coronary flow reserve before angioplasty was 1.26 ± 0.59 and remained at the same level (1.30 ± 0.42, p = NS) after the intervention. Although coronary flow reserve improved in nine myocardial regions, a rather steep decrease in reserve was observed in the three regions with the highest preangioplasty values (Fig. 4). In one patient this decrease could be explained by side branch occlusion. After 24 hours the mean coronary flow reserve showed a slight increase to 1.78 ± 0.90; $p < 0.05$) with an improvement in eight, a decrease in four, and no change in four myocardial regions compared with the immediate postangioplasty measurements. No correlation between the anatomic parameters (percentage diameter stenosis, minimal lumen diameter, and obstruction area) and the calculated coronary flow reserve could be found before, immediately after, and 24 hours after angioplasty, except borderline significance for the minimal lumen diameter and obstruction area immediately after the intervention (Table II).

DISCUSSION

Anatomic changes in the first 24 hours after coronary angioplasty. The mean values of the percentage diameter stenosis, minimal luminal diameter, and obstruction area remained unaltered 24 hours after the intervention. However, the smaller standard deviations indicate that with time there was a regression to the mean value. These unchanged values conflict with the findings of Nobuyoshi et al.,[22] who found a significant decrease in minimal luminal diameter from immediately after coronary angioplasty to day 1. Five vessels with the least optimal results immediately after angioplasty showed further improvement after 24 hours. This phenomenon might be explained

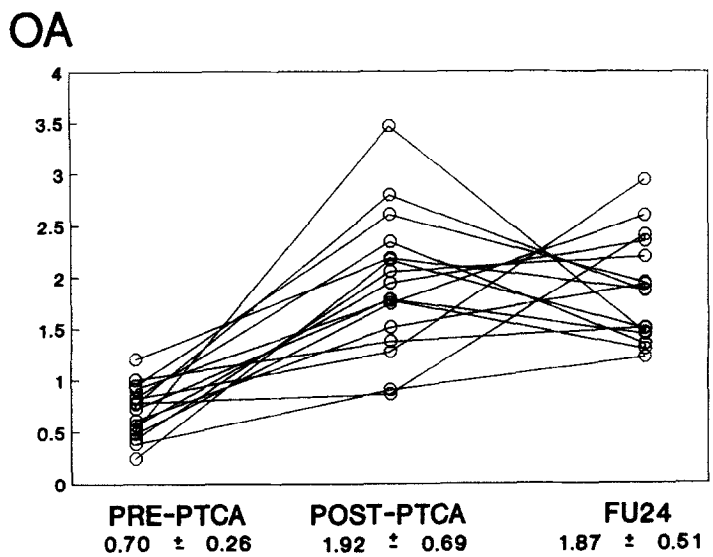

Fig. 3. Cross-sectional obstruction area (*OA*, mm^2) before *(PRE-PTCA)*, immediately after *(POST-PTCA)*, and 24 hours after *(FU24)* coronary angioplasty.

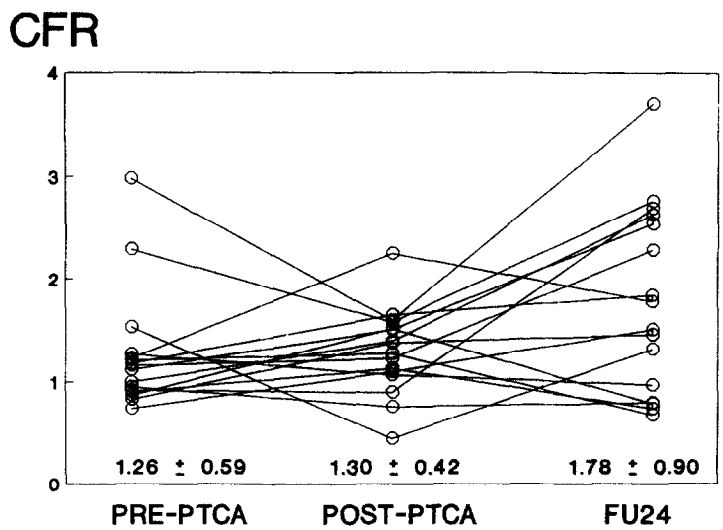

Fig. 4. Coronary flow reserve *(CFR)* measured with digital subtraction cineangiography before *(PRE-PTCA)*, immediately after *(POST-PTCA)*, and 24 hours after *(FU24)* coronary angioplasty.

by a transient spasm of the epicardial artery by intracoronary mechanical manipulations that was abolished 24 hours later,[23] although before angiography intracoronary isosorbide dinitrate was routinely administered in each instance. On the other hand, in six patients with the best postangioplasty results a decrease in minimal luminal diameter and obstruction area was demonstrated. This finding can be attributed to a delayed elastic recoil effect in contradistinction to the early recoil demonstrated immediately after coronary angioplasty.[24] The dimensions of the remaining vessels were essentially unchanged in the first 24 hours.

Coronary flow reserve measurements in the setting of coronary angioplasty. The concept of coronary flow reserve, introduced 15 years ago by Gould et al.[25] was and is essential in understanding the physiologic significance of a coronary artery stenosis. The expression of this significance in anatomic-geometric terms is hampered by the complex effects of factors such as percentage of stenosis, entrance angle, exit angle, stenosis length, and obstruction area on coronary blood flow. Coronary flow reserve is an integrated measure of the ability of the coronary circulation to increase blood flow after maximal vasodilatation, and the functional importance of a coronary stenosis is expressed in terms of restricted flow reserve. As a consequence this approach seems to be very attrac-

Table II. Relationships between coronary flow reserve measured with digital subtraction cineangiography and percentage diameter stenosis, minimal luminal diameter, and obstruction diameter before, immediately after, and 24 hours after coronary angioplasty.

	Diameter stenosis			*Minimal luminal diameter*			*Cross-sectional obstruction area*		
	CFR	*r*	*p Value*	*CFR*	*r*	*p Value*	*CFR*	*r*	*p Value*
Pre-PTCA	55.88 + 3.56.DS	0.262	NS	0.98 − 0.05.MLD	−0.149	NS	0.78 − 0.06.OA	−0.148	NS
Post-PTCA	21.69 + 11.58.DS	0.422	NS	1.97 − 0.34.MLD	−0.502	<0.05	3.17 − 0.96.OA	−0.584	<0.05
FU24	39.04 − 0.80.DS	−0.014	NS	1.50 + 0.02.MLD	0.073	NS	1.75 + 0.07.OA	0.122	NS

CFR, coronary flow reserve in "best fit" relation to coronary artery dimensions; *r*, correlation coefficient; DS, percentage diameter stenosis; MLD, minimal luminal diameter; OA, obstruction diameter; Pre-PTCA, before coronary angioplasty; Post-PTCA, immediately after coronary angioplasty; FU24, 24 hours after coronary angioplasty; NS, not significant.

tive in assessing the immediate results of coronary angioplasty. Assessment of coronary flow reserve in the setting of angioplasty has been described with the use of flow measurements in the coronary sinus and great cardiac vein with thermodilution techniques,[26, 27] hydrogen dilution detection,[28] intracoronary Doppler ultrasound,[2, 3, 21, 29] and digital subtraction angiographic methods.[1, 3, 8-11, 19] There are, however, significant inherent problems in the clinical application of coronary flow reserve measurements irrespective of the technique used: (1) Coronary flow reserve, defined as the ratio of hyperemic flow to resting flow, depends on the hyperemic stimulus. Maximal physical exercise or administration of contrast medium causes only moderate hyperemia, whereas the hyperemic response can be maximal after 10 to 20 seconds of arterial occlusion or administration of an adequate dose of papaverine or dipyridamol.[20, 21, 29] (2) The maximal coronary flow reserve in normal subjects varies over a wide range of values from 3.5 to more than 8.[20, 29] Therefore one cannot be sure if or to what extent the coronary flow reserve is normalized in a patient undergoing angioplasty. Moreover, there is no gold standard for assessing flow reserve available in the catheterization laboratory situation. (3) Many factors are known to disturb the coronary flow reserve measurements, such as previous myocardial infarction, unstable angina, anemia, left ventricular hypertrophy, hypertension, tachycardia, collateral vessels, small-vessel disease, diffuse disease, and drugs that influence the coronary circulation.[1-3, 8, 19, 30-35] In addition, it has been shown that in the presence of these factors coronary flow measurements correlate poorly with quantitative coronary angiographic parameters.[2, 3, 8, 19, 34, 35] The patient without any of these "disturbing" factors is an excellent human model for studying the physiologic significance of a single discrete lesion, but such a patient is rare in clinical practice.

To exclude factors known to disturb coronary flow reserve, many studies have been performed recently with patient subgroups in which criteria for patient selection were unclear[9] or patients were excluded with factors such as left ventricular hypertrophy,[2, 8, 10, 11, 19] hypertension,[2, 8, 10, 11, 19] previous infarction, hypokinesia or ejection fraction less than 50%[2, 8-11, 19] collateral vessels,[2, 8, 11, 19] multivessel disease,[2, 10, 19] or unstable angina pectoris.[10] Further selection was based on additional definitions of successful angioplasty such as postangioplasty translesional pressure gradients of less than 16 mm Hg[10] or 20 mm Hg,[11] normal exercise test results after angioplasty,[10] and the absence of filling defects on the immediate postangioplasty angiogram.[2] In some studies the exact timing of coronary flow reserve measurements after angioplasty was not well defined.[11]

After successful angioplasty coronary flow reserve improves in most of these selected patients but is not restored to normal values immediately after coronary angioplasty.[2, 8-11, 19, 36] Moreover, there was a weak relationship between coronary flow reserve and severity of stenosis assessed by quantitative coronary angiography immediately after angioplasty.[2, 3, 8, 19, 34, 35] When restudied several months after the intervention, in the absence of restenosis, coronary flow reserve was normalized in practically all patients, and the relationship between coronary flow reserve and severity of stenosis was also restored.[2, 8] We demonstrated that this restoration does not take place in the first 24 hours after the intervention.

In the present study flow reserve was severely impaired before angioplasty in all patients. Balloon dilatation resulted in improvement in flow reserve in nine myocardial regions, although the values remained abnormal in all patients. After 24 hours a slight but significant increase in flow reserve was observed with normalization in only one patient. No correlation could be demonstrated in this heteroge-

Table III. Comparison of coronary artery dimensions before and immediately after coronary angioplasty derived from three studies using quantitative coronary angiography

	Diameter stenosis (%)			*Minimal luminal diameter (mm)*		
Study	*Pre-PTCA*	*Post-PTCA*	Δ	*Pre-PTCA*	*Post-PTCA*	Δ
Nobuyoshi et al.[22]	—	—	—	1.04 ± 0.51	1.91 ± 0.53	+84%
Serruys et al.[38]	58.6 ± 12.8	28.6 ± 11.2	−51%	1.15 ± 0.40	2.07 ± 0.43	+80%
Present study	60.4 ± 8.0	36.8 ± 11.4	−39%	0.93 ± 0.18	1.53 ± 0.28	+65%

Pre-PTCA, before coronary angioplasty; Post-PTCA, immediately after coronary angioplasty; Δ, percentage difference between preangioplasty and post-angioplasty values.

neous population between parameters of stenosis severity and flow reserve before, immediately after, and 24 hours after angioplasty, except for the minimal lumen diameter and obstruction area immediately after angioplasty. In a previous study we demonstrated that severity of stenosis correlated poorly with coronary flow reserve estimated with subtraction cineangiography and Doppler flow velocity measurements, especially if hypertrophy, previous infarction, dissection, and collateral circulation were present.[3] However, there was good correlation between both methods for measuring coronary blood flow reserve, although the two approaches had nothing in common methodologically. This indicates that alterations of coronary flow reserve by clinical conditions may occur irrespective of the technique used to measure flow reserve. The various conditions that disturb flow reserve that were present in our patients contributed at least in part to these disappointing results.

Why is coronary flow reserve not restored to normal after successful coronary angioplasty? Inasmuch as coronary reserve is defined as the ratio of hyperemic to resting flow, changes in each of these flow levels will alter flow reserve. There may be a tendency for resting flow to increase after coronary angioplasty. Possible mechanisms of this phenomenon are a reduction of resting flow in the presence of high-grade coronary stenosis, a prolonged hyperemic response after coronary artery occlusion by the balloon, or embolization of microparticles after angioplasty.[36, 37] Attenuation of papaverine-induced hyperemia after angioplasty may be the result of several factors. Probably the most common cause is the presence of a residual flow limiting obstruction of the epicardial artery by disruption of the wall not appreciated by coronary angiography.[2, 3, 8, 19] Especially in the present study results of coronary angioplasty in some patients, although they were considered "clinically successful," were not optimal compared with findings in large clinical studies that use quantitative coronary angiography before and after angioplasty[22, 38] (Table III). Therefore in some patients the residual stenosis may have limited the hyperemic flow response, especially if a suboptimal angioplasty result is accompanied by a dissection or hazy aspect, conditions that are not always appreciated by quantitative coronary artery analysis. Further postulated explanations for attenuated hyperemia after angioplasty are diffuse atherosclerosis when the angiogram reveals only discrete lesions,[39] metabolic and humoral factors affecting vasomotor tone,[36] endothelial dysfunction and smooth muscle damage with enhanced vasoconstriction and inappropriate response to vasodilator stimulation,[36] embolization of microthrombi,[40] and dysregulation of the autoregulatory homeostasis of resistance vessels after long-standing hypoperfusion.[11] In the present study these potential effects are superimposed on the above-mentioned clinical "disturbing" conditions. As a result analysis of the coronary flow behavior after angioplasty in each patient is extremely complex, and it seems unpossible to unravel the relative importance of each factor.

The depressed coronary flow reserve 24 hours after angioplasty in all but one patient suggests that the postulated deleterious effects on flow reserve are not only important in the immediate postangioplasty period but tend to influence flow reserve at least 1 day and probably longer after the intervention. The presence of reversible thallium-201 defects shortly after angiographically successful angioplasty is another manifestation of transient impaired coronary flow reserve.[41]

Implications of this study. The mean dimensions of the coronary artery after angioplasty do not change in the first 24 hours after the procedure, but there was a tendency for regression to the mean value for the best and worst immediate postangioplasty results. Coronary flow reserve estimates in patients with clinical conditions known to disturb coronary flow are hazardous. It is particularly problematic in these patients to use this functional measurement for assessment of the efficacy of coronary angioplasty.

One day after the intervention only a gradual improvement can be observed. Whether this improvement continues with time remains to be established. Thus in spite of the promises of coronary flow reserve measurements in the setting of coronary angioplasty, its application remains restricted to carefully selected patients. A promising recently introduced technique by Pijls et al.[42] measures the mean transit time by videodensitometry during maximal vasodilatation. With this technique the ratio of mean transit times before and after angioplasty can be calculated, which excludes the variability of baseline flows.

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