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Improved Myocardial Ischemic Response and Enhanced Collateral Circulation With Long Repetitive Coronary Occlusion During Angioplasty: A Prospective Study

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Objectives. The goal of the study was to evaluate the progressive increase in ischemic threshold with multiple sequential transient coronary occlusions and to assess the role of the collateral circulation in adaptation to ischemia.

Background. It has been observed that the duration of balloon inflations during coronary angioplasty can be gradually prolonged during subsequent dilations with a reduction in patient symptoms and diminished ischemic electrocardiographic (ECG) changes. Although the mechanism has not been fully explained, recruitment of coronary collateral circulation induced by repeated coronary occlusion has been reported. The stimuli for recruitment and the natural history of coronary collateral circulation are not understood.

Methods. Seventeen patients with isolated stenosis of the left anterior descending coronary artery and a normal left ventricle were enrolled. Angioplasty consisted of five successive prolonged inflations. Sequential changes in clinical, intracoronary ECG and left ventricular indexes of myocardial ischemia were examined. Coronary collateral channels were evaluated during balloon inflations by ipsilateral and contralateral injections of contrast medium and hemodynamically by occlusion pressure.

Results. An improved tolerance to myocardial ischemia with repetitive coronary occlusions was demonstrated by a significant reduction of angina, ST segment deviation, left ventricular filling pressure and less impairment of ejection fraction. Left ventricular wall motion abnormalities remained unchanged. Collateral angiographic grade did not change in 7 patients and increased in 10.

Conclusions. This study confirms a progressive adaptation of myocardial ischemia to repetitive coronary occlusions and supports the concept that sequential episodes of myocardial ischemia are a stimulating factor for the recruitment of collateral channels in humans. These results also suggest that enhancement of recruitable collateral circulation might be an underlying mechanism of myocardial ischemic preconditioning.

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Percutaneous transluminal coronary angioplasty offers a unique opportunity to study the myocardial ischemic response to controlled coronary occlusion and to investigate the functional significance of the coronary collateral circulation in humans. Using this model, several studies (1,2) demonstrated a limitation of myocardial ischemia during transient coronary occlusion in patients with developed collateral flow toward the occluded vessel. Other studies (3–7) documented the dynamic nature of the collateral circulation: preexisting channels that are not visible on baseline coronary angiography can become visible when the recipient vessel is suddenly occluded. These studies have shown the protective effect of these so-called recruitable collateral vessels against sudden coronary ischemia; however, the time course of collateral recruitment remains unknown.

It is a common observation that patients undergoing angioplasty manifest less angina and fewer electrocardiographic (ECG) changes with successive coronary occlusions, as if the anginal threshold has progressively increased (8). In a recent study by Deutsch et al. (9), adaptation to ischemia during the second of two balloon inflations during angioplasty was documented, but the mechanism of this apparent ischemic preconditioning remains speculative.

The purpose of the present study was 1) to evaluate whether multiple prolonged balloon inflations during coronary angioplasty would further lessen the myocardial ischemic response to sequential coronary occlusion, and 2) to assess the early enhancement of the recruitable collateral circulation as a possible underlying mechanism.

Methods

Study group. Seventeen patients, 14 men and 3 women with a mean age of 53 ± 8 years (range 44 to 75), undergoing

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coronary angioplasty for chronic angina were prospectively selected on the basis of the following criteria: 1) single-vessel coronary artery disease of the proximal (2 patients) or mid (15 patients) left anterior descending coronary artery, 2) no previous myocardial infarction, 3) normal left ventricular ejection fraction, and 4) no or minimal wall motion dysfunction in the myocardial territory at risk.

Patients with total coronary occlusion, baseline ST segment elevation or depression >1 mm, additional cardiac disease, severe noncardiac disease or peripheral artery disease were excluded. Six other patients who met the inclusion criteria were excluded, one because the contralateral coronary ostium could not be selectively reached with the 5F catheter and five because the intensity of signs of myocardial ischemia associated with ventricular arrhythmias during the first coronary occlusion led to early balloon deflation before complete data recording.

The study was approved by the Comité de Protection des Personnes du Centre Hospitalier Universitaire de Rouen. Informed consent was obtained from each patient.

Medications. Beta-adrenergic blocking agents, calcium channel antagonists and long-acting nitrates were discontinued ≥24 h before the procedure. Patients were receiving a daily dose of aspirin (250 mg orally) for ≥1 week before coronary angioplasty; the last dose was given on the morning of the procedure. A continuous infusion of intravenous nitroglycerin (20 μg/min) was started 1 h before the procedure. Intravenous heparin (10,000 IU) was administered immediately before the first balloon inflation. No other drugs were given.

Catheterization and angioplasty procedure. Baseline selective coronary arteriography was performed in multiple projections, using an 8F guiding catheter introduced through an 8F sheath positioned in the right femoral artery. The optimal balloon size was selected by quantitative evaluation of the coronary artery diameters proximal and distal to the lesion, using the Philips DCI digital substraction imaging system. The severity of coronary stenosis was expressed as a percent reduction in lumen diameter. The balloon catheters (manufactured by either USCI or Boston Scientific) were advanced across the stenosis over a steerable 0.014-in. (0.036 cm) diameter guide wire (Hi-Torque floppy, Advanced Cardiovascular Systems, Inc.). Angioplasty consisted of five balloon inflations, each maintained for a minimum of 120 s (mean 231 ± 49, 120 to 370) with an inflation pressure of 6 to 8 bars. An interval of 3 to 5 min was allowed between each balloon inflation and the ST segment was observed at baseline before subsequent balloon inflations were instituted. A 5F right Amplatz coronary arteriographic catheter and a 5F pigtail catheter were sequentially advanced through a 5F sheath placed in the left femoral artery. These catheters were used for contralateral coronary arteriography and left ventricular angiography before, during and after coronary occlusions.

Assessment of Collateral Circulation and Myocardial Ischemia

Collateral circulation. Evaluation of the collateral circulation was done by visual gradation of the collateral vessels and measurement of coronary occlusion pressure. Contralateral coronary contrast injections were performed at baseline and during balloon inflation through the 5F diagnostic catheter positioned in the right coronary ostium. Eight milliliters of contrast medium (meglumine diatrizoate [Renografin 76]) was injected over 4 s, with the rate of contrast injection being carefully controlled. Washout was systematically recorded until the injected vascular bed was no longer opacified. Using the same technique of contrast injection, ipsilateral injections were performed during balloon occlusion through the guiding catheter. These injections also allowed us to confirm that there was no anterograde flow distal to the coronary occlusion. In two patients who had a left preponderant coronary anatomy, only ipsilateral contrast injections were performed.

Grading of collateral vessels was performed after completion of the procedure by analysis of the cine film from contralateral and ipsilateral coronary angiography performed in the 40° right anterior oblique view. Grading of collateral filling was made by three independent angiographers, who separately analyzed the cine films randomly without knowledge of other patient data. The extent of the collateral channels was quantified in 6 grades as follows: 0 = no visible collateral vessels; 1 = just visible intraseptal collateral channels; 2 = good visible intraseptal collateral channels, with no dye reaching the epicardial segments of the left anterior descending artery; 3 = partial filling of a segment of the left anterior descending artery or main side branches, or both; 4 = good but delayed filling of the epicardial segments of the left anterior descending artery with no dye reaching the inflated balloon and good filling of the side branches; and 5 = massive nondelayed filling of the left anterior descending artery and side branches, with the dye reaching the inflated balloon. In case the collateral vessels issued from both contralateral and ipsilateral arteries, the highest grade obtained with one artery was used for the quantification. The interobserver variability never exceeded one grade and any disagreement was subjected to a majority decision. The only disagreement involved undergrading of grade 0 in two cases, grade 1 in three cases and grade 2 in one case. The percentage agreement between the three observers from grade 0 to 5 was, 100%, 87%, 93%, 95% and 100%, respectively.

The mean coronary occlusion pressure was defined as the lowest mean pressure recorded distal to the coronary occlusion. This pressure was obtained from the distal tip of the balloon catheter during balloon inflation. To obtain good and undamped pressure tracings, the guide wire was removed for measurements. We previously observed that with the balloon catheters used in the study, no measurable changes in coronary pressure transmission were seen during balloon

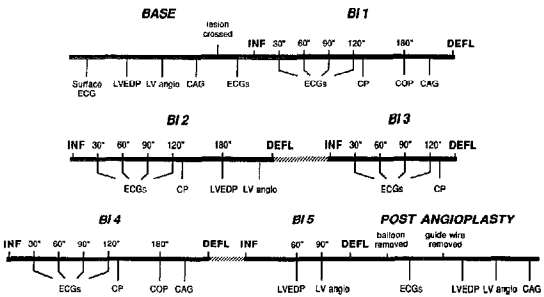


Figure 1. Summary of study protocol and chronology of variables recorded at baseline (BASE), during each of the five balloon inflations (BI) and after (POST) angioplasty. CAG = coronary angiogram; COP = coronary occlusion pressure; CP = chest pain; DEFL = balloon deflation; ECGs = 12-lead surface and intracoronary electrocardiograms; INF = balloon inflation; LV angio = left ventricular angiogram; LVEDP = left ventricular end-diastolic pressure.

inflation up to an inflation pressure of 10 bars. Mean coronary occlusion pressure was expressed in absolute terms and normalized for the mean proximal aortic pressure measured through the guiding catheter. The mean gradient was defined as the difference between the mean aortic pressure and mean coronary occlusion pressure.

Pressures were determined by using fluid-filled tubings and Viggo Spectramed T 150 AD pressure transducers and were recorded on Omnicorders 8 M 14 (Mennen Medical).

Myocardial ischemia. Myocardial ischemia was assessed by clinical, ECG, hemodynamic and angiographic indexes.

Chest pain. Patients were closely interrogated about chest pain during balloon inflations. The severity of pain was graded on a scale from 0 to 3, according to the intensity of discomfort.

Electrocardiograms. Surface ECGs were obtained by using a standard 12-lead recorder (Mingograf 7, Siemens) and displayed simultaneously with the intracoronary ECG. The intracoronary ECG was obtained with the distal end of the guide wire placed in the center of the ischemic zone by connecting lead V_6 of the standard ECG to the proximal end of the guide wire with a sterile clip. The 30-cm most distal section of the guide wire was not insulated, whereas the shaft was coated with Teflon. Special attention was given to the position of the guide wire in the left anterior descending artery. Misplacement into side branches was avoided by performing repeated coronary angiograms in multiple views. The distal tip of the guide wire was placed 5 to 6 cm beyond the balloon catheter tip and accurately positioned at the same site for each successive recording. Simultaneous surface and intracoronary ECGs were recorded before, during and after coronary occlusion. Regional transmural myocardial ischemia was defined as the presence of ST segment elevation >0.1 mV in at least one lead of the surface ECG or in the intracoronary ECG tracing, or both; ST segment shift was measured 80 ms after the J point on tracings recorded at a paper speed of 50 mm/s. Each lead of the surface ECG and the intracoronary lead were calibrated before the procedure (10 mm = 1 mV).

Angiographic analysis of global and regional left ventricular function. In the last 11 consecutive patients in the series, 40° right anterior oblique selective left ventriculograms were obtained before, during and after coronary occlusion by injection of 30 ml of contrast medium at a rate of 15 ml/s. Left ventricular end-diastolic pressure was measured before each contrast injection. End-diastolic and end-systolic left ventricular volumes (Simpson's rule) and ejection fraction were computed. Regional wall motion was studied according to the method of Leighton et al. (10). The percent shortening of 30 hemiaxes along the anterior and inferior left ventricular border was calculated, and hypokinesia was defined as a percent shortening <2 SD below normal values. The extent of the hypokinetic zone was quantified by two variables computed from the graphic wall motion outline according to a method described in an earlier report (11): a so-called hypokinetic surface (surface limited by the patient's curve and the lower limit of normal values) measured by planimetry and a so-called hypokinetic length, defined as the percent of left ventricular circumference demonstrating hypokinesia. These two variables provide an estimate of the importance of the hypokinetic zone, even though they cannot be considered as a true physical measure of this zone.

Study protocol and chronology of variables recorded (Fig. 1). Because of the limited balloon inflation time, all variables studied could not be recorded at each of the five balloon inflations:

1. At baseline study before angioplasty, the surface ECG was obtained, left ventricular end-diastolic pressure was measured and a left ventricular angiogram was performed, followed by left coronary artery and contralateral coronary arteriograms. The lesion was then crossed by the guide wire and the surface and intracoronary ECGs were recorded.

2. During angioplasty in the course of the first four

Table 1. Coronary Angiographic and Hemodynamic Variables in 17 Patients

Case No.	Age (yr)/ Gender	Before PTCA	Collateral Grade BI 1	Collateral Grade BI 4	After PTCA	COP (mm Hg) BI 1	COP (mm Hg) BI 4	COP/Ao (mm Hg) BI 1	COP/Ao (mm Hg) BI 4
1	61/F	0	0	1	0	20	24	0.22	0.26
2	53/M	0	2	4	0	30	41	0.28	0.28
3	49/M	0	2	3	0	16	23	0.20	0.27
4	52/M	1	5	5	0	25	28	0.40	0.37
5	52/M	0	2	2	0	29	36	0.24	0.26
6	75/M	3	4	5	0	44	42	0.41	0.48
7	59/M	0	2	3	0	26	36	0.21	0.25
8	49/M	2	5	5	0	24	24	0.32	0.34
9	44/M	1	3	5	0	30	46	0.33	0.48
10	70/F	0	2	2	0	32	34	0.52	0.52
11	51/M	0	2	2	0	31	36	0.25	0.28
12	44/M	0	3	4	0	44	58	0.37	0.46
13	55/M	0	1	2	0	32	28	0.25	0.26
14	47/M	2	5	5	0	48	56	0.31	0.37
15	46/M	0	1	2	0	32	49	0.29	0.48
16	60/M	0	3	4	0	29	29	0.24	0.23
17	52/M	0	2	2	0	30	30	0.26	0.25
Mean ± SD	53 ± 9					31 ± 8	36 ± 11	0.30 ± 0.10	0.34 ± 0.10
p Value						<0.01		<0.01	

Ao = mean aortic blood pressure; BI = balloon inflation; COP = mean coronary occlusion pressure; F = female; M = male; PTCA = percutaneous transluminal coronary angioplasty.

balloon inflations, surface and intracoronary ECGs were recorded every 30 s up to 120 s of coronary occlusion. At 120 s, heart rate was measured and chest pain graded. The other variables were recorded as follows: *a) During the first coronary occlusion*, at 180 s, coronary occlusion pressure was recorded and immediately thereafter, contralateral and ipsilateral coronary arteriograms were performed. The balloon was then deflated. *b) In the second coronary occlusion*, at 180 s, left ventricular end-diastolic pressure was measured and a left ventricular angiogram was performed, followed by balloon deflation. *c) During the third coronary occlusion*, the balloon was kept inflated for a period of 120 s without any hemodynamic or angiographic data being recorded. *d) In the fourth coronary occlusion*, all variables obtained during the first balloon inflation were recorded in the same sequence. *e) During the fifth coronary occlusion*, at 60 s of balloon inflation, left ventricular end-diastolic pressure was measured and a left ventricular angiogram was performed. The balloon was then deflated and the balloon catheter withdrawn from the coronary artery over the guide wire.

3. After angioplasty, surface and intracoronary ECGs were obtained before withdrawal of the guide wire. Left ventricular end-diastolic pressure was recorded and a left ventricular angiogram performed, followed by left coronary and contralateral coronary arteriograms.

Data analysis. Baseline and postangioplasty variables were compared. Similarly, data recorded during the first and fourth balloon inflations (collateral circulation variables) and those recorded during the second and fifth balloon inflations (left ventricular function variables) were compared. The grade of chest pain and ECG recording were sequentially compared during the first and fourth balloon inflations.

All variables are presented as mean value ± SD. Statistical analysis was performed by using standard chi-square analysis and paired *t* tests for paired data programs.

Results

Coronary angioplasty results. Before angioplasty, all patients had a left anterior descending coronary artery stenosis ≥70% (mean 78 ± 6%). After angioplasty, the mean residual stenosis was 28 ± 10%, and the most severe residual stenosis was 40%. Only one patient had an intimal tear at the site of dilation noted on postangioplasty coronary angiography; because acute coronary occlusion occurred in this patient within hours after the procedure, a second angioplasty procedure was performed with satisfactory results. There were no other complications.

Changes in Collateral Filling With Repetitive Coronary Occlusion (Table 1)

Angiographic findings. Baseline coronary arteriography demonstrated preexisting collateral channels in 5 of the 17 patients (grade 1 in 2 patients, grade 2 in 2 patients and grade 3 in 1 patient). During the first coronary occlusion, collateral filling improved in 16 patients, by 1 grade in 4 patients, 2 grades in 6 patients, 3 grades in 4 patients and 4 grades in 2 patients. Grade 5 collateral filling was observed in three patients, two of whom had a grade 2 stenosis and one a grade 1 stenosis on baseline coronary arteriography. Collateral filling was seen during the first balloon inflation in all but one patient, who had no collateral vessels at baseline study.

Table 2. Clinical and Electrocardiographic (balloon inflations 1 and 4), Hemodynamic and Angiographic (balloon inflations 2 and 5) Indexes of Myocardial Ischemia in 17 Patients

	Chest Pain		Intracoronary ST Segment Elevation (mV)		LVEDP (mm Hg)		LVEF (%)		HS (cm²)		HL (%)	
Case No.	BI 1	BI 4	BI 1	BI 4	BI 2	BI 5	BI 2	BI 5	BI 2	BI 5	BI 2	BI 5
1	2	1	1.3	0.6	26	17	49	64	15	13	51	43
2	3	1	1.3	0.3	24	24	54	66	16	14	45	41
3	2	0	2	0.7	21	12	60	65	7	6	31	32
4	0	0	0	0	—	—	—	—	—	—	—	—
5	3	1	1.8	1.7	27	23	48	60	10	16	33	36
6	0	0	0.1	0	—	—	—	—	—	—	—	—
7	2	0	0.6	0	—	—	—	—	—	—	—	—
8	0	0	0.8	1	10	10	70	79	0	0	0	0
9	3	2	0.3	0.2	14	14	54	61	14	12	45	46
10	0	0	0.8	0.4	12	13	58	53	15	15	43	46
11	3	2	—	—	25	8	46	52	19	13	62	39
12	3	0	1.1	0.7	—	—	—	—	—	—	—	—
13	2	0	0.5	0.1	—	—	—	—	—	—	—	—
14	1	0	2.5	0	18	17	56	61	6	1	39	9
15	2	0	1.4	1.2	—	—	—	—	—	—	—	—
16	1	0	2.3	0.9	25	12	40	47	21	20	62	61
17	1	1	0.6	0.3	18	14	44	43	20	19	69	53
Mean ± SD			1 ± 0.6	0.5 ± 0.5	20 ± 6	15 ± 5	53 ± 8	59 ± 10	13 ± 6	12 ± 7	44 ± 19	37 ± 18
p Value			<0.001		<0.02		<0.01		NS		NS	

HL = length of the hypokinetic zone; HS = surface area of the hypokinetic zone; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

During the fourth coronary occlusion, collateral channels were observed in all 17 patients.

Coronary hemodynamics. During the first balloon inflation, coronary occlusion pressure was 31 ± 8 mm Hg (0.3 ± 0.1 mm Hg when normalized for mean aortic pressure). These values were significantly higher during the fourth coronary occlusion: 36 ± 11 ($p < 0.01$) and 0.34 ± 0.1 mm Hg ($p < 0.01$), respectively.

The mean gradient between mean aortic and mean coronary occlusion pressures was not significantly different during the first and fourth coronary occlusions in the total series (74 ± 22 vs. 71 ± 24 mm Hg).

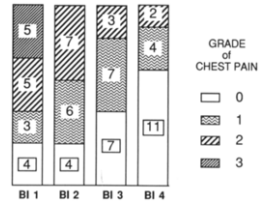
Indexes of Ischemia During Repetitive Coronary Occlusions (Table 2)

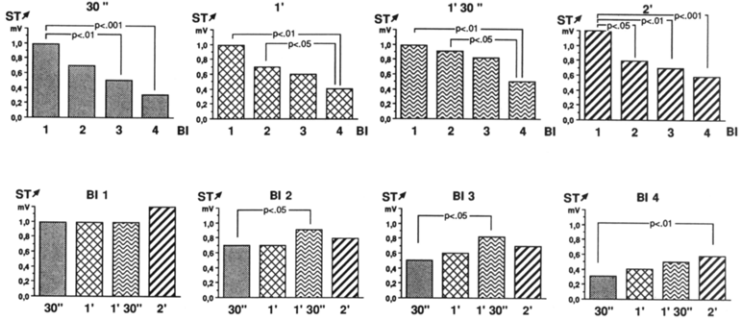
At baseline study, heart rate was 72 ± 13 beats/min and mean aortic pressure was 102 ± 19 mm Hg. These values remained statistically unchanged during each balloon inflation and after angioplasty.

Chest pain. The number of patients who experienced chest pain during coronary occlusion and the intensity of discomfort progressively decreased with repeated balloon inflations (Fig. 2). Thirteen of the 17 patients experienced chest pain during the first coronary occlusion; 6 patients had chest pain only during the fourth coronary occlusion.

Intracoronary ECG. An intracoronary ECG was obtained in 16 of the 17 patients but was not recorded in 1 patient for technical reasons. The ST segment elevation was observed in 15 patients during the first coronary occlusion, but no ST elevation was noted in the patient with grade 5 collateral filling (mean ST elevation was 1 ± 0.6 mV). In comparison, ST elevation was noted in 12 patients only during the fourth coronary occlusion and mean ST elevation was significantly lower (0.5 ± 0.5 mV, $p < 0.001$). Figure 3 shows the pattern of evolution of ST segment changes recorded every 30 s up to 120 s during the first to the fourth sequential balloon inflation. A greater regression of ST segment elevation was demonstrated with each of the four

Figure 2. Decrease in chest pain with sequential balloon inflations. Chest pain was graded from 0 to 3 at 120 s after the onset of each balloon inflation (BI), according to the intensity of discomfort. The number of patients with each grade appears in the squares.





balloon inflations. The rate of ST segment elevation in relation to time became less important with each balloon inflation.

The ST segment elevation was much lower in the surface ECG than in the intracoronary tracing in all patients (Fig. 4). The maximal ST segment shift was noted in precordial leads V_2 and V_3. The ST segment elevation decreased from 0.46 ± 0.5 mV at the first inflation to 0.24 ± 0.25 mV at the fourth ($p < 0.05$).

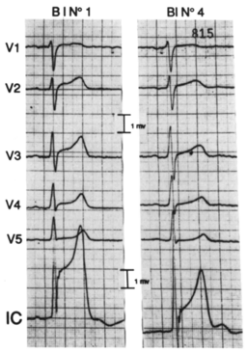
Left ventricular hemodynamic and angiographic data. Left ventricular end-diastolic pressure was normal at baseline (11 ± 5 mm Hg) and remained the same after angioplasty (11 ± 3 mm Hg). This pressure increased to 20 ± 6 mm Hg during the second coronary occlusion ($p < 0.01$), but a lesser increase was noted during the fifth coronary occlusion (15 ± 5 mm Hg, $p < 0.02$).

Left ventricular ejection fraction was 72 ± 6% at baseline and remained unchanged after completion of angioplasty (71 ± 10%). In the left ventricular angiogram performed during the second coronary occlusion, ejection fraction decreased to 53 ± 8% ($p < 0.01$). In comparison, a lesser decrease in ejection fraction was observed during the fifth coronary occlusion (59 ± 10%, $p < 0.01$).

The minimal segmental wall motion abnormalities seen in the territory at risk in the baseline left ventricular angiogram remained unchanged after angioplasty. The surface area and the length of the hypokinetic zone were, respectively, 1 ± 3 cm^2 and 6 ± 12% before and 1 ± 2 cm^2 and 5 ± 12% after angioplasty. In the opposite territory, marked and comparable regional anterior wall motion abnormalities occurred during sequential balloon inflations, with an increase in the surface area and length of the hypokinetic zone, respectively, to 13 ± 6 cm^2 and 44 ± 19% at the second inflation and to 12 ± 7 cm^2 and 37 ± 18% at the fifth.

Figure 3. Pattern of evolution of intracoronary ST segment elevation (ST↗) as recorded every 30 s up to 120 s during the first four coronary occlusions. **Upper panel.** Comparison of ST shift at a similar time during each of the four balloon inflations (BI) showing a progressive decrease in ST segment elevation. **Lower panel.** ST shift in relation to time, indicating a decreased rate of ST segment elevation with successive coronary occlusions. All statistically significant differences are indicated.

Figure 4. Patient 17. Representative example of ST segment changes observed at 120 s after the onset of balloon inflations (BI) 1 and 4 in surface electrocardiographic (ECG) leads V_1 to V_5 and in the intracoronary (IC) ECG. In the surface ECG, the maximal ST elevation was noted in precordial lead V_3; it was measured to be 0.4 mV at the first and 0.2 mV at the fourth coronary occlusion. In comparison, in the intracoronary ECG, a dramatic ST elevation of 2.3 mV was observed during the first balloon inflation but ST elevation was only 0.9 mV during the fourth balloon inflation.



Discussion

Increased anginal threshold with repeat coronary occlusions. At our institution, conventional balloon coronary angioplasty usually consists of successive brief balloon occlusions of 60- to 120-s duration for a total inflation time of 2 to 3 min. The optimal duration of balloon inflation is currently determined by both the physician's personal experience and the limitation resulting from the patient's discomfort and ST segment elevation on the surface ECG. However, it is frequently observed that the duration of balloon inflation can be gradually prolonged during subsequent dilation cycles because of improved clinical and ECG tolerance to coronary occlusion.

This observation was supported by the results of a recent study by Deutsch et al. (9), which showed less evidence of myocardial ischemia on clinical, ECG, hemodynamic and metabolic indexes during the second of two periods of 2-min coronary occlusion during angioplasty. Conversely, in previous studies (12–14), brief (≤1 min) sequential balloon inflations did not reveal evidence of any fading ischemia with repeated coronary occlusions. A lesser duration of balloon inflation and other methodologic differences probably explain these discrepancies.

As in the study by Deutsch et al. (9), the present investigation was conducted in a homogeneous group of patients with stable angina, isolated left anterior descending coronary artery stenosis and normal left ventricular anterior wall motion. Our results are in accordance with the observations of the former study (9) and expand on it because we demonstrated that signs of ischemic injury further lessen during each episode of coronary occlusion. At the end of 2 min of balloon inflation, myocardial ischemia was found to be progressively reduced during coronary occlusions 1 to 4, as demonstrated by lesser anginal discomfort and a decrease in ST segment elevation on the intracoronary ECG. The rate of change in ST segment shift was also shown to decrease with each sequential period of coronary occlusion. In contrast to previous studies (12–14) that used the surface lead ECG and could not demonstrate reduced ischemic response to repetitive coronary occlusions, we used the intracoronary ECG in addition to a 12-lead surface ECG to demonstrate more subtle changes. Several reports (15–17) have shown that transient ischemia during angioplasty was more readily detected and with greater sensitivity with the intracoronary ECG than with the surface ECG. This observation was confirmed in our study and in a previous report from our institution (18).

Furthermore, evidence of regression of myocardial ischemic injury with sequential coronary occlusions was also assessed on the basis of hemodynamic and angiographic indexes of global left ventricular function. A lesser increase in left ventricular filling pressures and a lesser decrease in ejection fraction at the fifth than at the second balloon inflation were observed. We could not demonstrate a significant improvement in left ventricular regional anterior wall motion abnormalities during these two periods of coronary occlusion, but this lack may be explained by important individual variations in regional dysfunction observed in our relatively small group of patients. We are aware that in our study protocol, we performed a left ventricular angiogram over a shorter period at the fifth than at the second balloon inflation and this difference might have altered the overall hemodynamic and angiographic results. However, a shorter fifth balloon inflation was performed only to obtain a left ventricular angiogram because the latter could not be performed immediately after a coronary angiogram at the end of the fourth balloon inflation.

Changes in collateral circulation with repeated coronary occlusions. Whereas experimental studies (19) have documented that coronary collateral flow could be induced by repetitive coronary occlusions, little is known concerning the natural history of collateral flow development in humans and, more particularly, about the stimuli for recruitable collateral formation. In a report by Hill et al. (12), no change in collateral vessels was observed after 10 brief (20- to 30-s) episodes of coronary occlusion during angioplasty in five patients. One of the goals of the present study was thus to assess whether repeated long episodes of coronary occlusion could stimulate the recruitment of the collateral circulation. The need for multiple and prolonged sequences of balloon inflations was further emphasized by experimental observations (19) in dogs, which showed that longer coronary occlusions were more effective than brief occlusions for the development of the collateral circulation. Our results suggest that in keeping with these experimental observations, recruitable collateral vessels may be stimulated in humans with sequential transient coronary occlusions of a relatively long duration.

Enhanced collateral filling. In this investigation, we used a six-grade scale for quantification of collateral filling, a modification of the grading in four grades proposed by Rentrop et al. (3), to reflect accurately the changes in collateral filling that we had to quantify. We divided the degree of filling of septal branches into two grades and the degree of filling of the epicardial segment into three grades. A striking development of the collateral circulation was observed at the first coronary occlusion compared with findings at baseline coronary angiography. A further increase in collateral filling was demonstrated in 58% of the patients at the fourth coronary occlusion, indicating enhancement of the collateral circulation to the ischemic myocardium. Among the seven patients whose pattern of collateral visualization was unchanged, three already had maximal (grade 5) collateral filling at the first coronary occlusion. These patients could possibly have had a further increase in collateral flow, but this could not be demonstrated angiographically.

Increased coronary occlusion pressure. The coronary occlusion pressure has been demonstrated in previous studies (5,20) to be mainly dependent on the extent of the collateral circulation when anterograde flow is eliminated by proximal

coronary occlusion. The coronary occlusion pressure is higher in patients with recruitable collateral vessels than in those without (5). Coronary occlusion pressure was noted to be almost consistently higher at the fourth than at the first balloon inflation. Heibig et al. (21) previously reported a case of acute coronary artery occlusion after angioplasty, showing that multiple prolonged (>2-min) balloon inflations resulted in disappearance of ischemic signs and an increase in coronary occlusion pressure. They hypothesized that these changes could be due to coronary collateral recruitment. In contrast, Deutsch et al. (9) showed an actual decrease in great cardiac vein flow at the second of two balloon inflations, thus concluding there was no enhancement of recruitable collateral channels by sequential coronary occlusion. However, these investigators did not visualize the collateral circulation by angiography, and measurement of flow in the great cardiac vein is probably too crude a method for evaluation of collateral vessel development and subsequent minimal flow changes. Another explanation for this discrepancy could be the different methodology in our study, particularly the multiple coronary occlusions and longer total balloon inflation time. In an experimental study in dogs, Murry et al. (22) showed no increase in collateral flow on sequential coronary occlusions. However, their results cannot be extrapolated to the clinical situation of our patient group because collateral circulation in animals is different from that in patients with coronary artery disease. Preexisting collateral vessels were demonstrated in our patients, whereas data from animals with high collateral flow were excluded in the study by Murry et al. (22).

We do not have enough evidence to conclude there is a causal relation between the slight increase in recruitable collateral vessels and the decrease in myocardial ischemic response to repeat coronary occlusions because in individual cases, myocardial ischemia was shown to decrease with repeated balloon inflation even though no evidence of improved collateral circulation could be demonstrated. This result suggests that, in addition to recruitment of collateral vessels, other mechanisms may exist for improvement of myocardial ischemia. As shown by Murry et al. (22), preconditioning due to washing out by intermittent reperfusion of catabolites that accumulate during ischemia might play a role in the decreased ischemia with subsequent balloon inflations.

Limitations of the study. Our study had several limitations. 1) For ethical reasons, the routine use of intravenous nitroglycerin was maintained in these patients undergoing angioplasty. However, the dose of nitroglycerin was the same in all the patients and was maintained at a constant rate during the study. Nitroglycerin could have some influence on the collateral circulation (23). 2) The subjective evaluation of chest pain as a manifestation of ischemia has definite limitations. Most investigators have correlated myocardial ischemia with chest pain associated with ST segment elevation on the surface lead ECG. Here, we objectively monitored the intracoronary ECG to obtain more accurate and sensitive criteria for assessing myocardial ischemia. 3) Coronary blood flow and metabolic variables were not measured in our study and deserve further investigation for better evaluation of the results.

Clinical implications. Prolonged balloon inflations can be performed in proximal and mid-left anterior descending artery stenosis in most patients, as shown in our study. Unusually long balloon inflations were performed with no long-lasting deleterious effect on left ventricular function. Thus, the concept of application of prolonged sequential balloon inflations to improve immediate angioplasty results (24,25) could be applied in most situations.

Our study expands the concept that repeated myocardial ischemic episodes due to decreased blood supply to the territory at risk may be an important factor for stimulation or enhancement of collateral circulation. This is consistent with the observation that patients with the most severe coronary lesions and a longer duration of angina have more developed collateral vessels than do those with a shorter history of angina (26). Finally, the model used for coronary angioplasty in our study provides a valuable setting for further investigations of therapeutic techniques that may enhance the human collateral circulation.

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