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Restenosis after coronary angioplasty: review of the literature

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Histopathology of restenosis

Knowledge on the histopathology of restenosis is scarce. This indicates that, despite its frequent occurrence, restenosis after coronary angioplasty is rarely a lethal disease. Animal models provide some information on what might occur after angioplasty. However, the results of these studies should only be applied to the situation in the atherosclerotic human artery with great caution.

Steele *et al.* described the stages of healing and restenosis in carotid arteries of pigs receiving no medication[1]. One hour after balloon angioplasty, endothelial denudation, medial tears and platelet deposition were found. One day later, there was necrosis of smooth muscle cells. A week later, the endothelium had completely regrown. About a month later, there was mild proliferation of smooth-muscle cells. Significant restenoses, however, were due to organized intraluminal thrombi.

Waller *et al.* reported on necropsies in three patients who died 80 to 150 days after coronary angioplasty[2]. Only one of these patients showed clinical evidence of recurrence, but all showed significant stenoses at the presumed site of antioplasty. The lesions were not discernible from genuine atherosclerotic plaques and there was no evidence of healed dissection.

More in keeping with the current understanding of the mechanism of balloon angioplasty is a case report by Essed *et al.* on a patient who died at the beginning of a redilatation attempt 5 months after a successful angioplasty with recurrence of symptoms at 3 months[3]. These authors found medial dissection with a narrowing of the new channel by fibrocellular tissue.

Coronary restenosis: a new disease entity

Restenosis was rapidly recognized as one of the major problems with coronary angioplasty. It is now a well known disease entity accounting for numerous hospitalizations and interventions.

The restenosis rate of the first 169 consecutive patients treated by Gruentzig in Zurich was 25% after a mean of 18 months[4].

In 1982, Balcon *et al.* published a restenosis rate of 67% 3 months after the six successful angioplasties in their first 11 patients[5]. With the benefit of angioplasty 3 months after the intervention in only two of 11 patients, their lack of enthusiasm for this treatment was understandable.

At the same time, the PTCA Registry of the National Heart, Lung, and Blood Institute (NHLBI) of the United States reported a clinical recurrence rate, after a mean of 12 months, of 17% in 232 patients treated at 34 different centres[6].

In 1983, Meyer *et al.* reported a recurrence rate of 21% in 100 consecutive patients after an average of 6 months[7]. Their patients were fully anticoagulated with coumadin. The recurrence rate of patients with unstable angina was higher than that of patients with stable angina (24% *vs.* 17%).

In 1984, Meier *et al.* reported, from Atlanta, a recurrence rate of 33% in 514 consecutive patients[8]. The recurrences were documented at a mean of 5 months (range 1–9 months) after angioplasty. Most of the patients were treated with acetylsalicylic acid. Male sex and stenoses in the left anterior descending coronary artery (LAD) were identified as risk factors for restenosis. Figure 1 provides the details of the long-term outcome and management of these patients.

Another report from the PTCA Registry of NHLBI on 665 patients followed for 6 months indicated an angiographic recurrence rate of 34% that correlated well with clinical symptoms[9].

In 1985, Bertrand *et al.* reported a recurrence rate of 27% in 269 patients followed for an average of 6 months[10]. In the same year the PTCA Registry of the NHLBI confirmed male sex as a risk factor for

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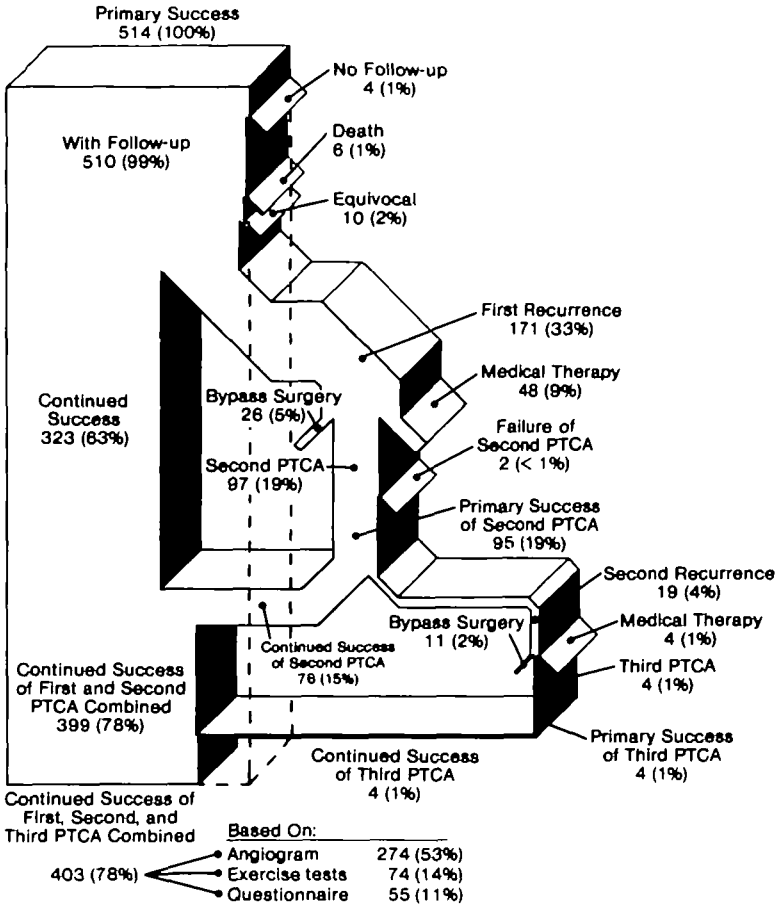

Figure 1 Follow-up for about 1 year of 514 consecutive patients with successful coronary angioplasty at Emory University in Atlanta, Georgia, U.S.A.

recurrence in the 3079 patients included up to that time[11]. The global recurrence rate was again calculated at 33%. In men it was 36% and in women it was 22% ($P < 0{\cdot}01$).

Kaltenbach *et al.*[12] and Kober *et al.*[13] reported the recurrence rates of the first 356 and 1000 patients in Frankfurt, respectively. The recurrence rate was about 15% for both initial patients followed for 6 months and for later patients followed for roughly 12 months. Virtually all the recurrences occurred within the first 3 months after angioplasty. They attributed their remarkably low recurrence rate to stringent adherence to a powerful follow-up regimen including high daily doses of acetylsalicylic acid (1·5 g), isosorbide dinitrate (120 mg), and verapamil (240–480 mg) or gallopamil (100 mg).

A third report from Atlanta on 1880 patients followed over an average of 7 months revealed a recurrence rate of 28%[14]. The presence of a visible local dissection after angioplasty in conjunction with a residual pressure gradient of < 15 mmHg identified a favourable subgroup with a recurrence rate of only 19%.

Mabin *et al.* reported a recurrence rate of 33% from the Mayo Clinic in 229 patients followed for a mean of 13 months[15]. In patients with symptoms at the time of the follow-up examination, restenosis was present in 71%. In those without symptoms, restenosis was found in only 14%

Table 1 summarizes the restenosis rates of some of the cited reports.

Recurrence in multilesion angioplasty or multivessel angioplasty

Assuming an independent restenosis rate of

Table 1 Reported recurrence rates of coronary angioplasty (in chronological order)

First author (place)	Year	Ref.	Number of patients	Follow-up time (months)	Recurrence rate	Remarks
Gruentzig (Zurich)	1982	[4]	169	18	25%	Including first patient
Kent (NHLBI Reg.)	1982	[6]	232	12	17%	Clinical data only
Meyer (Aachen)	1983	[7]	100	6	21%	Unstable 24%, stable 17%; anticoagulated with coumadin
Meier (Atlanta)	1984	[8]	514	10	33%	Higher in men and LAD acetylsalicylic acid, nifedipine
Holmes (NHLBI Reg.)	1984	[9]	665	6	34%	With symptoms 56%; without symptoms 14%
Bertrand (Lille)	1985	[10]	269	6	27%	
Cowley (NHLBI Reg.)	1985	[11]	3079	18	33%	Men 36%, women 22%
Kaltenbach (Frankfurt)	1985	[12]	356	6	12–17%	Repeat PTCA 33%, grafts 45% salicylate, nitrate, calcium blockers
Kober (Frankfurt)	1985	[13]	1000	12	15%	None after 3 months
Leimgruber (Atlanta)	1985	[14]	1880	7	28%	Less with dissection and residual gradient of $\leqslant 15$ mmHg
Mabin (Rochester)	1985	[15]	229	13	33%	With symptoms 71%; without symptoms 14%
Total			8493		28%	

Table 2 Theoretical recurrence rates in multilesion angioplasty (assumed recurrence rate per lesion: 33%)

Number of lesions	Recurrence rate per patient	
1	33%	1/3
2	56%	5/9
3	70%	19/27
4	80%	65/81
5	87%	211/243
n	$(3 \times 3^{n-1} - 2 \times 2^{n-1})/3^n \times 100\%$	

33% per lesion, the theoretical patient recurrence rate (recurrence in $\geqslant 1$ stenosis) in double lesion angioplasty (in 1 or 2 vessels) would be 56%. The formula used for this calculation and the respective recurrence rates for multiple lesion angioplasties are indicated in Table 2.

Hollman *et al.* reported a recurrence rate in single-vessel angioplasty of 38% and in multivessel angioplasty of 68%[16]. His findings concur with the expected recurrence rates and demonstrate that recurrence is a lesion-related phenomenon rather than a patient-related phenomenon. These figures should not be confused with follow-up data on patients with multivessel disease in whom angioplasty is done in one artery only[17].

Quantitative studies on restenosis

Fleck *et al.* reported on computer-assisted analysis of angiograms in 95 patients with follow-up angiography[18]. These authors manually traced two orthogonal views of the stenosis before and after angioplasty and again at follow-up. The catheter was used as calibration reference and the cross-sectional area of the stenosis was indicated in mm^2. Their definition for restenosis was a loss of $\geqslant 1\ mm^2$ of the cross-sectional area resulting in a $>70\%$ narrowing of the cross-section. The restenosis rate was 33%. It correlated well with subjective symptoms and stress-test data.

Johnson *et al.* compared a similar computer-assisted method for evaluating coronary stenoses with videodensitometry in 23 patients re-examined after coronary angioplasty[19]. The recurrence rate

was 35%. The two methods correlated fairly well ($r = 0{\cdot}77$).

Non-invasive detection of restenosis

Several non-invasive tests have been advocated for follow-up after coronary angioplasty. Bicycle exercise tests proved valid in documenting restenosis in the original patients of Gruentzig[20]. Treadmill exercise tests combined with thallium-201 scintigraphy detected six out of nine recurrences in a study from the Montreal Heart Institute[21].

Wijns *et al.* analyzed the predictive values of stress test and thallium-201 scintigraphy performed 1 month after angioplasty in relation to clinical and angiographic findings at 6 months[22]. For angina, the predicitive values of stress test and thallium-201 scintigraphy were 38% and 66% and for restenosis 50% and 74%, respectively ($P < 0{\cdot}005$ in favour of thallium-201 scintigraphy).

DePuey *et al.* found a similar predicitive value for restenosis (73%) with exercise radionuclide ventriculography performed shortly after angioplasty[23]. At the time of follow-up angiography, the predictive value of the same test was 75%.

Restenosis and drugs

In rabbits, both a combination of acetylsalicylic acid with dipyridamole and sulphinpyrazone significantly decreased the extent of restenosis 4 months after iliac ballon angioplasty[24].

A randomized study from Atlanta compared a daily dose of 325 mg acetylsalicylic acid with anticoagulation with coumadin[25]. Restenosis was slightly less frequent in patients treated with acetylsalicylic acid. However, statistical significance was only attained for patients in whom symptoms occurred >6 months before angioplasty where retensosis rates were 21% for acetylsalicylic acid and 44% for coumadin. The compliance in the coumadin group was rather poor and therapuetic prothrombin times were only documented in about one third of these patients.

Two calcium antagonists have been studied in randomized trials. Both failed to prove efficacious in preventing or significantly diminishing restenosis. Diltiazem, as an adjunct to a combination of acetylsalicylic acid and dipyridamole, did not reduce recurrence rate significantly in a study on 92 patients followed for 10 months at the Montreal Heart Institute[26]. The recurrence rate was 15% with diltiazem and 22% without. Nifedipine was examined as an adjunct to acetylsalicylic acid in a double-blind protocol on 241 patients followed for 4 months in Atlanta[27]. The restenosis rate was similar in patients receiving nifedipine (29%) and in patients receiving a placebo (33%).

Table 3 Risk factors for restenosis after coronary angioplasty

	Ref.
Male sex	[9,11]
Diabetes mellitus	[9,16]
Recent angina	[28]
Unstable angina	[7,9,28]
Variant angina	[29]
Stenosis in LAD	[8,16]
Stenosis in venous bypass graft	[9,12]
High initial degree of stenosis	[16]
High residual degree of stenosis	[28]
High residual pressure gradient	[14]
Absence of dissection after angioplasty	[14,16]
Coumadin therapy in stenoses older than 6 months	[25]
Interruption of therapy with acetylsalicyclic acid	[18]

Risk factors for restenosis

The risk factors for restenosis identified so far are listed in Table 3. The following risk factors were documented in at least two independent studies: male sex, diabetes mellitus, stenosis in the left anterior descending coronary artery or in a venous bypass graft, and absence of intimal dissection after angioplasty.

The conclusion from a study done in Munich[18] that the discontinuation of acetylsalicylic acid is a risk factor for the development of restenosis may be challenged. Acetylsalicylic acid was discontinued for gastric pain in all cases concerned and, therefore, these symptoms may already have been an expression of recurrent coronary stenosis.

It must be admitted that currently there is no proved and practicable method for reducing the recurrence rate after coronary angioplasty.

Summary

The average restenosis rate reported so far in the literature is just below 30%. Although restenosis correlates well with the recurrence of symptoms,

the two factors are not identical. The incidence of myocardial infarction during the first 2 years after coronary angioplasty is 4% and the incidence of death is 2%[30]. These two cardiac events are rarely the first symptom of restenosis. Restenosis, therefore, is not primarily a life threatening disease but still deserves prompt evaluation and correction.

Restenosis is stenosis-related rather than patient-related. Thus, restenosis rate per patient increases with the number of lesions or arteries treated.

Restenosis rates vary considerably with centres. Serial analyses of restenosis rates at individual centres revealed that the restenosis rates remained constant at a centre-specific level. Differences in case selection and particularities in data definition and analysis may account for both these observations. There is no sound evidence that procedural factors (ballon size, number, duration, or pressure of inflations, etc.) or drug regimens are capable of reducing the recurrence rate. All risk factors for restenosis identified so far are difficult to influence. Extinguishable factors such as smoking seem of little importance in this particular problem.

Efforts to find ways of reducing restenoses after coronary angioplasty are commendable and necessary. Their chance of success, however, is small. 'Old customers' will continue to represent 20–30% of the clientele for coronary angioplasty. Their risk for failure and complications is small, but they do carry a considerable risk of restenosis.

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