ANALYSIS OF THE EVOLUTION OF CORONARY ARTERY DISEASE

— Evaluation of 227 cases by restudy of coronary arteriography —

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Some 227 patients who showed a 50% or greater narrowing of at least one major coronary artery in the first study underwent recatheterization at a mean interval of 35.6 months. Coronary arterial lesions and the degree of narrowing [i.e., normal (absent), 25%, 50%, 75%, 90%, 99% and complete occlusion (100%)] were classified in accordance with the AHA reporting system. When the lesions in the second study showed a change of equal or more than 2 in the above 7 stages in comparison with the first study, either progression or regression was determined. Of the 227 patients, progression occurred in 73 (32%) and regression was found in 7 (3%). In the aggravated group in symptom, progression was noted in 58%, and even in the stabilized group, progression was observed in 22%. As a result of the second study, 15 (21%) out of 73 patients showing progression underwent surgical treatment, and more than half of these cases (9/15) were constituted by the stabilized group. During the above follow-up periods, myocardial infarction occurred subsequently in 14 (19%) out of 73 patients showing progression. Up to the present time, sudden deaths occurred in 8 patients, and 5 out of 8 patients were also of the stabilized group.

The authors wish to emphasize from these findings the necessity of aggressively pursuing restudy even in stabilized cases showing symptoms of ischemic heart disease.

THE progression of coronary arterial stenosis causes a new myocardial infarction in patients with angina pectoris and thus presents a serious problem. This progression also results in a re-attack in patients with old myocardial infarction at other sites. Finally, it produces a high possibility of death from myocardial infarction. However, the history of the use of coronary arteriograms is not long, and its spread has been delayed especially in Japan.

Key Words:

Progression
Regression
Coronary arteriography
Elective restudy
Coronary risk factor

Hence, hardly any studies have been made on chronological changes in coronary arterial lesions among Japanese patients. Reports in Japan concerning this problem have been made only by Nobuyoshi et al¹ and Hiraiwa². In addition, the number of cases in their reports is small, and the follow-up periods are short. Therefore studies involving a larger number of cases with extended periods of observation have long been awaited.

In the present study, the authors evaluated 227 patients for longer periods of time than those in the reports mentioned above. Coronary arteriography, therefore, could be repeated and a more detailed analysis conducted in comparison with previous reports in Japan.

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Fig.1. Progression and clinical symptoms.

MATERIALS AND METHODS

Out of a series of 3,158 patients who had coronary arteriograms in our department from March 1975 to March 1984, 227 patients who showed a 50% or greater narrowing of at least one major coronary artery in the initial study were selected to undergo subsequent coronary arteriography at specified intervals. Patients who had A-C bypass operations were excluded from the study.

Of these 227 patients, 127 (56%) had myocardial infarction and 100 (44%) had no infarction. The latter group included 11 patients who had of a variant form of angina pectoris. The patients consisted of 203 men (89%) and 24 women (11%) ranging in age from 35 to 70 years (average 54.6 ± 8.5 years). The intervals between studies was 6 to 103 months (average 35.6 ± 16.9 months) (Table I).

Similar to earlier reports^{2,3} coronary arteriography was performed either by the Sones or Judkins technique. In both methods, coronary arteriography was performed after sublingual administration of 0.3 mg nitroglycerine from more than 4 directions for the left coronary artery and at least 2 directions for the right coronary artery. Cinefilms were taken on a 6 inch image intensifier (philips Cardiodiagnost) at 30 frames per second using 35 mm film (Kodak CFS or CFX).

Coronary arterial lesions were classified in accordance with the AHA Reporting system⁴

Clinical symptoms vs. treatment

Fig.2. Relation of clinical symptoms to treatment.

into Segments 1 to 4 for the right coronary artery (RCA), Segment 5 for the main trunk (LMT), Segments 6 to 9 (10) for the left anterior descending artery (LAD), and Segments 11 to 14 (15) for the left circumflex coronary artery (LCX); the degree of narrowing of the coronary artery was divided into 7 stages; normal (absent), 25%, 50%, 75%, 90%, 99%, and complete occlusion (100%). When, as a result of observation by a number of experienced physicians, the lesions at the second coronary arteriography showed a change of equal or more than 2 in the above 7 stages, in comparison with the first study, either the progression or regression of coronary arterial lesions was determined. When the change of lesions was equal or less than 1 stage, non-progression or non-regression was judged to be the case. The cases in which regression and non-regression were noted were included in the non-progression group. Statistical analysis was performed using the chi-square test or the unpaired t-test.

RESULTS

The mean interval between studies was 35.6 ± 16.9 months (range 6–103 months). In the second study, 32% (73 patients out of 227) met the criteria for progression, while 68% (154 patients out of 227) did not (Fig. 1).

The mean age of the group which showed progression (Group P) and of the group which showed non-progression (Group N-P) were 53.6 ± 8.8 years and 55.0 ± 8.1 years, respectively, and the mean interval of coronary arteriography Group P and Group N-P were 37.5 ± 18.1 months and 34.8 ± 15.2 months, respectively. No statistically significant difference was found between the two groups in any

TABLE I RELATION OF AGE, SEX AND INTERVAL TO PROGRESSION

	Non progression	Progression	Total
Men	139 (68%)	64 (32%)	203 [89%]
Women	15 (63%)	9 (37%)	24 [11%]
Total	154 (68%)	73 (32%)	227
Age (yr) (Mean $\pm$ SD)	55.0 $\pm$ 8.1	53.6 $\pm$ 8.8	54.6 $\pm$ 8.5
	N.S.		
Interval between studies (month) (Mean $\pm$ SD)	34.8 $\pm$ 15.2	37.5 $\pm$ 18.1	35.6 $\pm$ 16.9
	N.S.		

TABLE II DEATHS POSSIBLY DUE TO CORONARY EVENTS

Pts	Age	Sex	History	Symptom	Arteriogram				Death mo.	Type of death
					LMT	LAD	LCX	RCA		
1	53	M	PMI	stable		75%	100%	75%	34	Sudden after brief pain
2	48	M	IMI	stable		50%		100%	25	Sudden; Pain 1hr
3	56	M	Angina	stable		75%	90%	50%	40	Sudden
4	48	M	AMI	stable	25%	75%		100%	29	CHF LV aneurysm
5	48	M	AMI	stable		90%			20	CHF LV aneurysm
6	59	M	AMI	stable		100%	100%	90%	49	Sudden Post SVG (remote)
7	52	M	AMI	stable		100%		75%	16	Sudden after brief pain
8	59	M	AMI	aggravated		100%		99%	26	Sudden
9	39	M	IMI	aggravated		75%		100%	15	Sudden Post SVG (remote)
10	56	M	IMI	aggravated		90%		100%	13	Sudden

PMI = Posterior myocardial infarction; IMI = Inferior myocardial infarction; AMI = Anterior myocardial infarction; LMT = Left main trunk disease; LAD = Left anterior descending coronary artery; LCX = Left circumflex coronary artery; RCA = Right coronary artery; CHF = Congestive heart failure; LV aneurysm = Left Ventricular aneurysm; Post SVG = Post Saphenous Vein Graft

parameter (Table I).

In the group in which subjective symptoms were aggravated (Aggravated Group), such as the occurrence of new angina of effort and rest, or the frequency of anginal attacks increased, progression was noted in 37 out of 64 patients (58%), whereas in the group in which the symptoms were stabilized (Stable Group), progression was found in 36 out of 163 patients (22%). The difference was significant. ($p < 0.005$) (Fig. 1).

As a result of the restudy, 15 (21%) out of 73 patients showing progression underwent elective coronary bypass graft surgery, and 9 (60%) out of these 15 patients belonged to the Stable Group. However, 58 (79%) out of these 73 patients continued medical treatment after the restudy; less than half (45%) belonged to the Stable Group. These differences were not significant (Fig. 2).

Since the restudy, deaths have occurred in 10 patients due to coronary events, including

Fig.3a. Relation of age to progression.

Fig.3b. Relation of interval between studies to progression.

8 sudden deaths. The cause of deaths of 2 other patients were attributed to congestive heart failure. In the 8 patients expiring suddenly, only 3 (3/64 5%) belonged to the Aggravated Group and 5 others (5/163 3%) to the Stable Group (Table II).

Grouped according to age, patients in the first study who were in their forties, fifties, and

sixties, showed progression in 36%, 35%, and 29% of cases, respectively, while in younger patients under 39 years of age, progression was observed in 45%, indicating a higher rate of progression than in the other 3 groups, but no significant difference (Fig. 3-a).

In the group in which the interval before restudy was 49 to 60 months, progression was

Fig. 4. The relationship between AHA's grades and progression for 98 arteries in which progression was noted, the relationship between AHA's grades and progression was studied, and progression of over 4 grades was observed in 25 out of 98 arteries.

noted in 46% of the patients. This was about 1/2 of all the patients, as compared with 27% to 35% in the other 5 groups, and the difference was significant. ($p < 0.05$) (Fig. 3-b).

When the degree of progression of coronary arterial lesions in 98 branches in 73 patients showing progression was examined, it was found that the number of branches in which 2-grade progression occurred was 44 (45%), followed by 29 branches (30%) of 3-grade progression, 16 branches (16%) of 4-grade progression, 6 branches (6%) of 5-grade progression, and 3 branches (3%) of 6-grade progression. In other words, about one quarter of the total number of branches (25/98) showed over 4-grade progression (Fig. 4).

The incidence of a high degree of progression above Grade 3 was examined. Progression in both the LAD and the LCX was found in 15 (44%) out of 34 patients, and 8 (40%) out of 20 patients, respectively, whereas that in the

RCA appeared in 29 (71%) out of 41 patients, showing a significant difference ($p < 0.05$) in percentages (Fig. 5).

Classification was made by the degree of narrowing of coronary arteries of patients in whom complete occlusion was discovered in the restudy. There were 6 (30%) complete occlusions in the LCX in 20 patients and 8 (24%) in the LAD in 34 patients, while in the RCA, there were 16 (39%) in 41 patients, but no significant difference was noted. In the LMT, no such cases were found (Fig. 5).

The appearance of a new lesion was classified by the degree of narrowing of coronary arteries. In the second study, new lesions were found in 39 (40%) out of 98 branches whose coronary arteriograms did not show any obstruction at the first study. They were most frequent in the LMT (67%, or 2 out of 3 patients). On the other hand, the incidence was least in RCA at 32% (13/41), followed by LCX at 40% (8/20) and LAD at 47% (16/34). These differences were not significant (Fig. 5).

Figure 6 shows the relationship between the degree of narrowing and the interval before studies in 98 branches showing progression. Within in short period of 20 months, progression was found in 13 branches in 12 patients, which included 3 patients in whom new infarction attacks were found. As is clear from Fig. 6, the speed and the degree of progression varied greatly according to the patient, and no definite trend was noted. In 14 (19%) out of 73 patients (including the above 3), constituting nearly one-fifth of the whole Group P, a high degree of progression developed into infarction in spite of various medical treatment.

Reviewing the 98 branches in which progression was detected and classifying them by the coronary artery, the authors found 41 RCA branches (42%), 34 LAD branches (35%), 20 LCX branches (20%), but only 3 LMT (3%) (Fig. 7).

Figure 8 shows the progression of the coronary artery lesions by the AHA Classification of each branch. In each RCA segment, the site most apt to show progression was Segment 1, which constituted 39% (16/41), followed by 24% (10/41) at Segment 4, 20% (8/41) at Segment 2, and 17% (7/41) at Segment 3. Among 16 patients in whom progression was observed at Segment 1, it developed into complete occlusion in 10 patients (63%), in 9 of them this complete occlusion was due to the

Fig.5. Incidences of progression of over 3 grades, complete occlusion and New Lesions, classified by the coronary artery.

Fig.6. Relation of grade and time course of progression.

98 arteries exhibiting progression in 73 cases

Fig. 7. Frequency of progression in 73 patients/98 arteries, classified by the coronary artery.

appearance of the new lesion.

At each segment in the LAD, the rate of progression was highest at Segment 6 where there were 47% (16/34), followed by 27% (9/34) at Segment 9, 21% (7/34) at Segment 7, and 5% (2/34) at Segment 8. On the other hand, the progression at the middle segment (Segment 7) and the distal segment (Segment 8) in the LAD was less than half that at the proximal segment (Segment 6).

In the LCX, the progression at Segment 11 was 35% (7/20), and 30% (6/20) at Segment 13. In both segments put together, about two-thirds of the whole was occupied, followed by 20% (4/20) at Segment 14, and 15% (3/20) at Segment 12 (Fig. 8).

Table III shows the relationship between the progression for coronary arterial lesions and the number of affected coronary arteries. Single vessel progression occurred most frequently in 53 (70.7%) out of 75 patients (i.e., in 2 out of 3 patients in whom progression was noted in the LMT). However, progression was also noted in

arteries other than the LMT, one in the RCA, and one in the LCX. Therefore, 75 patients were analyzed by adding these 2 to the 73 patients in Group P; progression in two vessels (double vessel progression) occurred less frequently in 19 (25.3%), and change in three vessels (triple-vessel progression) was noted in only 3 (4.0%) of a total of 75 (Table III).

Then, the extent of the coronary artery disease was judged on the basis of the number of vessels involved. Single vessel disease (SVD) was defined as significant coronary artery disease (50% or greater narrowing) of only one of the three major coronary arteries, while double (DVD) and triple (TVD) vessel disease indicated significant disease of two and three coronary arteries respectively.

When the SVD, DVD, TVD, and LMT ratios in the first and the second studies were compared, SVD was reduced by 1/3 from 33 patients (44%) in the first study to 9 patients (12%) in the second study, DVD was increased from 27 (36%) to 33 patients (44%), TVD was increased from 13 (17%) to 28 patients (37%), and LMT from 3 (3%) to 6 patients (7%). The overall increase was more than double (Fig. 9).

When regression was studied, these changes were found in 7 patients (3%) out of a total of 227. In 6 out of 7 patients regression was found in LAD. All of these were noticed in the sites of Segment 6, and the remaining one in Segment 2 of the RCA (Table IV).

DISCUSSION

The progression of coronary arterial stenosis is a decisive factor in the prognosis of ischemic heart disease. For its analysis, today, when much progress has been made in various diagnostic methods, coronary arteriography is an indispensable technique. It is not easy, however, to follow up patients on whom coronary arteriography was performed for years and to carry out restudy. In Japan as well as in other countries, this problem has not yet been sufficiently studied, and most reports have been made on a small number of patients with rather short periods before follow up.

Bruschke et al.¹⁷ reported that the time factor was closely associated with the progression of coronary arterial lesions and that the longer the period until the second angiography, the more progression occurred. Therefore, it is desirable to have as long a period of observation as possible in order to analyze this problem. The mean

Fig.8. Frequencies of progression, complete occlusion, and New Lesions, classified by the segment of the coronary artery.

TABLE III RELATION OF INITIAL DISEASE TO NUMBER OF VESSELS SHOWING PROGRESSION

Initial study	Second study			Total
	Pts with one-vessel progression	Pts with double-vessel progression	Pts with triple-vessel progression	
SVD	21 (61.8%)	11 (32.4%)	2 (5.8%)	34 (45.3%)
DVD	20 (80.8%)	4 (16.0%)	1 (4.0%)	25 (33.3%)
TVD	10 (76.9%)	3 (23.1%)	0	13 (17.3%)
LMT	2 (66.7%)	1 (33.3%)	0	3 (4.1%)
Total	53 (70.7%)	19 (25.3%)	3 (4.0%)	75

SVD = single vessel disease; DVD = double vessel disease; TVD = triple vessel disease; LMT = Left main trunk disease

follow up period of the present study was about 3 years, and, in consideration of the recent reports in Europe and America¹⁷⁻²⁰ on this problem, the period for observation should be as long as possible.

Coronary angiography was performed, and

from the patients who showed stabilized clinical symptoms over the course of about 3 years, some had to be hospitalized because of recurrent myocardial infarction attacks. Then, a restudy was run after a year when they became asymptomatic, and a high level of progression

TABLE IV PATIENTS WITH REGRESSION OF OBSTRUCTIVE CORONARY LESIONS

Patient	Age and Sex	Initial study	Interval (months)	Second study	Clinical picture
1	50 M	Proximal LAD: Segment (6) 99% narrowing	71	Proximal LAD: Segment (6) 60% narrowing	Old anterior myocardial infarction; at second study asymptomatic
2	52 M	Proximal LAD: Segment (6) 75% narrowing	47	Proximal LAD: Segment (6) 25% narrowing	Angina pectoris class 1; at second study asymptomatic
3	49 M	Proximal LAD: Segment (6) 90% narrowing	63	Proximal LAD: Segment (6) 50% narrowing	Angina pectoris class 1; at second study asymptomatic
4	63 M	Proximal LAD: Segment (6) 75% narrowing	60	Proximal LAD: Segment (6) 25% narrowing	Angina pectoris class 1; at second study asymptomatic
5	50 M	Proximal LAD: Segment (6) 90% narrowing	31	Proximal LAD: Segment (6) 25% narrowing	Old anterior myocardial infarction; at second study asymptomatic
6	65 M	Proximal LAD: Segment (6) 99% narrowing	29	Proximal LAD: Segment (6) 75% narrowing	Angina pectoris class 3; at second study almost asymptomatic
7	58 F	Proximal RCA: Segment (2) 99% narrowing	38	Proximal RCA: Segment (2) 75% narrowing	Old inferior myocardial infarction; at second study asymptomatic

was noted. A-C bypass operation was recommended, but emergency cases resulted in whom conditions indicated the recurrence of myocardial infarction. Consent to the operation was

withheld because they were asymptomatic. Finally, the operation was scheduled, but some patients died before it could be performed. From the foregoing experience, the authors consider that one cannot rest assured simply because a patient with ischemic heart disease shows stable signs. They believe that a restudy must be aggressively undertaken.

Among the 227 patients on whom the authors performed a restudy, the number of patients for whom a second study was carried out due to an attack or reattack of myocardial infarction, or the aggravation of angina pectoris, was 64 (28%). That is less than 1/3 of the total number of patients. The symptoms in the remaining 163 patients (72%) were more stabilized, yet an elective restudy was performed. The outcome revealed progression in 36 (22%) out of 163 patients in a clinically stabilized group. This finding signified that coronary arterial lesions do not surface for a certain period of time even if progression is under way, suggesting that it is necessary to perform a restudy in patients having many risk factors and not be content with the lack of subjective symptoms.

Reviewing the rates of progression in previous reports, the authors found rates varying from 89% by Nash et al.¹³ down to 22% by Shub

Fig.9. Relation of initial lesion to the number of vessels showing progression.

et al.¹⁶ These considerably different results might possibly be due to different patients or definitions of progression. Although a rate of progression of over 50% is predominant in the literature^{5,6,8,10,12,13} the rate of progression in the present study was as low as 32%, which may be for the following reasons. In the present study, an overestimation of the degree of progression of coronary arterial lesions was avoided; but changes of over 2 grades in the AHA classification alone were adopted in order to obtain a more objective evaluation. Furthermore, the patients in the elective restudy, as stated above, involved more than 2/3 of the patients.

Kimbiris et al.⁸ stated that the most accurate indicator of the progression of coronary arterial stenosis is the severity of the anginal symptoms, and it is quite natural that the rate of progression becomes high in patients when subjective symptoms are aggravated. In the results of the present study, on the other hand, the authors have noted the important finding, as stated above, of a clear progression in about 1/5 of the patients in whom subjective symptoms had been stabilized.

Gensini et al.⁵ stated that coronary arterial stenosis began in subjects who had diathesis when they were young. And in the majority of them the diathesis made rapid progress. Bemis et al.⁶ and Kramer et al.¹⁸ pointed out that progression more easily occurs in a comparatively younger group (i.e., under 40 years of age) than in other age brackets, while Marchandise et al.¹⁴ reported that the rate of progression was significantly higher in subjects under 45 years of age. In the present results, too, progression was found more in the group under 40 years of age than in other age groups, but a significant difference was not observed since the number of cases was small.

Concerning the relationship between the interval of restudy and the rate of progression, Bruschke et al.¹⁷ and Kramer et al.¹⁸⁻²⁰ reported that the longer the interval before restudy, the higher the rate of progression was. As is clear from Fig. 2, however, the outcome of the present study did not reveal such a tendency, but it is suspected that the reasons for this were differences in race and eating habits.

Only Hiraiwa's report² the data of which was compiled at our Institute, analyzes the relationship between the degree of stenosis and the period of observation. His findings showed a

large difference in the speed of progression according to the patients' diathesis. Although, in our study there were some cases that indicated rapid progression in short periods, many others were quite the opposite. Therefore, no definite tendency in the speed of progression was noticeable.

Gensini et al.^{5,21} clarified in an average follow-up period of 3 years that the incidence of ischemic heart disease was extremely low in subjects with normal coronary arteries or non-significant coronary atherosclerosis documented in a first study. Proudfit et al.²² also reported a follow-up study after 10 years and found that the possibility of coronary arterial lesions was low in subjects whose coronary arteriograms did not show any lesions in the first study, even after a certain period of time had elapsed. Additionally, even if some lesions did appear, progression was hardly observable. In the present study, however, new lesions appeared in the second study at a segment which had been evaluated as angiographically normal in the first study. Among a total of 98 branches in which progression was noted, new lesions were found in 39 branches (40%) in Group P. In addition, not only did new lesions appear in the patients under study but in 3 cases progression to complete occlusion was detected in the second study, due to the severe progression. This suggested that one must be careful about progression, even if the lesions were mild in the first study. Kramer et al.²⁰ identified some patients with normal coronary arteries in the first study but, by the second study, 1% of their coronary segments showed progression to complete occlusion.

These results were similar to the present ones. Such findings indicated that, in patients who have diathesis with many risk factors, it is very difficult to maintain normalcy in their coronary arteries after a long term, even if they were normal at the first study. Consequently, there is no doubt about the necessity of an elective restudy in such cases.

Kramer et al.²⁰ and Bruschke et al.¹⁷ recognized the highest rate of progression in the proximal segment of RCA, followed by the middle segment of LAD (at the distal segment from the bifurcation of the first septal perforator and the diagonal branch) and the middle segment of RCA. In the present results, progression was found mostly in the proximal segment of RCA (Segment 1 according to the AHA Classification),

followed by LAD and LCX. These results agree well with the reports of American and European researchers. In LAD segments, however, our results differed from those of Western researchers, and the rate of progression was the highest in the proximal segment (Segment 6 in the AHA Classification), similar to the segments of the RCA. The authors found 2 out of 3 patients in whom progression was noted in LMT, due to the above-mentioned appearance of new lesions. Bruschke et al.¹⁷ also reported new lesions in 2 out of 186 patients in whom lesions had not been detected in LMT in the first study. Thus there must have been a small number of cases in which progression existed in LMT. The previous study made it clear that the prognosis for LMT progression was very poor in comparison to patients with lesions in other segments. It is further pointed out that, in the follow up study of the patients with LMT lesions, the prognosis was better surgical treatment rather than merely medical care. In the results of the present study, as well as in those of Bruschke et al.,¹⁷ some rare cases showed a definite probability of progression in LMT.

Finally, reviewing the reports^{15-18,23,24} concerning the regression of coronary arterial lesions, the present investigators found that the incidence was similar to that in progression, ranging from 0.7% to 15%, and varying considerably with the literature. Reports covering many patients were made by Kramer et al.¹⁹ and Bruschke et al.¹⁷ and the rate of regression in the former was 15 (5%) out of 317 patients, and 12 patients (4.7%) out of 256 in the latter. Thus, the results of both groups of researchers agreed well. The results of the present study were similar, too, at a regression rate of 7 (3%) out of 227 patients.

On the basis of our observation, it may be concluded that restudy must be aggressively undertaken even in clinically stabilized patients.

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