Effect of Nifedipine on the Progression of Coronary Atherosclerosis in Humans

Analysis of Coronary Angiogram by Videodensitometry

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SUMMARY

This study was conducted retrospectively to elucidate whether the long-term use of nifedipine is effective against the progression of coronary atherosclerosis in humans. Twenty-nine subjects with ischemic heart disease, on whom repeated coronary angiographic examinations (CAG) were performed, were randomly selected. Sixteen subjects were on nifedipine therapy (40 mg/day; NIF group, age 53 ± 2) and 13 subjects not on nifedipine therapy served as the control group (C group, age 58 ± 3). No significant differences were observed in clinical backgrounds, including the interval between CAG, between the 2 groups. The lesions with 25 to 75% stenosis on the first CAG were defined as the regions of interest (ROI), and the magnitude of stenosis was quantitatively measured by videodensitometry for each ROI on the first and the second CAG. The magnitude of stenosis showed a small increase (54.1 ± 2.6 to $58.6 \pm 3.3\%$; N.S.) for 37 ROIs in the C group. In contrast, it showed a significant decrease (52.5 ± 3.8 to $46.2 \pm 4.3\%$; $p < 0.05$) for 33 ROIs in the NIF group. The trend was more apparent in the left coronary artery. The change in the mean value for ROIs in each subject produced similar results. These results suggest that the long-term use of nifedipine might be effective in retarding the progression of coronary atherosclerosis in humans. However, a prospective study should be performed to confirm this.

Key Words:

Calcium antagonist Coronary artery stenosis

EVIDENCE was first provided by Rosenblum et al¹⁾ that a calcium antagonist may exert an antiatherogenic action. They showed that sodium ethane hydroxydiphosphonate, which had been known to possess an anti-calcifying effect, prevented the accumulation of lipids in the aorta of cho-

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Received for publication December 21, 1989.

Accepted July 1, 1991.

lesterol-fed rabbits. Since then, many experimental studies have suggested the antiatherogenic action of various kinds of calcium antagonists, including lanthanum,²⁾ azacychoheptone diphosphonate,³⁾ nifedipine,^{4),5)} verapamil,⁶⁾ diltiazem⁷⁾ and nilvadipine.⁸⁾

Although the prevention of ischemic heart disease due to coronary atherosclerosis has been an important clinical issue, until recently few studies have been done to elucidate whether calcium antagonists prevent the development or progression of coronary atherosclerosis in humans. One of the major reasons for the lack of the clinical data might be a limitation of methodology available for the quantitation of the magnitude of coronary artery stenosis on coronary angiogram (CAG), which has been established as a reliable method for the diagnosis of coronary atherosclerosis. The recently developed video-densitometric method for the analysis of CAG, however, permits reliable measurement of the magnitude of coronary artery stenosis.⁹⁾ Thus, we performed a retrospective study to examine the possibility that the long-term use of nifedipine is effective against the progression of coronary atherosclerosis in humans.

SUBJECTS AND METHODS

Subjects

Twenty-nine patients with ischemic heart disease, on whom repeated CAG examinations were performed, were randomly selected. Sixteen subjects were on nifedipine therapy (40 mg/day; NIF group) and 13 subjects were not on nifedipine therapy (C group). The C group consisted of 11 males and 2 females (age 58 ± 3) and the NIF group consisted of 14 males and 2 females (age 53 ± 2). As shown in Table I, no significant differences were observed between the 2 groups in clinical backgrounds, including cardiac diagnosis, the presence of coronary risk factors, and therapy with drugs other than nifedipine. The severity of coronary artery stenosis was also similar (Fig. 2). The interval between the two CAG examinations was 733 ± 237 days for the C group and 561 ± 103 days for the NIF group.

Coronary angiography

The CAG examination was performed using the Judkins method in patients who had been suspected of having ischemic heart disease. Right and left coronary angiograms were taken at several positions of the right and left anterior oblique views before and after sublingual administration of 0.3 mg of nitroglycerine. These angiograms were recorded on 35 mm cinefilm and those after nitroglycerine administration were analyzed by an XR-70

Table I. Summary of the Clinical Backgrounds of the Subjects

	NIF group	C group	Significance between NIF and C groups
Number of subjects :	16 (M 14, F 2)	13 (M 11, F 2)	N. S.
Age :	53±2	58±3	N. S.
Clinical diagnosis :	MI 8, AP 8	MI 8, AP 5	N. S.
Coronary risk factors :			
Hypertension*	4→0	7→0	N. S.
Smoking*	7→1	6→2	
Diabetes mellitus*	1→1	3→3	
Obesity (%)**			
1st CAG	22.3± 3.7	13.8± 4.1	N. S.
2nd CAG	13.1± 3.5††	11.0± 4.0	N. S.
Plasma cholesterol level (mg/dl)			
1st CAG	213.8±11.0	201.1±12.7	N. S.
2nd CAG	217.2± 8.9	200.7±13.2	N. S.
Treatments (No. of subjects) :			N. S.***
Nifedipine	16	0	
β-blocker	4	7	
Nitrate	11	12	
Nicorandil	2	3	
Others	4	9	
No treatment	0	1	
CAG interval (days) :	561±103	733±237	N. S.

NIF group=subjects on nifedipine therapy; C group=subjects not on nifedipine therapy; MI=myocardial infarction; AP=angina pectoris; N. S.=not significant; M=male; F=female. †† p<0.01 vs. 1st CAG.

* Number of subjects with each risk factor at the time of 1st and 2nd CAG is shown.

** Degree of obesity (%) was calculated as $100 \times [\text{Weight (kg)} / \text{Ideal Weight (kg)}] - 100$. Ideal Weight was calculated as $0.9 \times [\text{Height (cm)} - 100]$.

*** Statistical analysis was performed on the drugs other than nifedipine.

coronary analyzer (Vanguard, Melville, USA) as described later. A left ventriculogram was taken after the completion of the CAG examination.

Quantitation of the magnitude of coronary artery stenosis

The first CAG was carefully observed, and all lesions with 25 to 75% stenosis were defined as regions of interest (ROI). The regions which were judged to have more than 75% stenosis were excluded from this study to avoid the possible influence of such factors as vasospasm and thrombus formation on the course of angiographic stenosis. The CAG cinefilm was loaded into the projector (Vanguard XR-35) and the magnitude of coronary artery stenosis was quantitatively measured using videodensitometry (XR-70 coronary analyzer, which was connected to the XR-35 projector), for each ROI on the first and the second CAG. The magnitude of coronary artery stenosis was

Fig. 1. An example of the videodensitometric measurement of coronary artery stenosis. The magnitude of stenosis in the proximal portion (segment 6) of the left anterior descending artery (LAD) was calculated to be 68% (B). White arrows indicate the normal portion of LAD which was taken as the reference site for the calculation. The portion just distal to the reference site was judged to have no stenosis (A).

measured from a single plane angiogram which provided the details of the stenotic site. The magnitude of stenosis for each ROI on the first CAG was again measured on the same view of the second CAG, and the change in magnitude was compared between the control group and the nifedipine group. The coefficient of variation of the measurement for moderate coronary artery stenosis was 2.9% ($n=10$). An example of the measurement is shown in Fig. 1.

Statistics

Data were analyzed using Student's t-test for paired and unpaired data.

Fig. 2. The change in the magnitude of stenosis for the regions of interest (ROIs) during the first and second coronary angiography (CAG). Solid lines indicate the nifedipine (NIF) group and broken lines indicate the control (C) group. RCA=right coronary artery; LCA=left coronary artery.

Fig. 3. The change in the mean value of the magnitude of stenosis of regions of interest in each subject during the first and second coronary angiography (CAG).

The independence of variables concerning clinical backgrounds was tested with contingency table analysis using chi-square distribution. A p value of less than 0.05 was considered to be significant. All data presented in the text, table and figures are the means ± SEM.

RESULTS

As shown in Fig. 2, the magnitude of stenosis showed a small and statistically insignificant increase (54.1 ± 2.6 to $58.6 \pm 3.3\%$; N.S.) for the 37 ROIs in the C group. In contrast, it showed a significant decrease (52.5 ± 3.8 to $46.2 \pm 4.3\%$; $p < 0.05$) for 33 ROIs in the NIF group. The trend was more apparent in the ROIs of the left coronary artery than in the ROIs of the right coronary artery.

As shown in Fig. 3, the change in the mean value of the magnitude of stenosis for the ROIs in each subject produced similar results, that is, from 53.1 ± 2.3 to $57.5 \pm 3.6\%$ ($n=13$; N.S.) in the C group and from 57.6 ± 4.2 to $47.9 \pm 4.2\%$ in the NIF group ($n=16$; $p < 0.01$).

DISCUSSION

In the present study, we demonstrated the possibility that the long-term use of the calcium antagonist nifedipine might be effective in retarding the progression of coronary atherosclerosis in humans. This was based on the observation that the coronary artery stenosis in the nifedipine group significantly decreased, while that in the control group tended to increase, and thus the magnitude of stenosis on the second CAG in the control group was significantly greater than that in the nifedipine group. The effect of nifedipine was more apparent on the lesions of the left coronary artery than on those of the right coronary artery. The reason for this is not clear. It is unlikely that nifedipine is more effective on left coronary artery lesions. Moreover, the location of coronary artery stenosis was not found to affect the progression and regression rate.¹⁰⁾ The possible cause might be the difference in the magnitude of stenosis between the right and left coronary arteries on the first CAG.

Many experimental studies have been done to elucidate the effect of calcium antagonists on atherogenesis by using animal models such as cholesterol-fed rabbits¹⁾⁻⁷⁾ and Watanabe heritable hyperlipidemic rabbits.^{8),11)} Although the results from these experimental studies are still controversial, the focus has been placed on a clinical trial to determine the effect of calcium antagonists on the development or progression of coronary atherosclerosis. Klein et al¹²⁾ analyzed repeated CAG in patients on and not on nifedipine or diltiazem therapy, and they reported that the incidence of the regression of coronary artery stenosis was higher in patients on diltiazem therapy. Yabe¹³⁾ also reported that the incidence of progression of coronary artery stenosis was lower and that of regression was higher in patients on nifedipine

therapy for approximately 1 year. The results of two large-scale, prospective clinical trials have recently been reported. The International Nifedipine Trial on Antiatherosclerotic Therapy (INTACT)¹⁴⁾ performed in Europe showed that the long-term use of nifedipine (80 mg/day) for 3 years did not affect the magnitude of stenosis in existing lesions; however, nifedipine significantly inhibited the occurrence of new lesions. From these findings, they concluded that nifedipine can retard the progression of atherosclerosis in the early stage. The other study¹⁵⁾ using nicardipine (90 mg/day), and performed in Canada, showed that nicardipine did not affect the progression or regression rate; however, nicardipine significantly decreased the progression rate in lesions with less than 20% stenosis. The results were essentially compatible with those presented in this study in terms of the inhibitory effect of nifedipine on the progression of mild to moderate coronary stenosis. In the present study, a slight but significant decrease in the magnitude of coronary stenosis was observed in the nifedipine-treated group. This does not necessarily mean the regression of coronary atherosclerosis. The possible contribution of the reversal of coronary vasospasm by nifedipine to this finding cannot be excluded, although CAG was taken after sublingual administration of nitroglycerine. Further studies are required to clarify this point using for example, intracoronary administration of nitroglycerine.

We used videodensitometry for quantitation of the magnitude of coronary artery stenosis on CAG. The technical limitations of the method should be noted. A nonstenotic site in the vicinity of the ROI should be used as an internal reference for the quantitation of the magnitude of coronary artery stenosis, and the positioning of the reference may affect the measurement. Furthermore, accurate measurement is impossible at the site where the angiographic image of another coronary branch falls. Be that as it may, videodensitometry seems advantageous over conventional methods for several reasons.⁹⁾ First, a subtle change in the magnitude of the stenosis can be detected. Second, it is not necessary to determine the edge of the stenotic site to measure the magnitude of stenosis. Third, the measurement is possible from a single-plane angiogram. Since atherosclerosis usually occurs eccentrically, the conventional method in which the edge of the stenotic site should be determined necessitates the analysis of biplane images of CAG. Fourth, reproducibility of the measurement is excellent; the coefficient of variation of the measurement for moderate stenosis was only 2.9% for 10 measurements.

Another distinctive feature of the present study was that only moderate lesions were included, although the severe lesions were of clinical importance from a hemodynamic point of view. Actually, in this study, the mean value of coronary artery stenosis was 54.1% for the ROIs in the control group,

and 52.5% for the ROIs in the nifedipine group. The reason why we included only coronary lesions with moderate stenosis was that the aim of this study was to assess the progression of "true" coronary atherosclerosis. The exclusion of severe coronary artery stenoses might make the interference of factors other than "true" atherosclerosis less possible. These factors include thrombus formation and recanalization, which may mimic angiographic progression or regression of coronary atherosclerosis. Moreover, Moise et al¹⁶⁾ pointed out that the application as the criterion for the progression of atherosclerosis of a 20% or more increase in stenosis, would preclude any detection of progression with initial stenoses of 80% or more. Since this study was performed as a preliminary one for the forthcoming prospective study, we followed their study design. The INTACT study¹⁴⁾ and the study performed in Canada¹⁵⁾ used similar inclusion criteria concerning the stenosis of coronary lesions.

Recent experimental studies have suggested several mechanisms of the antiatherogenic action of calcium antagonists. These include the hypotensive effect of calcium antagonists,^{4),15)} the increase in prostacyclin production in vascular endothelial cells,¹⁷⁾ the inhibition of platelet aggregation,¹⁸⁾ the inhibition of the migration¹⁹⁾ and proliferation of vascular smooth muscle cells provoked by some kinds of growth factors,²⁰⁾ and the increase in the uptake and metabolism of low-density lipoprotein in vascular endothelial cells and smooth muscle cells.²¹⁾ However, the exact mechanism by which calcium antagonists exert an antiatherogenic action in humans remains to be elucidated. Further studies will be required to ascertain this.

In conclusion, we demonstrated the possibility that the calcium antagonist nifedipine exerts an antiatherogenic action in humans. Although this study was done retrospectively, the results obtained were encouraging. The potential benefit of nifedipine on the progression of coronary atherosclerosis in humans requires further confirmation by a prospective and multi-centric double-blind study.

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