Original Article

Vascular Protecting Effect of Angiotensin Receptor Blocker (ARB) on the Radial Artery Graft

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Purpose: We hypothesized that the vascular protecting effect of an angiotensin receptor blocker (ARB) reduced endothelial damage of the radial artery (RA) after coronary bypass and conducted a comparative study.

Patients and Methods: One hundred and sixty four patients were divided into the following two groups, Group C: 92 subjects who were orally administered Candesartan 8 mg/day, Group I: 72 subjects who were administered Imidapril at 5 mg/day. Graft angiography was performed one year after surgery and the RA intima was evaluated using an angioscope.

Results: Total cholesterol of Group C was 151.4±66.9 mg/dL, which was significantly lower than in Group I (182.2±27.8 mg/dL), and LDL cholesterol of the ARB-treated group, i.e., Group C was 96.1±32.5 mg/dL and significantly lower than in Group I (139.1±48.7 mg/dL). In angioscopy, yellow plaque was detected in the proximal RA in 7 (8.0%) and 8 (11.6%) patients of the Groups C and I, respectively, showing a lower tendency in the ARB-treated group.

Conclusions: The results of evaluation one year after surgery revealed no significant difference in effects on the RA endothelium between ARB and ACE inhibitor. ARB reduced cholesterol and its effect was confirmed with blood examination data and endoscopic findings. (Ann Thorac Cardiovasc Surg 2008; 14: 25–28)

Key words: radial artery, angiotensin converting enzyme blocker, LDL cholesterol

Introduction

Hypertension is a risk factor for arteriosclerosis. Independent angiotensin-II (A-II) generating systems exist in the vascular vessel and have an important role in onset and progress of hypertension-induced arteriosclerosis. A-II enhances oxidation of low density lipoprotein (LDL) cholesterol and plays a role in all stages of arteriosclerosis including endothelial damage, plaque formation, lipid deposition, plaque rapture and thrombotic artery occlusion, aggravating arteriosclerosis.[1)]

A-II receptor blocker directly inhibits the above A-II action on vascular walls. A chymase-dependent A-II generating pathway has recently been found, and in cardiac patients particularly this chymase-generated A-II significantly exists.[2)] Conventional angiotensin-converting enzyme (ACE) inhibitors have a poor effect on chymase-generated A-II, in contrast, angiotensin receptor blocker (ARB) also inhibits chymase-generated A-II and effectively prevents arteriosclerosis.[3)]

We hypothesized that the vascular protecting effect of ARB reduced endothelial damage of the radial artery graft after coronary artery bypass grafting (CABG) and improved the distal patency rate, and then, conducted a comparative study of ARB and ACE inhibitors.

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Patients and Methods

Of 277 patients who underwent CABG with the RA from January 2003 to May 2005, 164 were enrolled in this study. Excluded from this trial were elderly patients aged over 81 years of age, patients with hypotension, uncontrollable diabetes mellitus and/or cardiac depression with left ventricular ejection fraction of 35% or less. The subjects comprised 138 males and 26 females and the mean age was 64.3±8.3 years old (range: 44 to 80 years old). Only one RA in the non-dominant hand was used and the vessels used other than the RA were the left internal mammary artery and the greater saphenous vein. The mean graft was 2.96±0.80. The subjects were assigned to the following two groups: Group C: 92 subjects who were administered Candesartan 8 mg/day, Group I: 72 subjects who were administered Imidapril at 5 mg/day.

The patients were administered 100 mg/day of Aspirin and 2.5 mg/day of amlodipinefor prevention of postoperative spasm of artery spasm. If necessary the Amlodipine dose was doubled to hypertension patients. Pravastatin as an anti-cholesterol drug was combined at a dose of 5 mg/day. The interim blood examination including total cholesterol, triglyceride, HDL and LDL cholesterol, renin, A-II, aldosterone, and serum and urinary 8-isoprostane as oxidative stress marker were conducted one year after surgery and the results were compared between groups. Graft angiography was also performed one year after surgery and intimal thickening of the proximal RA was evaluated using an angioscope simultaneously.

Results

No significant differences in age, sex and coronary risk factors were found between two groups (Table 1). Also in the anastomotic site of RA and the preoperative stenosis of an anastomosed artery, no significant difference was observed (Table 2). The blood renin, A-II, aldosterone and 8-isoprostane values did not show significant differences as well as HDL cholesterol and triglyceride, however, total cholesterol of Group C was 151.4±66.9 mg/dL, which was significantly lower than 182.2±27.8 mg/dL of Group I, and LDL cholesterol of the ARB-treated group, i.e., Group C, was 96.1±32.5 mg/dL and significantly lower compared with 139.1±48.7 mg/dL of Group I (Table 3). The graft angiography one year after surgery detected 4 and 3 occlusions in the Groups C and I, respectively. But there was no cardiac event such as recurrent angina or heart failure during a one year follow-up.

Table 1. Patient profiles

	Group C	Group I	*P* value
Age	64.4±7.9	64.1±8.2	NS
Sex	M78/F14	M60/F12	NS
HT	88.0%	77.8%	NS
SM	68.5%	70.8%	NS
HL	85.9%	81.9%	NS
DM	42.4%	40.3%	NS

M, male; F, female; HT, hypertension; SM, smoking; HL, hyperlipidemia; DM, diabetes mellitus.

Table 2. Target coronary artery

	Group C	Group I	*P* value
LAD	3	3	NS
Diagonal	7	8	NS
CX	72	48	NS
RCA	10	13	NS
Stenosis	91.4±5.6	92.1±7.4	NS

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

Table 3. Comparative data

	Group C	Group I	*P* value
T.chol	151.4±66.9	182.3±27.8	**0.046**
TG	160.2±112.0	154.4±123.2	NS
LDL	96.1±32.5	139.1±48.7	**0.038**
HDL	48.7±13.6	48.4±14.6	NS
Renin	15.8±8.8	14.6±3.4	NS
AT-II	21.1±37.7	22.4±28.7	NS
Aldosterone	103.3±80.0	100.0±72.9	NS
S-8isopr	11.4±1.5	14.0±13.8	NS
U-8isopr	129.8±106.5	162.2±117.0	NS

T.chol, total cholesterol (mg/dL); TG, triglyceride (mg/dL); LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; AT-II, angiotensin II; S-8isopr, serum 8-isoprostane; U-8isopr, urinary 8-isoprostane.

The RA patency rates were 95.7 and 95.8%, respectively, showing no significant difference. In angioscopy, yellow plaque (Fig. 1) was detected in the proximal RA in 7 (8.0%) and 8 (11.6%) patients of the Groups C and I, respectively, showing a lower tendency in the ARB-treated group but with no significant difference.

Discussion

Based on our performance of 2,000 RAs grafting, we have reported that the 3-year patency rate of RA grafts was 98.1% and superior to vein grafts.[4] It has recently been

reported that strict control of hyperlipidemia improved the patency rate both in artery and vein grafts.[5] However, another study indicated that the patency rate of RA grafts was inferior to that of vein grafts.[6] Some measures to improve the patency of RA grafts further are required.

The tissue renin-angiotensin system plays an important role not only in progress but also persistency of arteriosclerosis. According to the following reasons, there is evidence that an arteriosclerotic lesion is hyperresponsive to locally generated A-II, i.e., (i) the activity of renin-like enzyme converting angiotensinogen to angiotensin I (cathepsin D, tonin, chymase, etc.) and ACE activity are increased in arteriosclerotic vessels; and (ii) LDL cholesterol increases production of A-II type I receptors in vascular smooth muscle cells. A-II has a proliferative effect via oncogene and growth factor expression including proliferation of vascular smooth muscle and extracellular matrix,[7] an oxidative effect such as LDL oxidation,[8] a transmitting effect including LDL accumulation and enhancement in oxidized LDL uptake by macrophage,[9] and furthermore activates transcription factors.[10] As a result, A-II accelerates arteriosclerosis. This A-II arteriosclerosis-accelerating effect is mediated mainly by AT receptors, especially AT1 receptors, therefore, we hypothesized that ARB has an antiatherogenic effect, also an inhibiting effect of oxidative stress to vascular wall, and thus, investigated vascular protecting effect of ARB on the RA.

The results of this study showed that ARB and ACE inhibitors had an almost similar effect on inhibition of the renin-angiotensin system. Serum and urinary 8-isoprostanes were kept low in both groups, suggesting that ARB and ACE inhibitor had a similar inhibiting effect on oxidative stress to vascular walls.The total and LDL cholesterol values were significantly lower in the ARB-treated group than the ACE inhibitor–treated group. Patients of both groups showed no difference in hyperlipidemia incidence and were orally given same statin at half of an ordinary dose. Therefore, these differences in cholesterol values are considered to be dependent on the difference in efficacy of ARB and ACE inhibitors. It was reported that ARB itself reduced total and LDL cholesterol values,[11] furthermore, it was also confirmed that combination therapy of ARB and statin showed a synergistic effect on the reduction of cholesterol.[12] Yamakado showed evidence of the vascular protecting effect of ARB with a decrease in carotid artery intimal thickening,[11] and explained that the mechanism was involved in ARB-enhanced activity to eliminate active enzymes and subsequently ARB-inhibited lipid peroxidative reaction, and also reported a reducing effect on serum lipid peroxide. Also in this study, the endoscopic results exhibited that yellow plaque was observed in the radial artery endothelium less in the ARB-treated group, which is probably due to low maintenance of LDL cholesterol. Similar to the carotid artery endothelium, LDL-cholesterol–reducing and oxygen-radical–inhibiting effects of ARB probably acted on the radial artery endothelium, therefore, it is suggested that the antiatherogenic effect of ARB is involved in the inhibition of lipid peroxidation by reducing oxidative stress, especially inhibition of LDL oxidation. It was reported in an arteriosclerosis animal model study that plaque was reduced in size by ARB. In contrast, ACE inhibitor reduced ischemic events in humans but no significant reduction in plaque size was found.[13]

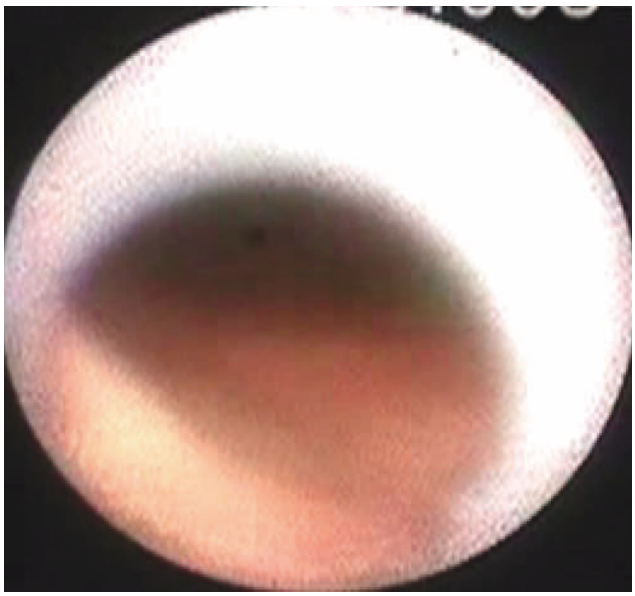

Fig. 1. Yellow plaque in the radial artery.

In the interim examination of this study, the patency of radial artery grafts was good and no significant difference was found between the two groups. However, the endoscopic results showed suspected further progress of arteriosclerotic plaque in the late phase and follow-up was considered to be necessary. In this study, to prevent spasm in the radial artery, the entrance of the radial artery was endoscopically observed. Considering significant low LDL values due to ARB alone, and the, synergistic effect of combination with statin, findings of the central RA endothelium was probably the same as those of the peripheral RA endothelium.

Conclusions

The results of evaluation one year after surgery revealed no significant difference in the effects on the RA endothelium between ARB and ACE inhibitors. ARB reduced cholesterol and its effect was confirmed with blood examination data and endoscopic findings. Long term follow up is thus necessary.

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