COMPARATIVE STUDY ON CALCIUM CHANNEL ANTAGONISTS IN THE HUMAN RADIAL ARTERY: CLINICAL IMPLICATIONS

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Objectives: The radial artery is spastic, and calcium channel antagonists have been used clinically in the radial artery for their antispastic effects. To choose a proper calcium channel antagonist for such a purpose, we compared the in vitro antispastic effects of 4 clinically used calcium channel antagonists (nicardipine, nifedipine, verapamil, and diltiazem) in the human radial artery. **Methods:** Radial artery segments taken from patients undergoing coronary bypass operations were studied in the organ bath. The relaxation by the calcium channel antagonists was compared in the potassium-precontracted (25 mmol/L) radial artery. The inhibitory effect of the calcium channel antagonists at the clinically relevant plasma concentration and a higher concentration was also studied for the calcium channel antagonists. **Results:** All calcium channel antagonists induced a full relaxation (97.8%-100%, $n = 5-7$ for each), with higher sensitivity ($P = .005$, analysis of variance [ANOVA] among the calcium channel antagonists for the effective concentration of the constrictor [or dilator] agent that caused 50% of maximal contraction [or relaxation]) to nifedipine ($-7.37 \pm 0.20 \log_{10} M$) than nicardipine ($-6.43 \pm 0.39 \log_{10} M$, $P = .1$), verapamil ($-6.08 \pm 0.13 \log_{10} M$, $P = .03$), and diltiazem ($-5.87 \pm 0.07 \log_{10} M$, $P = .01$). Pretreatment with the plasma concentration of the calcium channel antagonists (60 nmol/L for diltiazem and 20 nmol/L for the others) inhibited the potassium-induced contraction ($n = 6$ for each) by nicardipine (from $138.6\% \pm 5.8\%$ to $101.4\% \pm 7.6\%$, $P = .001$) and nifedipine (to $87.7\% \pm 6.8\%$, $P = .0003$) but not by verapamil (to $140.3\% \pm 15.2\%$, $P = .9$) or diltiazem (to $132.8\% \pm 7.3\%$, $P = .8$), although at higher contractions ($-4.5 \log_{10} M$) all 4 calcium channel antagonists abolished the contraction. **Conclusions:** Although all calcium channel antagonists have antispastic effects in the radial artery, the vessel has different sensitivities to them. Dihydropyridine derivatives may be the most potent calcium channel antagonists and therefore are recommended for the clinical use for this purpose. (J Thorac Cardiovasc Surg 2000;119:94-100)

Autologous arteries have been used as grafts for coronary artery bypass grafting (CABG) and have gained popular use recently.¹⁻⁴ At the moment, 4 arteries are the major arterial grafts. These are the internal

thoracic artery (ITA),¹ the gastroepiploic artery,² the inferior epigastric artery,³ and the radial artery (RA).⁴ The ITA is probably the first choice for arterial grafts in most institutions. A unique opinion with regard to the

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Table I. Potency (EC_{50}) of calcium channel antagonists in relaxation of the human RA precontracted with potassium (25 mmol/L)

	Nifedipine	Nicardipine	Verapamil	Diltiazem
EC_{50} ($-\log_{10}$ M)	7.37 ± 0.20	6.43 ± 0.38	6.08 ± 0.13	5.87 ± 0.07
95% CI of the mean difference of EC_{50} compared with nifedipine	—	-0.07 to 1.95	-1.85 to -0.72	-2.02 to 0.99
P value*	—	.06	.0006	.0001

EC_{50} is expressed in $-\log_{10}$ M. The difference between nifedipine and other calcium-channel antagonists is the 10^{difference}-fold concentration. The P value is .005 among the 4 groups (ANOVA).

*Compared with nifedipine (unpaired t test).

second choice of arterial grafts has not been formed. However, in some institutions^{4,6} and recently at the University of Hong Kong, Grantham Hospital, the RA has become the preferred arterial graft after the ITA.

We previously classified all arterial grafts into 3 types⁷: type I, somatic arteries; type II, splanchnic arteries; and type III, limb arteries. Type II and III arteries are more spastic than type I arteries. According to this classification, the RA belongs to the type III arterial graft and is more spastic than type I arteries, such as the ITA.⁷⁻⁹ From our experience and in accordance with that of others,⁴ the RA contraction (or spasm) is almost inevitably encountered during the surgical dissection. In fact, the revival of the RA was largely due to the use of calcium channel antagonists.⁴ Diltiazem was used in Acar and colleagues⁴ initial surgical experience to release RA spasm. We have recently developed an antispastic protocol (University of Hong Kong protocol) for using the RA as an arterial graft¹⁰ and have reported its efficacy in the prevention and relief of vasospasm¹¹ and in the preservation of endothelium in the RA.¹⁰ In the University of Hong Kong protocol, verapamil is used. It is believed that use of calcium channel antagonists played a key role in antispastic therapy for the RA to obtain high patency and low incidence of vasospasm.

There is a wide range of calcium antagonists. Classically, there are 3 chemically divergent groups: dihydropyridines (eg, nifedipine and nicardipine), phenylalkylamines (eg, verapamil), and benzothiazepines (eg, diltiazem). New calcium channel antagonists structurally different from these 3 groups have also been developed but are not yet used clinically. The choice of calcium channel antagonists for relief of RA spasm has been empirical.⁴ We designed the present study to compare the spasmolytic effect of 4 calcium channel antagonists currently used in the RA to provide information for their clinical application. One of the first-generation calcium channel antagonists (nifedipine, verapamil, and diltiazem) from each of the 3 chemically divergent groups was studied. In addition,

because nifedipine is not available for intravenous infusion, another clinically used dihydropyridine derivative available for intravenous infusion (nicardipine) was also studied.

Methods

General. Ninety-four human RA segments were collected from 25 patients undergoing CABG with the RA. Approval to use discarded RA tissue was given by the Grantham Hospital Human Ethics Committee. Any redundant or discarded RA segments were collected and placed in a container with oxygenated physiologic solution (Krebs solution) maintained at 4°C and then transferred to the laboratory immediately. The RA was transferred into a glass dish and dissected out from its surrounding connective tissue. The vessels were cut into 3-mm long rings and suspended on wires in organ baths.^{12,13} The number of rings taken from each patient varied from 2 to 6. The Krebs' solution had the following composition: 144 mmol/L Na⁺, 5.9 mmol/L K⁺, 2.5 mmol/L Ca²⁺, 1.2 mmol/L Mg²⁺, 128.7 mmol/L Cl⁻, 25 mmol/L HCO₃⁻, 1.2 mmol/L SO₄²⁻, 1.2 mmol/L H₂PO₄⁻, and 11 mmol/L glucose. The solution was aerated with a gas mixture of 95% oxygen and 5% carbon dioxide at 37°C.

Organ bath technique. A technique that allowed for vascular rings to normalize to a physiologic pressure in the organ bath was used in this study. The vascular rings were set at a pressure comparable with that used in the in vivo situation. The details of the technique were published before^{14,15} and repeatedly used in in vitro studies for human vessels, including the ITA and RA.^{7,9-13,15} Briefly, the rings were stretched up in progressive steps to determine the length-tension curve for each ring. A computer iterative fitting program (VESTAND 2.1; Yang-Hui He, Princeton, NJ) was used to determine the exponential line, pressure, and the internal diameter. When the transmural pressure on the rings reached 100 mm Hg, as determined from their own length-tension curves, the stretch-up procedure was stopped, and the rings were released to 90% of their internal circumference at 100 mm Hg. This degree of passive tension was then maintained throughout the experiment.

In this study the endothelium was intentionally preserved by cautiously dissecting and mounting the rings because endothelium plays a modulatory role in the contractility of arterial grafts.^{13,14} We previously found that this technique

Fig 1. Mean concentration ($-\log_{10} M$) response (percentage relaxation) curves for 4 calcium channel antagonists in the human radial artery precontracted by potassium chloride (diltiazem, potassium 25 mmol/L; $n = 6$ for nicardipine [NIC], $n = 6$ for nifedipine [NIF], and $n = 5$ for verapamil [VER] and diltiazem [DIL]). The rings were taken from 4 to 6 patients in each group. Vertical error bars are 1 SEM of mean values.

allowed for the experiments to be carried out with an intact endothelium, as determined by the functional relaxation response to acetylcholine or calcium ionophore in the human arteries.^{9,10,12}

Protocol. After the normalization procedure, the RA rings were equilibrated for at least 1 hour. If more than one ring was taken from the same patient, the vessels were randomly assigned to different groups to maximally reduce the possible influence to the results because of multiple rings from the same patient allocated in a certain group of experiments. This was feasible for the contraction studies. For the same reason, in the relaxation studies multiple RA ring segments taken from the same patient were also allocated to different treatments whenever possible.

Relaxation. Calcium antagonist-induced relaxation was studied in the precontraction induced by potassium (25 mmol/L). Cumulative concentration-relaxation curves to each calcium channel antagonist were then established. Only one concentration-relaxation curve was obtained from each RA ring. From 6 rings (taken from 4-6 patients), a mean concentration-relaxation curve was constructed.

Depression of contraction by pretreatment with calcium antagonists. Using separate RA rings, after equilibration, potassium (100 mmol/L) was added into the organ bath, and the contraction force was recorded. The ring was frequently washed to restore the baseline. To determine whether pretreatment with plasma concentrations of calcium channel antagonists would alter the contraction response to potassi-

um, cumulative concentration-contraction curves were constructed with RA rings. The contraction was expressed as a percentage of the contraction force induced by a 100-mmol/L concentration of potassium. In contraction studies, whenever possible, the rings from the same patient were allocated to different groups in which the rings were treated with different concentrations of the calcium channel antagonist. In these experiments one group of RA segments served as controls without pretreatment of calcium channel antagonists, and a second group of RA segments was treated with one of the 4 calcium channel antagonists at plasma concentrations for 20 minutes before the concentration-contraction curves to potassium were constructed. According to the literature, the free plasma concentrations for nifedipine, verapamil,¹⁶ and nicardipine¹⁷ have been measured at levels equivalent to approximately 20 nmol/L, and that for diltiazem has been measured at 60 nmol/L.¹⁶ These concentrations (20 nmol/L for nifedipine, verapamil, and nicardipine and 60 nmol/L for diltiazem) were chosen to study the inhibitory effect of calcium channel antagonists in the present study. To test the possible effect of higher concentrations (30 μ mol/L) of calcium channel antagonists, which can be reached for topical treatment during surgery, RA rings were treated with calcium channel antagonists in separate groups at these concentrations for 20 minutes before the concentration-contraction curves to potassium were constructed ($n = 6$ in each group).

Data analysis. The effective concentration of the constrictor (or dilator) agent that caused 50% of maximal contraction (or relaxation) (EC_{50}) was determined from each concentration-contraction (or relaxation) curve by a logistic, curve-fitting equation:

$$E = MA^p / (A^p + K^p)$$

where E is response, M is maximal contraction (or relaxation), A is concentration, K is EC_{50} concentration, and p is the slope parameter.¹⁴ A computerized program was used for the curve fitting.

From this fitted equation, the mean EC_{50} value $\pm$ SEM was calculated in each group. Unpaired *t* tests or analyses of variance were used to test statistical significance between different constrictors and dilators regarding the maximal response or EC_{50} . The Scheffe F test was used as a post hoc test between groups.

Drugs. All drugs used in this study were purchased from Sigma Chemical Co (St Louis, Mo). Calcium antagonists were freshly made in a glass vial and protected from light.

Results

Resting vessel parameters.¹⁴ The mean internal diameter of the 94 rings at an equivalent transmural pressure of 100 mm Hg was 2.7 ± 0.1 mm, as determined from the normalization procedure. When the RA rings were set at a resting diameter of 0.9 times a transmural pressure of 100 mm Hg, the equivalent transmural pressure was 66.1 ± 1.7 mm Hg, and the resting force was 2.3 ± 0.2 g.

Table II. Inhibitory effect of calcium channel antagonists at the plasma concentration on the maximal contraction (expressed as percentage of 100 mmol/L KCl-induced contraction) to potassium in the human RA

	Control	Nifedipine	Nicardipine	Verapamil	Diltiazem
E _{max}	138.6 ± 5.7	87.7 ± 6.8	101.4 ± 7.6	140.3 ± 15.2	132.8 ± 7.3
95% CI of the mean difference of E _{max} compared with nifedipine	—	31.0 to 70.8	15.9 to 58.5	−37.9 to 34.4	−15.0 to 26.6
P value*	—	.0002	.003	.9	.5

E_{max}, Maximal concentration.

*Compared with the control by using the unpaired *t* test.

Relaxation by calcium antagonists in the potassium-precontracted RA. The time course for the relaxation induced by each dose of the calcium channel antagonist was 20 minutes. All 4 calcium channel antagonists caused a full or nearly full relaxation in the RA precontracted by potassium (25 mmol/L; $P = .13$, ANOVA among the 4 calcium channel antagonists at the maximal relaxation; Table I and Fig 1). However, there was a significant difference with regard to the EC₅₀ ($P = .005$, ANOVA; Table I). Nifedipine is significantly more potent than either verapamil ($P = .0006$, 95% confidence interval [CI] for the mean difference: -1.85 to -0.72 [$-\log_{10}$ M]) or diltiazem ($P = .0001$; 95% CI, -2.02 to 0.99 [$-\log_{10}$ M]; Table I). By comparison of the EC₅₀ values at the actual concentration, nifedipine is 19.5-fold more potent than verapamil ($P = .0006$) and 31.6-fold more potent than diltiazem ($P = .0001$). With regard to the potency of nicardipine, it is marginally more potent than verapamil (2.2-fold higher, $P = .8$) and diltiazem (3.6-fold higher, $P = .5$, Scheffe test).

Depression of contraction to potassium by pretreatment with calcium antagonists. With pretreatment with calcium channel antagonists at these plasma concentrations, the depressive effect of dihydropyridines (nifedipine and nicardipine) was more significant than that of verapamil and diltiazem. Both nifedipine and nicardipine significantly depressed the maximum contraction ($P = .0002$ for nifedipine and $P = .003$ for nicardipine; Table II and Fig 2, A and B). In contrast, neither verapamil ($P = .9$) nor diltiazem ($P = .5$) reduced the maximum contraction (Table II and Fig 2, C and D).

However, when the higher concentration (30 μ mol/L) was used to treat the RA, all 4 calcium channel antagonists nearly completely abolished the contraction (Fig 2).

Discussion

In this study we found that in the human RA dihydropyridine derivatives have higher potency than verapamil or diltiazem. Among the 4 calcium antagonists,

potency is in the following order: nifedipine > nicardipine > verapamil > diltiazem. Therefore dihydropyridine derivatives may have a role in CABG with the RA. Furthermore, at high concentrations for topical use, any one of the 4 calcium channel antagonists tested would provide effective antispastic effect.

In the present study nifedipine is 19.5-fold more potent than verapamil ($P < .001$) and 31.6-fold more potent than diltiazem ($P < .001$) in the RA precontracted with potassium. Its efficacy on prevention of RA spasm is shown by the observation that at the usual plasma concentration, nifedipine significantly reduced RA contraction (from 138% to 87.7%, $P < .001$), whereas neither verapamil nor diltiazem had any effect on the RA contraction at an equal (for verapamil) or higher (for diltiazem) concentration (Table II). Therefore nifedipine expressed a better spasmolytic effect in the RA than verapamil or diltiazem in 2 ways: it is more potent in reversing existing contraction, as well as in preventing contraction in RA. Cable and colleagues¹⁸ also reported that diltiazem has little effect on human RA contraction.

Another dihydropyridine derivative, nicardipine, also expressed a better spasmolytic effect than either verapamil or diltiazem. Although nicardipine-induced relaxation in potassium precontraction is only marginally more potent than that of verapamil (2.2-fold higher, $P = .8$) and diltiazem (3.6-fold higher, $P = .5$), it showed a significant depressive effect on the potassium-induced contraction (from 138.6% to 101%, $P = .003$; Table II) at the plasma concentration when used before contraction to prevent it. In contrast, as mentioned above, neither verapamil nor diltiazem showed any depressive effect on such contraction at the plasma contraction, which is the same for verapamil as for nifedipine and nicardipine and is even 3-fold higher for diltiazem.

In the present study the depression effect on the RA contraction was examined at 2 concentrations. The experiment at the plasma concentration is essential to simulate the clinical condition when systemic administration of calcium channel antagonists is given. The

Fig 2. Mean concentration ($-\log_{10}$ M)-contraction (percentage of 100 mmol/L potassium-induced contraction) curves for 4 calcium channel antagonists: nifedipine (NIF, **A**), nicardipine (NIC, **B**), verapamil (VER, **C**), and diltiazem (DIL, **D**). Rings taken from the same patient were allocated to each treatment. One ring was the control (filled circles) without pretreatment of calcium antagonists. The second ring was treated with the plasma concentration of the particular calcium channel antagonists (open circles): 20 nmol/L ($-7.7 \log_{10}$ M) for nifedipine (**A**), nicardipine (**B**), and verapamil (**C**) and 60 nmol/L ($-7.2 \log_{10}$ M) for diltiazem (**D**). The third ring was treated with a high concentration of the calcium channel antagonists (filled triangles, 30 μ mol/L [$-4.5 \log_{10}$ M]), which implies the topical use of the drug. The drug was added into the organ bath 20 minutes before the start of the concentration-contraction curve. Symbols represent data averaged from 6 rings (from 6 patients) for each calcium antagonist. Vertical error bars are 1 SEM of mean values ($P = .0002$ for nifedipine [**A**], $P = .003$ for nicardipine [**B**], $P = .9$ for verapamil [**C**], and $P = .5$ for diltiazem [**D**]; ANOVA). * $P < .05$; ** $P < .01$; *** $P < .001$ compared with control (Scheffe F test).

study on another concentration (as high as 30 μ mol/L, which is not achievable by systemic administration) is to simulate the clinical situation when topical use of

calcium channel antagonists is indicated. As expected at such a high concentration, all 4 calcium channel antagonists have superior depressive effects on the

potassium-induced contraction. This implies that for topical use at high concentrations, any one of the calcium channel antagonists tested would provide effective antispastic effect.

To compare the effect of the 4 calcium antagonists, in the present study we used KCl as the precontraction agent, as well as the agent to test the depression effect on contraction. This is due to the fact that calcium channel antagonists are selective vasodilators that selectively inhibit the voltage-dependent calcium channel in human arteries.¹² Potassium induces vascular contraction through depolarizing the smooth muscle membrane and therefore increases the membrane potential that subsequently opens the voltage-dependent calcium channel.^{12,13} Therefore calcium channel antagonists are particularly effective in inhibition of potassium-induced contraction, and this has been shown in human vessels, such as the ITA¹² and saphenous vein.¹⁹ On the other hand, calcium channel antagonists are less effective to inhibit vascular contraction mediated by receptor mechanisms.^{12,20,21} By using potassium as the contraction agent, we may investigate the maximal effect of calcium channel antagonists, and this would provide an excellent basis to compare the effect among various calcium antagonists. As seen in the present study, all 4 calcium channel antagonists induced a full or nearly full relaxation, and therefore the potency (expressed by EC₅₀) among those calcium channel antagonists can be accurately compared.

In Acar and colleagues'⁴ protocol for RA grafting, diltiazem is used as the systemic spasmolytic agent. In contrast, we have been using verapamil in our clinical protocol for RA grafting because nifedipine is not available for intravenous infusion, and we believe that verapamil is more potent than diltiazem on the basis of data from previous studies on the ITA¹² and saphenous vein.^{14,19} However, both verapamil and diltiazem have a negative chronotropic effect that induces bradycardia in some patients, particularly when used in combination with β -blockers. The present study provides a scientific basis for the claim that dihydropyridine derivatives may be used as systemic spasmolytic agents instead of verapamil or diltiazem for a potent effect. In our practice, if the patient cannot tolerate oral verapamil postoperatively because of bradycardia, nifedipine is used instead. Because of the fact that nifedipine is not available for intravenous infusion, nicardipine may be recommended for systemic use intraoperatively.

Finally, the necessity of use of diltiazem or other calcium channel antagonists perioperatively for RA grafting is questioned.¹⁸ However, RA graft spasm is encountered frequently if no vasodilators are used.^{4-6,9,11}

Continuous search for the best regimen to overcome RA spasm is clinically important.

In conclusion, the results from our in vitro study suggest that dihydropyridine derivatives are highly potent spasmolytic agents in the human RA. Among the 4 calcium antagonists, the potency is in the following order: nifedipine > nicardipine > verapamil > diltiazem. Therefore dihydropyridine derivatives may be recommended for systemic administration in CABG with RA. Furthermore, at high concentrations for topical use, any one of the 4 calcium channel antagonists tested would provide effective antispastic effect.

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