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Pharmacological Comparison of Human Internal Mammary Artery and Radial Artery in Terms of Conduits for Revascularization

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Internal mammary arteries (IMA) are routinely used for coronary artery bypass grafting (CABG), but can exhibit impairment of endothelium-dependent vascular relaxation. The use of radial artery (RA) grafts for CABG has been recently reintroduced. The long-term patency of these grafts may depend on the ability of these vessels to produce endothelium-derived nitric oxide (NO). We therefore sought to determine if the RA exhibits better endothelial function compared with IMA harvested from the same patient. Using the organ bath technique, vessels were preconstricted with the thromboxane A_2 analogue (U46619) and exposed to increasing concentrations of either acetylcholine (ACh), calcium ionophore A23187 (A23187), or nitroglycerin (NTG). We prepared the rubbed RA for comparison of between RA with and without endothelium on response to ACh relaxation. KCl and U46619 constricted RA (11.3 ± 4.9 g and 16.0 ± 4.3 g respectively) more than IMA (2.4 ± 1.4 g and 4.5 ± 1.7 respectively). Both RA and IMA relaxed 100% of the preconstricted tension to NTG. ACh induced less relaxation in the IMA (28 ± 24 %) when compared with the RA (49 ± 16%) ($p<0.05$). A23187 demonstrated relaxation in both the RA (86 ± 14%) and IMA (76 ± 18%), but there was no statistical difference. RA without endothelium showed same response to ACh as IMAs. Compared with the IMA, the RA has better ACh induced endothelium-dependent relaxation. This pathway mainly involves NO production which also inhibits the atherosclerotic process. Therefore, the RA may provide longer term graft patency than IMA.

Key Words: human, internal mammary artery, radial artery, endothe lium function, coronary artery bypass grafting

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Introduction

The internal mammary artery (IMA) is an important conduit for coronary artery surgery. Both short and long-term patency are greater compared with the saphenous vein, and endothelium-dependent relaxation is greater in arterial grafts[1,3,4)]. The ability to perform a complete arterial revascularization has been limited by the availability of vessels that can be harvested. Radial arteries (RA) and gastroepiploic arteries are considered to have increased vasospastic properties[5−7)]. Although the RA was initially used for revascularization by Carpentier in 1971, this technique was previously abandoned because of a high incidence of vasospasm and low patency rates[6,8,9)]. Recently, the use of RA grafts for coronary artery bypass grafting (CABG) has been reintroduced because it represents an additional option for an arterial graft[2)]. Internal mammary arteries, although routinely used for coronary artery surgery, can exhibit impairment of endothelium-dependent vascular relaxation, and their availability may be limited[1)]. The long-term patency of arterial grafts may depend on the ability of these vessels to produce endothelium-derived nitric oxide (NO). Moreover, endothelial injury predisposes to thrombosis, leukocyte adhesion, and proliferation of smooth muscle cells in the arterial wall[10)]. We therefore sought to determine if the RA might exhibit better endothelial function as compared to the IMA harvested from the same patient.

Materials and Methods

Vessel Preparation

Following institutional approval, residual human IMA and RA segments were collected from 18 patients following CABG. The discarded distal end was carefully removed and placed in 4℃ chilled modified Krebs-Hepes buffer of the following composition (in g/L): NaCl, 6.9; KCl, 0.35; $CaCl_2$, 0.373; $MgSO_4$, 0.141; KH_2PO_4,

0.16; $NaHCO_3$, 2.1; D-Glucose, 2.0; HEPES, 5.206; pH 7.40 ± 0.05. The both vessels were transferred to the laboratory and then cleaned of adherent connective tissue and cut into 3mm ring segments immediately. The time delay between the vessels harvest and preparation was less than 30 minutes.

Organ-Chamber Experiments

The rings were suspended between two wire hooks in organ chambers filled with 25 ml of Krebs-Henseleit solution (in g/L: NaCl, 6.9; KCl, 0.35; $CaCl_2$, 0.373; $MgSO_4$, 0.141; KH_2PO_4, 0.16; $NaHCO_3$, 2.1; D-Glucose, 2.0; 37℃, pH 7.40 ± 0.05) aerated with 95% O_2 and 5% CO_2. The upper hook was connected to force transducer (Kent-Scientific Corporation), and changes in isometric force were recorded (Mac Lab® system, Milford MA). After a resting tension (RA 2.0 g, IMA 2.5 g), defined by preliminary studies, was progressively applied, the rings were allowed to stabilize for 30 minutes. The ring preparations were then precontracted with the KCl (60mM), washed 3 times with fresh buffer and allowed equilibrate for an additional 30 minutes. To prevent the effect of prostanoid, indomethacin was added first. After that, both arteries, which were constricted with the thromboxane A_2 analogue, U46619 (0.1nM), were relaxed with increasing doses of acetylcholine (10^{-9}to10^{-4} M). The vessels were then randomly separated into two groups of calcium ionophore A23187 (A23187) (n=12) and nitroglycerin (NTG) (n=10). After additional washing and equilibration, indomethacin was added again and both groups were contracted with U46619. Cumulative dose-response curves were obtained by adding of A23187 (10^{-10}-$10^{-5.5}$ M) or NTG (10^{-11}-$10^{-5.5}$ M) to the organ baths in 0.5 log-unit increments.

Comparison of RA with and without endothelium

Seven RA with and without endothelium from the same patients were compared. Endothelium was removed by inserting microforceps inside the lumen of the vessels and gently rubbing the surface. The vessels were constricted with KCl and U46619, and relaxed with ACh (n=7) according to the methods described above.

Drugs and buffer solutions

The following drugs were used; U46619: 10 mg/ml in methyl acetate, a gift from Upjohn company, Kalamazoo, Michigan; KCl powder: Supplied by Malinckrodt, St. Louis, Missouri ; acetylcholine chloride : supplied by Sigma Chemical, St. Louis, Missouri; A23187 : supplied by Sigma Chemical, St. Louis, Missouri; nitroglycerin : supplied by SoloPak Laboratories Inc., Elk Grove, Illinois; indomethacin : supplied by Sigma Chemical, St. Louis, Missouri

An aliquot of U46619 was evaporated to dryness under nitrogen, redissolved in absolute ethanol to 1mM and then diluted to 10^{-5} M in distilled water. A23187 was diluted with ethanol to 1mM and dissolved in distilled water to 10^{-4}-10^{-7} M. The concentration of ethanol in the bath did not exceed 0.1%. 4M KCl solution was used as a stock solution. All other drugs were diluted in distilled water. Drugs were prepared 5 minutes before each experiment and stored on ice. The concentrations of the drugs are expressed as final moles/litter concentration in the bath.

Data and Statistical analysis

Relaxation was expressed as a percentage of U46619 induced contraction (=100%). Responses from vascular segments were averaged for one patient's RA and IMA. A Mann-Whitney U test was used to compare the data. $P<0.05$ was considered significant. In all experiments, n equaled the number of patients from whom the both RA and IMA segments were obtained. Data are given as mean±SD.

Results

Patients characteristics

All patients (n=18) were men 58.3 ± 8.1 years old. There were 5 patients with a history of smoking, 14 with hypertension, 5 with non-insulin-dependent diabetes mellitus, and 11 with hypercholesterolemia.

Vessel constriction and relaxation

There were significant differences in constriction and relaxation responses between RA and IMA. Addition of KCl resulted in constriction of 11.3 ± 4.9g in RA and 2.4 ± 1.4g in IMA. For U46619 constriction was 16.0 ± 4.3g and 4.5 ± 1.7g respectively. Acetylcholine relaxed RA much better than IMA, E_{max} 49 ± 16% (range from 26 to 74%) and E_{max} 28 ± 24 % (range from 1 to 79%) respectively (Figures1 and 2). The degree of ACh relaxation of RA without endothelium and IMA with endothelium were very similar and there was no significant difference between the two vessels. Also, there was no significant difference in the response to A23187 in both arteries. Relaxation were 86 ± 14% (range from 54 to 100%) and 76 ± 18% (range from 45 to 100%) in RA and IMA respectively (Figure 3). Similarly, there

was no difference in NTG effects on both vessels. Highest concentration of NTG caused 100% relaxation in both RA and IMA (Figure 4 and Table 1).

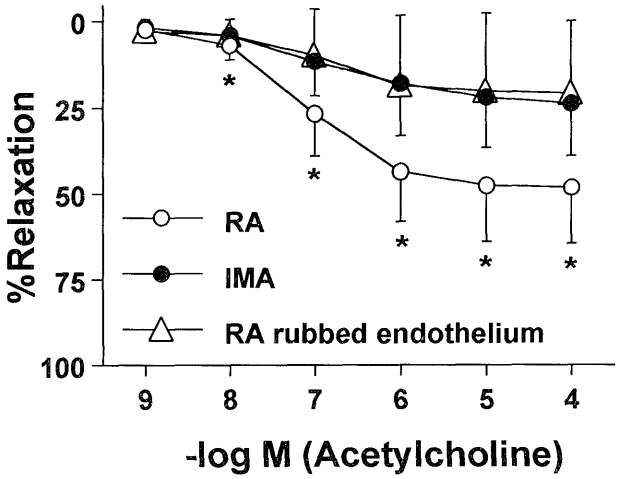

Figure 1. Concentration-response curve of acetylcholine (ACh) on human internal mammary artery (IMA; ●) and radial artery (RA; ○). Both arteries were preconstricted with U46619. Data are shown as mean ± SD (n = 12,*p<0.05 versus IMA). RA rubbed endothelium is shown as △ (n=7)

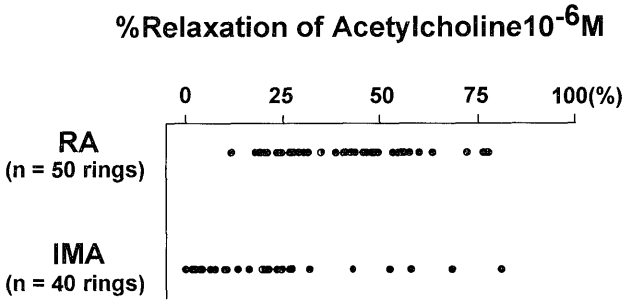

Figure 2. The response of radial artery (RA) and internal mammary artery (IMA) rings to acetylcholine 10^{-6} M.

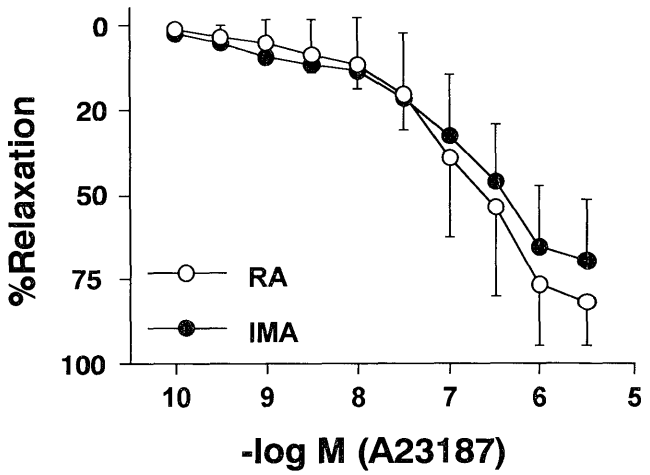

Figure 3. Concentration-response curve of calcium ionophore, A23187, on human internal mammary artery (IMA; ●) and radial artery (RA; ○). Both arteries were preconstricted with U46619. Data are shown as mean ± SD (n = 12)

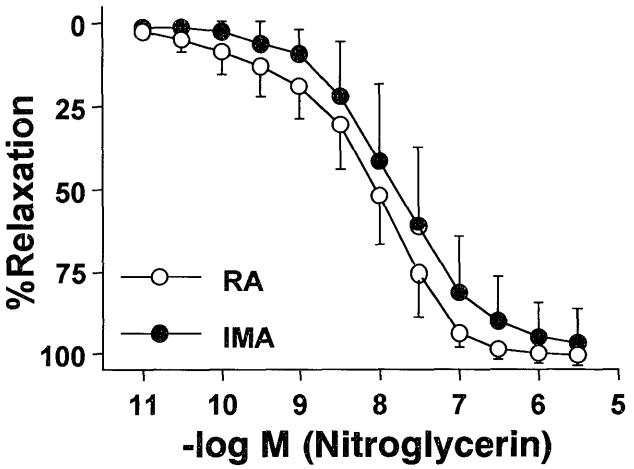

Figure 4. Concentration-response curve of nitroglycerin (NTG) on human internal mammary artery (IMA; ●) and radial artery (RA; ○). Both arteries were preconstricted with U46619. Data are shown as mean ± SD (n = 10).

Table 1. The EC_{50} and E_{max} of acetylcholine, A23187 and nitroglycerin on radial artery and internal mammary artery

	EC_{50} (mol/L)			E_{max} (%)		
	radial artery	internal mammary artery		radial artery	internal mammary artery	
acetylcholine	1.47 ± 1.4 x 10^{-7}	1.73 ± 1.6 x 10^{-7}	NS	49.0 ± 16.0	27.9 ± 23.6	*
A23487	2.26 ± 2.3 x 10^{-7}	1.57 ± 1.4 x 10^{-7}	NS	86.2 ± 14.0	76.2 ± 18.3	NS
nitroglycerin	9.17 ± 5.5 x 10^{-9}	2.4 ± 2.6 x 10^{-9}	NS	>100	>100	NS

Data are shown as mean ± SD

*P<0.05 radial artery versus internal mammary artery

Discussion

We noted that the RA demonstrated better endothelial function than IMA as measured by relaxation response to ACh. These findings may affect long-term patency of vascular grafts. Our study is also the first to directly compare IMA and RA from the same patient, and evaluate endothelial function in both grafts. This is important in the potential decision for isolated or combined vascular grafting during coronary artery surgery. Although thromboxane A_2 constricts the RA more than IMA, this difference can be explained by the greater amount of vascular smooth muscle in the RA[5]. On the other hand, RA and IMA showed same relaxation to A23187 and NTG. Therefore, our study suggests RA have better receptor-mediated endothelial function than IMA.

Different arteries including the internal mammary artery, gastroepiploic artery[11], inferior epigastric artery[12], splenic artery[13,14], have been used as a conduit for CABG. The RA was first used for coronary revascularization in 1971, but this practice was abandoned due to narrowing and occlusion several years later. Although it has not been established whether the RA has long-term patency, Acar reported that RA grafting showed excellent short term patency rates. Early angiographic controls (less than 2 weeks) were obtained in the first 50 consecutive patients. They studied and revealed 56 of 56 patent RA grafts, 48 of 48 patent left IMA grafts, 11 of 11 patent right IMA grafts, 14 of 18 patent free IMA grafts, and 8 of 9 patent vein grafts. For these reasons, RA grafting was reintroduced as a conduit for CABG[2].

The advantage of using a RA conduit is involved that it represents an arterial graft accustomed to systemic pressures, and its diameter corresponds exactly to the diameter of most coronary arteries, and the quality of its wall offers good technical conduits for coronary and aortic anastomosis, and its length allows it to reach all target vessels on the surface of the heart. Moreover, in the some instances, two distinct grafting sites can be performed using two segments of the same radial artery[2]. Further, the RA is usually macroscopically normal and rarely affected by atherosclerosis[2,15]. After the initial reports by Acar, additional investigators have suggested the usefulness of RA as a conduit for CABG, because of high patency rates[16-18].

The characteristics that influence long-term patency are multiple. RA is a muscular artery and was considered to be prone to vasospasm, an important cause of low patency[6]. He-Wei described many spasmogens for blood vessels that may include endothelium derived contracting factor (endothelin-1), prostanoids (thromboxane A_2, prostaglandin $F_{2\alpha}$), circulating sympathomimetic factor (α-adrenoceptor agonist (norepinephrine, methoxamine, phenylephrine)), platelet derived contracting substances (5-hydroxytryptamine, thromboxane A_2), substances released from mast cells and basophils (histamine), muscarinic receptor agents, factors arising from renin angiotensin system (angiotensin II) and KCl[19]. As shown not only in this study but other studies also, RA constricts considerably more than IMA when exposed to different constrictor agents, which may be the results of greater smooth muscle content[5,19,20]. Endothelium, although it releases vasoconstricting factors too, also protects the smooth muscle from vasoconstrictor effects of such agents as thromboxane A_2, norepinephrine, endothelin-1, angiotensin II, for example during perioperation period when plasma concentrations of these constrictors are increased[21-24]. Moreover endothelium-dependent vascular relaxation may contribute to the long-term patency of arterial grafts as NO inhibits atherosclerosis. The present study suggests that RA have better endothelium function than IMA, because of better relaxation to ACh but not to A23187. ACh produces NO by stimulating muscarinic receptors on endothelial membranes signaling, but in patients with atherosclerotic disease, the G-protein is impaired[25-27]. However, our data suggests that the endothelium receptor mediated function of RA is better than IMA in patients with vascular disease, a finding that may relate to long-term patency.

Several studies report the IMA exhibits impairment of endothelium-dependent vascular relaxation[28]. Our study is the first to directly compare the IMA with the RA in the same patient, and evaluate endothelial function. In patients who have coronary artery disease, atherosclerotic change is likely to exist in IMA as well. RA grafting may represent an alternative conduit to IMA. Further clinical studies are needed to support this hypothesis.

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