CHARACTERISTICS OF ADRENOCEPTORS IN THE HUMAN RADIAL ARTERY: CLINICAL IMPLICATIONS

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Objectives: The radial artery has been suggested to be spastic. Endogenous and exogenous catecholamines and the use of β -blockers may be related to radial artery spasm, but the characteristics of adrenoceptors in this artery are unknown. This study was designed to characterize the α - and β -adrenoceptor in the human radial artery. **Methods:** Ring segments of the radial artery ($n = 59$) taken from patients undergoing coronary artery bypass grafting were studied in organ chambers. α -Adrenoceptor agonists (norepinephrine, methoxamine, and UK14304) and antagonists (phentolamine hydrochloride [INN: phentolamine], prazosin, and yohimbine) were used to characterize the α -adrenoceptor. β -Adrenoceptor function was studied in U46619-precontracted rings in response to isoproterenol (INN: isoprenaline). **Results:** Norepinephrine induced 6.9 ± 0.6 gm ($80.6\% \pm 6.8\%$ of the contraction by 100 mmol/L KCl), and this was almost fully inhibited by phentolamine hydrochloride ($10 \mu\text{mol/L}$, $p < 0.0001$). The contraction force induced by methoxamine (2.9 ± 0.8 gm) was abolished by $0.5 \mu\text{mol/L}$ prazosin ($p = 0.017$). The contraction force induced by UK14304 (1.7 ± 0.4 gm) was abolished by $1 \mu\text{mol/L}$ yohimbine. In contrast to the porcine coronary artery used as the control (fully relaxed to isoproterenol), radial artery rings did not have significant relaxation ($1.1\% \pm 0.8\%$). **Conclusions:** The human radial artery is an α -adrenoceptor-dominant artery with little β -adrenoceptor function. The use of β -blockers will not likely evoke the spasm of the radial artery. Furthermore, the radial artery has a dominant α_1 -adrenoceptor function, but the postjunctional α_2 -adrenoceptor is also functional. Circulating catecholamines will mainly contract the human radial artery by activation of the α_1 -adrenoceptors and to a lesser extent also by α_2 -adrenoceptors. (J Thorac Cardiovasc Surg 1998;115:1136-41)

Various autologous arteries have been used as grafts for coronary artery bypass grafting (CABG) with success. Those arteries are the inter-

nal thoracic artery (ITA) and more recently arterial grafts such as the gastroepiploic artery and the inferior epigastric artery. Compared with these, the use of the radial artery has been more eventful. The radial artery was initially applied as a graft for CABG in 1971.¹ However, it was soon abandoned because of the reported high incidence of vasospasm and low patency rates.²⁻⁴ With increased knowledge of spastic characteristics of this artery and of methods to overcome the spasm using pharmacologic agents, this arterial graft is again used.⁵ However, the long-term results of this graft are still pending.

According to the functional classification of arterial grafts,⁶ the radial artery belongs to type III, a type of graft that is more spastic than type I arteries (somatic arteries, such as the ITA and inferior epigastric artery). From our experience in agreement with others,⁷⁻¹¹ the radial artery contraction

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(or spasm) is almost inevitably encountered during the operative dissection and warrants the use of vasodilators during harvesting, which is a key step in the revival of the use of the radial artery.⁵

The nature of the spastic characteristics of the radial artery is still unknown. Various vasoconstrictor substances have been suggested to be the spasmogens of human arterial grafts.¹² Among those spasmogens, α -adrenoceptor stimulants are important vasoconstrictors. Studies have demonstrated that the radial artery has a higher response to norepinephrine (NE), 5-hydroxytryptamine,⁷ angiotensin II, and endothelin-1¹¹ than the ITA. It is obviously important to identify the characteristics of the adrenoceptors in the radial artery. First, the responses of the human radial artery to catecholamines are clinically important during and after operation. The stimulation by catecholamines of α -adrenoceptors may be the cause of the radial artery spasm. As to the response to catecholamines, knowledge of the subtypes of α -adrenoceptors in the human radial artery is important because the effects of circulating catecholamines (endogenous or exogenous) on this artery might therefore be predicted. During the perioperative period in patients in critical condition receiving intravenous catecholamines, this is particularly important; also, many patients who undergo CABG are taking β -blockers. Whether the use of the β -blockers will evoke radial artery spasm perioperatively depends largely on the function of the β -adrenoceptor in this artery and this is unknown.

In view of these clinical implications this work was designed to investigate the subtypes of α -adrenoceptors and the function of β -adrenoceptors in the human radial artery by receptor agonists and antagonists.

Methods

General. Human radial artery segments were collected from patients undergoing CABG with these grafts. Approval to use discarded radial artery tissue was given by the Human Ethics Committee of the Grantham Hospital. After the radial artery was dissected, the required length was carefully measured. Any discarded segments of radial artery were immediately collected and placed into a container with oxygenated physiologic (Krebs) solution maintained at 4° C and then transferred to the laboratory. The vessels were placed in a glass dish and dissected out from their surrounding connective tissue. The arteries were cut into 3 mm long rings and then suspended on wires in organ baths.¹³ The number of rings provided by each patient varied from 2 to 4. The Krebs solution had

Fig. 1. Mean concentration ($-\log$ mol/L)-contraction (percentage of 100 mmol/L K^+ -induced contraction) curves for NE in the human radial artery. Two rings obtained from each patient were allocated to each treatment. One ring was the control (●) without pretreatment of phentolamine. For the other ring phentolamine, 10 μ mol/L (○), was added into the organ bath 30 minutes before the start of the NE curve. Symbols represent data averaged from six rings (from six patients). Vertical error bars are 1 standard error of mean values. * $p < 0.0001$.

the following composition (in millimoles per liter): Na^+ , 144; K^+ , 5.9; Ca^{2+} , 2.5; Mg^{2+} , 1.2; Cl^- , 128.7; HCO_3^- , 25; SO_4^{2-} , 1.2; $H_2PO_4^-$, 1.2; and glucose, 11. The solution was aerated with a gas mixture of 95% oxygen to 5% carbon dioxide at $37^\circ \pm 0.1^\circ$ C.

Organ-bath technique. A specially designed organ-bath technique was used for this study. This technique allows for the vascular rings to be subject to normal physiologic pressure in vitro comparable to that in vivo. The details of the technique were previously published.^{14,15} In brief, each arterial ring was stretched in progressive steps to determine the individual length-tension curve. A computer iterative fitting program (VESTAND 2.1, Yang-Hui He, Princeton University, N.J.) was used to determine the exponential line, pressure, and internal diameter. When the transmural pressure on the rings reached 100 mm Hg, determined from their own length-tension curves, the stretch procedure was stopped and the rings were released to return to 90% of their internal circumference at 100 mm Hg. This degree of the passive tension was then maintained throughout the experiment.

Because of the importance of endothelium on vascular tone, we intentionally preserved the endothelium by cautiously dissecting and mounting the rings. We previously found that this technique allowed the experiments to be

Fig. 2. Mean concentration ($-\log$ mol/L)-contraction (percentage of 100 mmol/L K^+ -induced contraction) curves for MO in the human radial artery. Two rings obtained from each patient were allocated to each treatment. One ring was the control (●) without pretreatment of phentolamine. For the other ring prazosin, 0.5 μ mol/L, (○) was added into the organ bath 30 minutes before the start of the NE curve. Symbols represent data averaged from six rings (from six patients). Vertical error bars are 1 standard error of mean values. * $p < 0.001$.

carried out with an intact endothelium, as determined by the functional relaxation response to endothelium-derived relaxing factor agonists in the human radial artery¹¹ and porcine coronary artery.¹⁶ To examine the role of endothelium in our study, the endothelium in four rings was removed mechanically by using a fine wood stick moistened with Krebs solution to gently rub the intima of the rings.^{14, 16} The response to an endothelium-derived relaxing factor stimulus, calcium ionophore A23187, in U46619-precontracted radial artery rings was compared in the endothelium-intact and the endothelium-denuded rings.

Protocol. After the normalization procedure, the radial artery rings were equilibrated for 60 minutes. KCl (100 mmol/L) was added to test the viability of the vessel, and the contraction force was used as the control. Vessels were discarded if they did not respond to KCl. The radial artery ring was then washed and subject to the following protocols. The radial artery rings were randomly distributed to different groups, disregarding preoperative drug therapy. However, in β -adrenoceptor functional studies pilot experiments showed that this function is weak in the radial artery; therefore, for this part of the study, radial artery rings were taken from four patients (in three patients no β -adrenoceptor blockers were given preoperatively to exclude any possible effect of the drug).

α -Adrenoceptor agonists and antagonists

α_1 - and α_2 -Adrenoceptor agonist NE and α_1 -, α_2 -antagonist phentolamine. Two rings from a patient were allocated in two groups (six rings for each group). One ring was set as a control for NE concentration-contraction curve while the other ring was incubated in $-5 \log$ mol/L phentolamine hydrochloride (INN: phentolamine) (an α_1 - and α_2 -adrenoceptor antagonist) for 30 minutes before the NE concentration-contraction curve was constructed.

α_1 -Agonist methoxamine and α_1 -antagonist prazosin. Two radial artery rings obtained from a patient were allocated into two groups (six rings for each group). One ring was used as a control, and a concentration-contraction curve to methoxamine (MO) was constructed from this ring. The second ring was incubated in $-6.3 \log$ mol/L (0.5 μ mol/L) prazosin (an α_1 -adrenoceptor antagonist) for 30 minutes before a concentration-contraction curve to MO was constructed.

α_2 -Agonist UK14304. A highly selective α_2 -adrenoceptor agonist UK14304 was given to test the α_2 -adrenoceptors in the radial artery ($n = 11$). Concentration-contraction curves to UK14304 (-9 to $-5 \log$ mol/L) were constructed. Rings ($n = 9$) were then washed and incubated in $-6 \log$ mol/L yohimbine (a selective α_2 -adrenoceptor antagonist) for 30 minutes before the second concentration-contraction curves were constructed.

β -Adrenoceptor agonists and antagonists. Ten radial artery rings were contracted by U46619 (10 nmol/L). When the contraction reached a stable plateau, cumulative concentration-response curves for isoproterenol (INN: isoprenaline) were obtained by adding this agent to the organ chamber. After the isoproterenol curve was completed, nitroglycerin (30 μ mol/L) was added to determine whether the rings were still capable of further relaxation. Because the relaxation induced by isoproterenol was minimum in the radial artery rings, the porcine coronary artery, a vessel known to possess a strong β -adrenoceptor function, was studied in terms of its response to isoproterenol as the control ($n = 6$).

In all experiments except those with UK14304 each radial artery ring was used for only one concentration-contraction curve.

Data analysis. The effective concentration of the contraction or relaxation agent that caused 50% of maximal contraction (or relaxation) was defined as ED_{50} . The EC_{50} was determined from each concentration-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, 15} From this fitted equation, the mean EC_{50} value $\pm$ standard error of the mean was calculated for each group.

Maximal responses in two groups of rings were compared by unpaired t test. Results are expressed as mean ($\pm$ standard error).

Drugs. Drugs used in this study and their sources were: (–) NE bitartrate, MO, phentolamine (Sigma Chemical Company, St. Louis, Mo.); yohimbine (Tokyo, Kasei, Japan); UK14304 and prazosin (Pfizer, New York, N.Y.); stock solutions were kept in the refrigerator.

Results

Fifty-nine human radial artery ring segments were used in this study. The diameter of the rings at a transmural pressure of 100 mm Hg was 2.3 ± 0.2 mm (standard error). The transmural pressure on the vascular wall during the experiments determined by their own length-tension curves was 71.9 ± 5.2 mm Hg. The resting force on the vascular wall was 2.2 ± 0.19 gm.

Functional test on endothelium. In the endothelium-preserved rings A23187 caused $62.9\% \pm 6.0\%$ of relaxation of U46619-induced contraction, whereas in the endothelium-denuded rings A23187 caused no relaxation at all.

α_1 - and α_2 -agonist NE and antagonists. NE induced 6.9 ± 0.6 gm ($80.6\% \pm 6.8\%$ of the contraction by 100 mmol/L KCl), and α_1 - and α_2 -antagonist phentolamine (10 μ mol/L) almost fully inhibited this contraction (0.9 ± 0.4 gm, $p < 0.0001$, Fig. 1). Compared with the EC_{50} of -6.63 ± 0.12 log mol/L in the control rings, in those treated with phentolamine, because of the total abolishment of the contraction, the EC_{50} could not be calculated with the above equation.

α_1 -Agonists and antagonists. The maximum contraction force induced by MO was 2.9 ± 0.8 gm ($57.1\% \pm 10.5\%$ of the contraction by 100 mmol/L KCl), and it was abolished (0.2 ± 0.2 gm) by 0.5 μ mol/L prazosin ($p = 0.017$, Fig. 2). Similar to the results in the NE experiments, compared with the EC_{50} of -4.77 ± 0.33 log mol/L in the control rings, in those treated with phentolamine, because of the total abolishment of the contraction, the EC_{50} could not be calculated with the above equation.

α_2 -Agonist UK14304. The maximum contraction force induced by UK14304 was 1.7 ± 0.4 gm ($28.3\% \pm 6.4\%$ of the contraction by 100 mmol/L KCl), and it was abolished (0.1 ± 0.1 gm) by 1 μ mol/L yohimbine (Fig. 3). In one ring UK14304 did not evoke contraction. The EC_{50} for the rest of the rings ($n = 10$) was -6.13 ± 0.2 log mol/L.

β -Adrenoceptor agonists and antagonists. In the radial artery rings contracted by U46619 isoproterenol did not induce any significant relaxation ($1.1\% \pm 0.8\%$, Fig. 4), although the vessels were fully relaxed with nitroglycerin (30 μ mol/L) at the end of the experiment. In contrast, the porcine coronary artery was fully relaxed with isoproterenol ($97.6\% \pm 1.2\%$, Fig. 4).

Discussion

This study, for the first time, demonstrates that (1) the human radial artery is an α_1 -adrenoceptor-

Fig. 3. Mean concentration ($-\log$ mol/L)-contraction (percentage of 100 mmol/L K^+ -induced contraction) curves for UK14304 in the human radial artery. Cumulative concentration-contraction curves were established for UK14304 ($\bullet$, $n = 11$). The rings were then repeatedly washed to reestablish the baseline. Yohimbine (1 μ mol/L) was added 30 minutes before the second concentration-contraction curves to UK14304 were established ($\circ$, $n = 9$). Vertical error bars are 1 standard error of mean values. $*p < 0.01$.

dominant artery with little β -adrenoceptor function and (2) the post- α_1 -adrenoceptor is dominant although α_2 -function also exists. Therefore circulating catecholamines will primarily contract the radial artery through the α_1 -mechanism and the use of β -blockers will unlikely evoke radial artery contraction or spasm during and after CABG.

Operative results (early mortality and long-term patency) of CABG depend at large on the function of the graft. For the radial artery the major concern is its spastic characteristic with subsequent occlusion leading to the initial abandonment of this arterial graft. The spastic characteristic of the radial artery has been demonstrated experimentally.^{7, 11} The radial artery is more reactive to NE, 5-hydroxytryptamine,⁷ angiotensin II, and endothelin-1¹¹ than is the ITA.

Adrenoceptors are composed of α - and β -subtypes. In large arteries α -adrenoceptors mediate contraction, whereas β -adrenoceptors, relaxation. If the function of the β -adrenoceptor is strong, the artery tends to contract when β -blockers are given

Fig. 4. Mean concentration ($-\log$ mol/L)-response (% relaxation) curves for isoproterenol in the human radial artery (RA) precontracted by U46619 (10 nmol/L) (●, $p = 10$, taken from four patients). All the artery segments were fully relaxed to nitroglycerin (30 μ mol/L) at the end of the experiment. Porcine coronary arteries (PCA) were used as the control (○, $n = 6$). Vertical error bars are 1 standard error of mean values. * $p < 0.0001$.

because the β -adrenoceptor-mediated relaxation is eliminated as reported in coronary arteries.¹⁷ One of the aims of this study is to investigate whether this mechanism is involved in the radial artery spasm. Our study results clearly demonstrate that this is not the case because the human radial artery has little β -adrenoceptor-mediated function. This is shown in the result that isoproterenol, a full β -agonist, did not induce significant relaxation. In these experiments the radial artery was taken from four patients while three of them were not taking β -blockers. This ruled out the possibility that the minimal β -mediated relaxation was due to the preoperative use of β -blockers. The full relaxation induced by isoproterenol in the porcine coronary artery suggests that our method is suitable to study the β -function and reveals a tremendous difference in β -function between these two arteries. We previously studied the β -adrenoceptor function in the human ITA¹⁵ and showed weak relaxation of the artery. In this study we have demonstrated that the β -adrenoceptor function is even weaker in the radial artery than in the ITA.

Postjunctional α -adrenoceptors are composed of α_1 - and α_2 -subtypes. It is generally recognized that

in vascular smooth muscle postjunctional α_1 -adrenoceptor is the predominant vasoconstrictor type, although stimulation of postjunctional α_2 -adrenoceptors can also induce vasoconstriction.¹⁸⁻²⁰ The contribution of α_2 -adrenoceptors to drug-induced vasoconstriction depends on particular vessels and species, as well as the diameter of the blood vessels.²¹⁻²² It has been suggested that α_1 -adrenoceptors are predominantly norepinephrine in nature and are located extrajunctionally and prejunctionally.²³⁻²⁵ Medgett and Langer²⁶ reported that vasoconstrictor responses to exogenous agonists are mainly mediated by the α_2 -adrenoceptors in the cat middle cerebral artery, but the α_2 -adrenoceptors do not mediate neuronal sympathetic vasoconstrictions because they are mainly located extrajunctionally. However, more recently, it has been shown that postsynaptic α_2 -adrenoceptors can be involved in the vasoconstrictor response to sympathetic nerve stimulation to a significant²⁰ or even predominant degree.¹⁸ In this article we use the term postjunctional α_2 -adrenoceptor to differ from the presynaptic α_2 -adrenoceptor. In this study we found that NE (an α_1 - and α_2 -agonist) produced a significantly greater maximum contraction force than MO (an α_1 -agonist) did (6.9 ± 0.6 vs 2.9 ± 0.8 gm, $p < 0.01$), and this suggests that postjunctional α_2 -adrenoceptors may play a role in the NE-induced contraction in the human radial artery. This is further supported by the UK14304-induced contraction. UK14304 is a pure α_2 -agonist,²⁷ and it produced contractions in 10 of 11 radial artery rings in our experiments. The contraction could be totally inhibited by yohimbine, an α_2 -antagonist. These experiments suggest that the postjunctional α_2 -adrenoceptor is functional in the human radial artery. Compared with the previous finding in the human ITA showing the ITA to have little α_2 -adrenoceptor function, the radial artery probably had slightly higher α_2 -adrenoceptor-mediated function.

Although both postjunctional α_1 - and α_2 -adrenoceptors mediate contraction, the identification of the subtypes of the adrenoceptors has some clinical implications in predicting the role of circulating catecholamines, which are frequently administered perioperatively for CABG. In our study the response to the pure α_1 -agonist MO has demonstrated the functional role of this subtype of the adrenoceptor. In contrast UK14304 evoked significantly less contraction ($57.1\% \pm 10.5\%$ vs $28.3\% \pm 6\%$, $p < 0.05$). This shows the predominance of the α_1 -adrenoceptor in the human radial artery. Therefore this study demonstrates that the human radial ar-

tery, like the human ITA, is α_1 -predominant and has weak β -mediated relaxation. However, unlike the human ITA in which there is little evidence of the existence of postjunctional α_2 -adrenoceptors, the human radial artery evidently has such α_2 -function.

In conclusion, our study demonstrates that the human radial artery is an α -adrenoceptor-dominant artery with little β -adrenoceptor function. The use of β -blockers will not likely evoke spasm of the radial artery. With regard to the subtypes of the α -adrenoceptors, the radial artery has a dominant α_1 -function, but the postjunctional α_2 -adrenoceptor is also functional. Circulating catecholamines will mainly contract the human radial artery, and the contraction is mediated by activation of the α_1 -adrenoceptors and, to a lesser extent, the α_2 -adrenoceptors. Therefore such contraction may be effectively antagonized by α_1 - and α_2 -adrenoceptor antagonists.

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