VASORELAXANT EFFECT OF PHOSPHODIESTERASE-INHIBITOR MILRINONE IN THE HUMAN RADIAL ARTERY USED AS CORONARY BYPASS GRAFT

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Objective: The radial artery is a spastic coronary bypass graft. We investigated the effect of the phosphodiesterase III inhibitor milrinone on the human radial artery.

Methods: Radial artery segments ($n = 76$) taken from 15 patients were studied in an organ chamber. Concentration-relaxation curves for milrinone were established in the radial artery precontracted with 3 vasoconstrictors (phenylephrine, K^+ , and U46619). In radial artery rings incubated with therapeutic plasma concentrations of milrinone (7 and 70 $\mu\text{mol/L}$) for 10 minutes, concentration-contraction curves for the 3 vasoconstrictors were constructed.

Results: Milrinone caused a submaximal relaxation in phenylephrine ($98.6\% \pm 1.4\%$), K^+ ($89.1 \pm 4.5\%$), or U46619 ($74.2 \pm 8.0\%$) precontracted radial arteries at $-4.5 \log_{10} \text{ M}$. The EC_{50} was higher against K^+ ($-5.85 \pm 0.24 \log_{10} \text{ M}$, $P = .02$) or U46619 ($-5.21 \pm 0.61 \log_{10} \text{ M}$, $P = .03$) than phenylephrine ($-6.68 \pm 0.11 \log_{10} \text{ M}$). Pretreatment with milrinone depressed the contraction by phenylephrine from $70.0\% \pm 7.9\%$ to $23.5\% \pm 9.3\%$ ($P = .003$) and by K^+ from $138.6\% \pm 5.8\%$ to $73.0\% \pm 13.9\%$ ($P = .006$) and shifted the EC_{50} 3.8-fold higher ($P = .03$) for phenylephrine and 2.2-fold higher for K^+ ($P = .01$). Milrinone reduced the U46619 contraction at low concentration ($-8.5 \log_{10} \text{ M}$) but had little effect on the maximal contraction.

Conclusion: Milrinone is a potent vasodilator for the radial artery, with possibly higher potency in α -adrenoceptor- and depolarizing agent K^+ -mediated, but less potency in thromboxane A_2 -mediated, contraction. Because it also has a positive inotropic effect, this vasodilator may be particularly indicated for use in patients receiving radial artery grafts in coronary artery bypass grafting. (J Thorac Cardiovasc Surg 2000;119:1039-45)

Autologous arteries have been used as grafts for coronary artery bypass grafting (CABG). We have recent-

ly classified all arterial grafts into 3 types according to their pharmacological reactivity and embryological origins¹: type I (somatic arteries), type II (splanchnic arteries), and type III (limb arteries). In this classification on arterial grafts, the radial artery (RA) belongs to the type III, a type that is more spastic than the type I artery, such as the internal thoracic artery (ITA).¹⁻⁴ Considering the more spastic biological characteristics of this artery, taken together with the history of the abandonment of the RA because of its vasospasm problem,^{5,6} antispastic therapy for this arterial graft in CABG is particularly important.^{7,8} In fact, the revival of the RA largely resulted from the use of calcium antagonists.⁵ However, the use of calcium antagonists may be contraindicated in patients with poor left ventricular function and bradycardia. The search for the best antispastic method for the RA is therefore clinically important.

In addition, although many vasodilators such as calcium antagonists, ACE-inhibitors, and long-lasting

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nitrates are available, there is an obvious need for a vasodilator that also has positive inotropic effects. Cardiac contraction and vascular smooth muscle relaxation are related to the biological activity of second messengers, including cAMP and cGMP, that are hydrolyzed by phosphodiesterases (PDEs). PDE inhibitors are of clinical importance because of their positive inotropic, as well as vasodilator, effects.^{9,10} In coronary bypass surgery, the use of PDE inhibitors may have a particularly important implication. The positive inotropic and vasodilator effects of PDE inhibitors are favorable in the early postoperative period, particularly for patients with impaired left ventricular function who have received arterial grafts. In patients undergoing CABG and receiving arterial grafts, milrinone has been used clinically for its inotropic and relaxant effects on the coronary artery as well as on the ITA.¹¹⁻¹⁴

However, the effect of milrinone or other PDE III inhibitors has been reported to be species- and vessel-selective.¹⁵ As demonstrated by Monrad and associates,¹⁶ milrinone is a direct and selective coronary vasodilator, compared with its effect on renal or cerebral arteries. Despite the fact that milrinone is a potent vasodilator in animal arteries,¹⁰ as well as in human arteries such as mesenteric arteries¹⁷ and the ITA,¹¹⁻¹⁴ the effect of milrinone on the human RA has not been studied. The present study was therefore designed to investigate this effect.

Methods

General. Seventy-six human RA segments were collected from 15 patients (mean age, 64.5 ± 2.0) undergoing CABG with use of the RA. The preoperative drug therapy was disregarded. However, none of the patients received milrinone therapy. 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, physiological solution (Krebs) maintained at 4°C, and then transferred to laboratory immediately. The RA was transferred into a glass dish and dissected out from its surrounding connective tissue. The vessels were cut into rings 3-mm long and suspended on wires in organ baths.^{18,19} The number of rings taken from each patient varied from 2 to 6. The Krebs solution had the following composition (in millimoles per liter): Na⁺ 144, K⁺ 5.9, Ca²⁺ 2.5, Mg²⁺ 1.2, Cl⁻ 128.7, HCO₃⁻ 25, SO₄²⁻ 1.2, H₂PO₄⁻ 1.2, and glucose 11. The solution was aerated with a gas mixture of 95% O₂-5% CO₂ at 37°C.

Organ-bath technique. A technique was used for this study that allowed vascular rings to normalize to a physiological pressure in the organ bath. The vascular rings were set at a pressure comparable to that in the *in vivo* situation. The details of the technique were published before.^{18,19} Briefly, the rings were stretched 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, the 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 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.

The endothelium was intentionally preserved by cautiously dissecting and mounting the rings, since endothelium plays a modulatory role in the contractility of arterial grafts.²⁰ We previously found that this technique allowed for a functionally intact endothelium, as determined by the functional relaxation response to substance P or calcium ionophore in the RA.²

Protocol. After the normalization procedure, the RA rings were equilibrated for at least 45 minutes. Two experimental protocols, relaxation and depression of contraction by pretreatment with milrinone, described below, were designed (in this study, multiple RA rings taken from each patient were allocated to different experimental groups).

Relaxation. Milrinone-induced relaxation was studied in RA rings contracted with potassium chloride (K⁺, 25 mmol/L, n = 7), U46619 (10 nmol/L, n = 7), and phenylephrine (3 μ mol/L, n = 7). The concentrations of these vasoconstrictor substances were submaximal, as determined from the logistic-curve fitting equation.^{18,19} These concentrations are equal to EC₅₀ to EC₈₀ for the U46619-, K⁺-, and phenylephrine-induced contraction in the human RA from the present study. Cumulative concentration-relaxation curves to milrinone were then established. Only 1 concentration-relaxation curve was obtained from each RA ring. A mean concentration-relaxation curve was constructed as shown in a group of rings.

Depression of contraction by pretreatment with milrinone. After equilibration, 100 mmol/L K⁺ was added to the organ bath and the contraction force was recorded. The ring was frequently washed to restore the baseline. To determine whether pretreatment with milrinone would alter the contraction response to various vasoconstrictors (phenylephrine, K⁺, and U46619), we constructed cumulative concentration-contraction curves from RA ring segments. These rings were equilibrated for 10 minutes with 7 or 70 μ mol/L milrinone. These concentrations were chosen since they are similar to optimal plasma concentration reached clinically.²¹ The time for the pretreatment was chosen from the average time to reach a plateau for each dose of milrinone in the relaxation experiments in the present study. Contraction was expressed as a percentage of the contraction force induced by 100 mmol/L K⁺.

Phenylephrine. Three or four rings were taken from each of 6 patients. One or two of these rings were used as a control, and the other two were equilibrated for 10 minutes with one of the two concentrations (7 or 70 μ mol/L) of milrinone. A cumulative concentration-contraction curve was then constructed for phenylephrine.

K⁺. Three rings were taken from each of 6 patients. One of these rings was used as a control, and the other two were equilibrated for 10 minutes with one of the two concentra-

tions (7 or 70 $\mu\text{mol/L}$) of milrinone. A cumulative concentration-contraction curve was then constructed for K^+ .

U46619. Three rings were taken from each of 6 patients. One of these rings was used as a control, and the other two were equilibrated for 10 minutes with one of the two concentrations (7 or 70 $\mu\text{mol/L}$) of milrinone. A cumulative concentration-contraction curve was then constructed for U46619.

Data analysis. The data are presented as mean $\pm$ standard error of the mean (SE). The effective concentration of the constrictor (or dilator) agent that caused 50% of maximal contraction (or relaxation) was defined as EC_{50} ($-\log_{10} \text{M}$). The EC_{50} was determined from each concentration-contraction (or relaxation) curve by a logistic, curve-fitting equation:

$$E = \text{MAP} / (\text{AP} + \text{K}^p)$$

where E is response, M is maximal contraction (or relaxation), A is concentration, K is EC_{50} concentration, and p is the slope parameter.^{18,19} A computerized program was used for the curve-fitting.

From this fitted equation, the mean EC_{50} value was calculated in each group. Unpaired *t* test or analysis of variance was used to test statistical significance among different constrictors and dilators regarding the maximal response or EC_{50} . The Scheffé test was used as post hoc test between 2 groups when ANOVA was used to compare among 3 groups. $P < .05$ was considered significant.

Materials. Drugs used in this study and their sources were as follows: phenylephrine (Sigma, St Louis, Mo); U46619 (Cayman Chemical, Ann Arbor, Mich); stock solution of U46619 was held frozen until required; milrinone was generously provided by Sterling-Winthrop Pharmaceutical Research Division.

Results

Resting vessel variables. The mean internal diameter of the 76 rings at an equivalent transmural pressure of 100 mm Hg (D100) was 2.5 ± 0.2 mm as determined from the normalization procedure.^{18,19} When the RA rings were set at a resting diameter of $0.9 \times \text{D100}$, the equivalent transmural pressure was 71.1 ± 1.9 mm Hg, and the resting force was 2.1 ± 0.4 g.

Relaxation by milrinone in the RA precontracted by phenylephrine, K^+ , or U46619. Milrinone caused a submaximal relaxation in U46619- ($74.2\% \pm 8.0\%$), phenylephrine- ($98.6\% \pm 1.4\%$), or K^+ - ($89.1\% \pm 4.5\%$) precontracted RA (Fig 1) at the concentration of $-4.5 \log_{10} \text{M}$. The EC_{50} was significantly higher against K^+ - ($-5.85 \pm 0.24 \log_{10} \text{M}$, 95% confidence interval [CI]: $0.17 \sim 1.50 \log_{10} \text{M}$, $P = .02$), or U46619 ($-5.21 \pm 0.61 \log_{10} \text{M}$, 95% CI: $0.12 \sim 2.83 \log_{10} \text{M}$, $P = .03$) than phenylephrine ($-6.68 \pm 0.11 \log_{10} \text{M}$) (unpaired *t* test).

Depression of contraction by pretreatment with milrinone. Pretreatment with milrinone significantly inhibited phenylephrine-induced contraction ($P = .016$,

Fig 1. Mean concentration ($-\log_{10} \text{M}$)-response (% relaxation) curves for milrinone in the human radial artery precontracted by potassium chloride (closed circles, K^+ , 25 mmol/L, $n = 7$), phenylephrine (open circles, 3 $\mu\text{mol/L}$, $n = 7$), and U46619 (triangles, 10 nmol/L, $n = 7$). The rings were taken from 6 patients. Vertical error bars are 1 SEM of mean values.

Fig 2). In comparison to $70.0\% \pm 7.9\%$ in the control, the maximal contraction was reduced to $63.4\% \pm 9.2\%$ and $23.5\% \pm 9.29\%$ (95% CI: $19.9 \sim 73.1\%$, $P = .03$, Scheffé test) with the treatment of milrinone at the concentration of 7 or 70 $\mu\text{mol/L}$. The treatment of milrinone also changed the EC_{50} . Pretreatment with 70 $\mu\text{mol/L}$ milrinone shifted the EC_{50} 3.8-fold (95% CI: $-11.5 \sim -1.3$) higher (Table I, $P = .02$, 95% CI: $-1.06 \sim -0.12 \log_{10} \text{M}$).

Pretreatment with milrinone also significantly inhibited K^+ -induced contraction ($P = .016$, Fig 3). In comparison to $138.6\% \pm 5.76\%$ in the control, the maximal contraction was reduced to $117.3\% \pm 4.0\%$ and $73.0\% \pm 13.9\%$ (95% CI: $32.1 \sim 99.1\%$, $P = .006$, Scheffé test) with the treatment of milrinone at the concentration of 7 or 70 $\mu\text{mol/L}$. The treatment of milrinone also changed the EC_{50} . Pretreatment with 70 $\mu\text{mol/L}$ of milrinone shifted the EC_{50} 2.2-fold higher for K^+ (Table I, 95% CI: $-39.5 \sim 12.8 \text{ mmol/L}$, $P = .01$).

In contrast, in U46619-induced contraction, the pretreatment with milrinone did not significantly reduce the maximal contraction (Fig 4 and Table I). However, at a lower concentration ($-8.5 \log_{10} \text{M}$), treatment of milrinone significantly reduced the U46619-induced contraction ($P = .02$, Fig 4).

Fig 2. Mean concentration ($-\log_{10}$ M)-contraction (percentage of 100 mmol/L K^+ -induced contraction) curves for phenylephrine. Three rings obtained from each patient were allocated to each treatment. One ring was the control (closed circles) without pretreatment of milrinone. For the other 2 rings, milrinone 7 (open circles) or 70 (triangles) $\mu\text{mol/L}$ was added into the organ bath 10 minutes before the start of the phenylephrine curve. Symbols represent data averaged from a group of rings (taken from 6 patients). Vertical error bars are 1 SEM of mean values; double asterisks, $P < .01$, ANOVA among the 3 groups and Scheffé test compared with the control at the maximal contraction.

Discussion

In this study of the human RA, the alternative arterial graft for coronary artery bypass surgery, we have found that (1) milrinone at clinically relevant concentrations is a potent vasodilator that inhibits the contraction mediated by various vasoconstrictors and that (2) milrinone may have slight selectivity with higher potency to α -adrenoceptor- and depolarizing agent K^+ -mediated contraction than the contraction mediated by thromboxane A_2 (TXA_2).

Intracellular cAMP and cGMP play a role in modulation of vascular smooth muscle tone.²² Concentrations of cAMP and cGMP are controlled through synthesis by cyclases and through hydrolysis by PDEs. PDEs are classified into at least 5 types.²³ PDE III inhibitors, such as amrinone or milrinone, are known to inhibit cGMP-inhibitable low K_m cAMP PDE.¹⁰ The pharmacologic activities of PDE III inhibitors are to increase cardiac contractility, reduce pulmonary and systemic resistance, and inhibit platelet aggregation.^{15,24} The cardiac and vascular smooth muscle actions are favorable in the

Fig 3. Mean concentration ($-\log_{10}$ M)-contraction (percentage of 100 mmol/L K^+ -induced contraction) curves for K^+ . Three rings obtained from each patient were allocated to each treatment. One ring was the control (closed circles, $n = 6$) without pretreatment of milrinone. For the other 2 rings, milrinone 7 (open circles, $n = 6$) or 70 (triangles, $n = 6$) $\mu\text{mol/L}$ was added into the organ bath 10 minutes before the start of the K^+ curve. Vertical error bars are 1 SEM of mean values; triple asterisks, $P < .001$, Scheffé test compared with the control at the maximal contraction.

postoperative management of patients who undergo heart surgery, particularly in patients who have ventricular dysfunction and received arterial grafts for coronary artery bypass surgery.

In the present study, the α_1 -adrenoceptor agonist phenylephrine, K^+ , and TXA_2 mimetic U46619, were used to contract the RA. The human RA has been demonstrated to be an active artery that responds to many vasoconstrictors.^{2,3,7,25} Therefore, it was necessary to test the effect of milrinone on the contraction mediated by various vasoconstrictors. In particular, exogenous and endogenous sympathomimetic amines have been demonstrated to be spasmogens for arteries²⁶ and α_1 -adrenoceptors have been demonstrated to be predominant in the human RA.²⁵ In addition, during cardiopulmonary bypass TXA_2 has been shown to have increased plasma concentrations.²⁷ For these reasons, phenylephrine, an α_1 -adrenoceptor agonist, and U46619, a TXA_2 mimetic, were used to contract the RA. The contraction mediated by the depolarizing agent K^+ was also studied since this is the primary mechanism for vasoconstriction.

This study shows that milrinone is a potent vasodilator of the RA. It almost fully relaxed the contraction

Table I. Inhibition of milrinone on the contraction (mean $\pm$ SE) induced by various vasoconstrictors in the human radial artery

	Maximal contraction (g)	Contraction to K^+ (100 mmol/L) (g)	%	P Value	EC_{50} ($-\log_{10} M$)	P Value
K^+						
Control	12.6 $\pm$ 1.4	9.2 $\pm$ 1.0	138.6 $\pm$ 5.8	.0004	21.5 $\pm$ 2.6	.018
Milrinone (7 μ mol/L)	9.2 $\pm$ 0.7	7.8 $\pm$ 0.4	117.3 $\pm$ 4.0		35.0 $\pm$ 7.2	
Milrinone (70 μ m)	6.3 $\pm$ 1.3	8.6 $\pm$ 0.9	73.0 $\pm$ 13.9		47.6 $\pm$ 5.7*	
Phenylephrine						
Control	4.5 $\pm$ 0.8	6.7 $\pm$ 1.2	70.0 $\pm$ 7.9	.004	-5.86 $\pm$ 0.17	.03
Milrinone (7 μ mol/L)	3.9 $\pm$ 0.5	6.8 $\pm$ 1.4	63.4 $\pm$ 9.2		-5.50 $\pm$ 0.13	
Milrinone (70 μ m)	0.9 $\pm$ 0.3	5.7 $\pm$ 1.3	23.5 $\pm$ 9.3*		-5.28 $\pm$ 0.08†	
U46619						
Control	12.4 $\pm$ 2.4	9.1 $\pm$ 1.5	143.6 $\pm$ 20.6	.9	-7.93 $\pm$ 0.15	.47
Milrinone (7 μ mol/L)	11.6 $\pm$ 2.6	8.2 $\pm$ 1.7	148.1 $\pm$ 13.5		-7.27 $\pm$ 0.62	
Milrinone (70 μ m)	10.2 $\pm$ 2.0	8.9 $\pm$ 1.6	142.1 $\pm$ 45.2		-7.67 $\pm$ 0.09	

%, Percentage of the maximum contraction (g) divided by the contraction induced by 100 mmol/L K^+ ; EC_{50} , the drug concentration causing 50% of the maximal effect, derived from a logistic curve fitting program (see "Methods"); EC_{50} for K^+ is in millimoles per liter.

P values are ANOVA among the 3 groups.

* $P < .05$, Scheffé test as the post hoc test, compared with the control.

† $P < .01$, Scheffé test as the post hoc test, compared with the control.

induced by all of the three vasoconstrictors at a concentration of $-4.5 \log_{10} M$ (Fig 1). The EC_{50} s for phenylephrine-, K^+ -, and U46619-induced contraction are between -6.68 and $-5.21 \log_{10} M$ (0.2 and 6.2 μ mol/L) (see "Results"). The therapeutic plasma concentration for milrinone was measured by Likoff and associates²⁷ at 1479 ± 849 ng/mL after intravenous bolus infusion of 50 μ g/kg, and this concentration translates to about 7 μ mol/L. In our experiments, this concentration relaxed nearly 100% of phenylephrine-, 75% of K^+ -, and 60% of U46619-precontracted RAs. Further, in the present study, we also studied the effect of milrinone at the 10-fold higher concentration (70 μ mol/L), and the results showed that this concentration of milrinone further relaxed the contraction mediated by all 3 vasoconstrictors. Taken together, the therapeutic plasma concentration and the experimental results from the present study show that milrinone is a clinically potent vasodilator for the RA. Even in U46619-contracted RA, in which milrinone was least potent, as demonstrated by a higher EC_{50} (5.21 $\log_{10} M$ [6.2 μ mol/L]) compared with the other vasoconstrictors, this EC_{50} value is still within the therapeutic plasma concentration as described above.

On the other hand, pretreatment of milrinone may have a selectivity on inhibition of various vasoconstrictor-induced contractions if used before vasoconstrictor. In phenylephrine- and K^+ -mediated contractions, pretreatment with milrinone significantly reduced the maximal contraction, and the EC_{50} was significantly higher with milrinone treatment in contractions medi-

ated by both vasoconstrictors. In contrast, in U46619-induced contraction, although at lower concentrations milrinone significantly reduced the contractions (Fig 4), the maximal contractions were not significantly altered by the pretreatment of milrinone.

We have previously reported the vasorelaxant effect of milrinone in the human ITA.¹¹ Milrinone has a similar effect in the RA in phenylephrine- and U46619-mediated contraction. However, the inhibitory effect of milrinone in the K^+ -mediated contraction is more significant in the RA. As demonstrated in the present report, milrinone significantly depressed maximal contraction induced by K^+ at both concentrations (7 and 70 μ mol/L). This difference may suggest that milrinone may have even better vasorelaxant effect in the RA than the ITA; therefore, use of milrinone may have an especially desirable benefit in patients with an RA graft.

In previous studies, we have found that some vasodilators, such as nitroglycerin, are markedly able to reverse the existing vascular contraction but are less effective if applied before the contraction.^{11,18} As described by Maurice and colleagues,²⁸ there may be critical differences in the state of the vascular smooth muscle before and after induction of contraction that affect the responses to vasodilator substances. Increases in intracellular Ca^{2+} concentration and the phosphorylation of myosin light chain are important in the contraction of vascular smooth muscle²⁹; therefore, compounds that block these processes will inhibit contraction. However, relaxation of smooth muscle that involves reversal of a latch state is less dependent on

Fig 4. Mean concentration ($-\log_{10}$ M)-contraction (percentage of 100 mmol/L K^+ -induced contraction) curves for U46619. Three rings obtained from each patient were allocated to each treatment. One ring was the control (closed circles) without pretreatment of milrinone. For the other 2 rings, milrinone 7 (open circles) or 70 (triangles) μ mol/L was added into the organ bath 10 minutes before the start of the U46619 curve. Symbols represent data averaged from 6 rings (from 6 patients). Vertical error bars are 1 SEM of mean values.

the inhibition of Ca^{2+} mobilization or on dephosphorylation of myosin.³⁰ In the present study, we have demonstrated that the effect of milrinone also depends on the state of the contraction in the human RA. In the present study, this is more obvious in the contraction mediated by U46619 and K^+ . In the RA precontracted with either U46619 or K^+ , $-4.5 \log_{10}$ M (30 μ mol/L) milrinone relaxed the vessels to more than 60% (Fig 1). In contrast, even a higher concentration ($-4.15 \log_{10}$ M, 70 μ mol/L), milrinone only inhibited the contraction of the arteries to 54% (Fig 3) of the K^+ -induced contraction and had no effect on the maximal contraction induced by U46619. These data further demonstrate that the differences between relaxant effect and inhibition of contraction demonstrated in the present study are constrictor-dependent.

In conclusion, the results of our study suggest that milrinone is a potent vasodilator for the human RA. It may have selectivity with a greater effect to α -adrenoceptor- and depolarizing agent K^+ -mediated contraction than the contraction mediated by TXA_2 , and the inhibitory effect in depolarizing agent-mediated contraction may be superior in the RA to that in the ITA. Because it also has a positive inotropic effect, this vasodilator may have par-

ticular indications to be used in patients receiving RA grafts during coronary bypass operations.

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REFERENCES

1. He G-W, Yang C-Q. Comparison among arterial grafts and coronary artery. An attempt at functional classification. *J Thorac Cardiovasc Surg* 1995;109:707-15.
2. He G-W, Yang C-Q. Radial artery has higher receptor-selective contractility but similar endothelium function compared to mammary artery. *Ann Thorac Surg* 1997;63:1346-52.
3. Chardigny C, Jebara VA, Acar C, et al. Vasoreactivity of the radial artery. Comparison with the internal mammary artery and gastroepiploic arteries with implications for coronary artery surgery. *Circulation* 1993;88(part II):115-27.
4. He G-W. Arterial grafts for coronary artery bypass grafting: biological characteristics, functional classification, and clinical choice. *Ann Thorac Surg* 1999;67:277-84.
5. Acar C, Jebara VA, Portoghese M, et al. Revival of the radial artery for coronary bypass grafting. *Ann Thorac Surg* 1992;54:652-60.
6. Carpentier A. Discussion of Geha AS, Krone RJ, McCormick JR, Baue AE. Selection of coronary bypass: anatomic, physiological, and angiographic considerations of vein and mammary artery grafts. *J Thorac Cardiovasc Surg* 1975;70:414-31.
7. He G-W, Yang C-Q. Use of verapamil and nitroglycerin solution for preparation of radial artery for coronary bypass grafting. *Ann Thorac Surg* 1996;61:610-4.
8. He G-W. Verapamil plus nitroglycerin solution maximally preserves endothelial function of the radial artery: comparison with papaverine solution. *J Thorac Cardiovasc Surg* 1998;115:1321-7.
9. Alousi A, Canter J, Montenegro M, Fort D, Ferrari R. Cardiotonic activity of milrinone, a new potent cardiac bipyridine, on normal and failing heart of experimental animals. *J Cardiovasc Pharmacol* 1983;5:791-803.
10. Silver PJ, Lepore RE, O'Connor B, Lemp BM, Hamel LT, Bentley RG, Harris AL. Inhibition of the low Km cyclic AMP phosphodiesterase and activation of the cyclic AMP system in vascular smooth muscle by milrinone. *J Pharmacol Exp Ther* 1988;247:34-42.
11. He G-W, Yang C-Q. Inhibition of vasoconstriction by phosphodiesterase III inhibitor milrinone in human conduit arteries used as coronary bypass grafts. *J Cardiovasc Pharmacol* 1996;28:208-14.
12. He G-W, Yang C-Q, Gately H, et al. Potential greater than additive vasorelaxant actions of milrinone and nitroglycerin on human conduit arteries. *Br J Clin Pharmacol* 1996;41:101-7.
13. He G-W. Effect of milrinone on coronary artery bypass grafts. *J Thorac Cardiovasc Surg* 1997;114:302-4.
14. Liu JJ, Doolan LA, Xie B, Chen JR, Buxton BF. Direct vasodilator effect of milrinone, an inotropic drug, on arterial coronary bypass grafts. *J Thorac Cardiovasc Surg* 1997;113:108-13.
15. Dundore RL, Pagani ED, Bode DC, et al. Species-dependent pharmacodynamic effects of the selective low Km cyclic AMP phosphodiesterase III inhibitors WIN 58993 and WIN 62005. *J Cardiovasc Pharmacol* 1995;25:14-21.

16. Monrad ES, Baim DS, Smith HS, Lanoue A, Braunwald E, Grossman W. Effects of milrinone on coronary hemodynamics and myocardial energetics in patients with congestive heart failure. *Circulation* 1985;71:972-9.
17. Lindgren S, Anderson K-E, Belfrage P, Degerman E, Manganiello VC. Relaxant effects of the selective phosphodiesterase inhibitors milrinone and OPC 3911 on isolated human mesenteric vessels. *Pharmacol Toxicol* 1989;64:440-5.
18. He G-W, Buxton B, Rosenfeldt F, Angus JA. Reactivity of human isolated internal mammary artery to constrictor and dilator agents. Implications for treatment of internal mammary artery spasm. *Circulation*. 1989;80(Suppl):I-141-50.
19. He G-W, Buxton B, Rosenfeldt F, Wilson AC, Angus JA. Weak β -adrenoceptor-mediated relaxation in the human internal mammary artery. *J Thorac Cardiovasc Surg* 1989;97:259-66.
20. He G-W. Endothelial function and interaction between the endothelium and smooth muscle in arterial grafts. In: He G-W, editor. *Arterial grafts for coronary artery bypass surgery: a textbook for cardiovascular clinicians and researchers*. Singapore: Springer-Verlag; 1999.
21. Pagani ED, Buchholz RA, Silver PJ. Cardiovascular cyclic nucleotide phosphodiesterases and their role in regulating cardiovascular function. In: Hasenfuss G, Holubarsch C, Just H, Alpert NR, editors. *Cellular and molecular alterations in the failing heart*. Darnstadt: Steinkopff Verlag; 1992. p. 73-86.
22. Beavo JA, Reifsnyder DH. Primary sequences of cyclic nucleotide phosphodiesterases isozymes and the design of selective inhibitors. *Trends Pharmacol Sci* 1990;11:150-5.
23. Weishaar RE, Kobylarz-Singer DC, Steffen RP, Kaplan HR. Subclasses of cyclic AMP-specific phosphodiesterase in left ventricular muscle and their involvement in regulating myocardial contractility. *Circ Res* 1987;61:539-47.
24. He G-W, Yang C-Q. Characteristics of adrenoceptors in the human radial artery. Clinical implications. *J Thorac Cardiovasc Surg* 1998;115:1136-41.
25. Heusch G. α -adrenergic mechanisms in myocardial ischemia. *Circulation* 1990;81:1-13.
26. Davies GC, Sobel M, Salzman EW. Elevated plasma fibrinopeptide a and thromboxane B2 levels during cardiopulmonary bypass. *Circulation* 1980;61:803-13.
27. Likoff MJ, Weber KT, Andrews V, Janicki JS, Wilson H, Rocci ML. Milrinone in the treatment of chronic cardiac failure: a controlled trial. *Am Heart J* 1985;110:1035-42.
28. Maurice DH, Crankshaw D, Haslam RJ. Synergistic actions of nitrovasodilators and isoprenaline on rat aortic smooth muscle. *Eur J Pharmacol* 1991;192:235-42.
29. Kamm KE, Stull JT. The function of myosin and myosin light chain kinase phosphorylation in smooth muscle. *Ann Rev Pharmacol Toxicol* 1985;25:593.
30. Dillon PF, Aksoy MO, Driska SP, Murphy RA. Myosin phosphorylation and the cross-bridge cycle in arterial smooth muscle. *Science* 1981;211:495.