Potent Vasodilatory Effect of Fasudil on Radial Artery Graft in Coronary Artery Bypass Operations

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Background. The radial artery (RA) is a useful conduit for coronary artery bypass grafting (CABG) but is susceptible to vasospasm during harvesting. We evaluated the usefulness of fasudil, a Rho kinase inhibitor, in dilating the RA graft and increasing graft free flow (GFF) compared with the conventional graft-dilating agents papaverine and verapamil-nitroglycerin (VG).

Methods. Between June 2012 and January 2013, 45 patients with ischemic heart disease who underwent isolated CABG using the RA were enrolled and randomly assigned to fasudil (n = 15), papaverine (n = 15), or VG (n = 15). Fasudil (2.67 mmol/L), papaverine (1.0 mmol/L) mixed with heparinized blood, or VG (30 μmol/L each of verapamil and nitroglycerin) was injected intraluminally into the RA graft after harvesting. Main outcome measures were RA GFF, hemodynamic changes, and histopathologic examination of the RA.

Results. In the fasudil group, GFF increased significantly ($p < 0.001$) from 36.8 ± 20.4 at baseline to 148.0 ± 88.3 mL/min after injection. GFF increased significantly ($p < 0.001$) from 36.0 ± 19.0 to 72.3 ± 36.7 mL/min in the papaverine group and increased significantly ($p < 0.001$) from 39.5 ± 23.3 to 64.3 ± 29.9 mL/min in the VG group. The GFF was significantly higher ($p = 0.001$) in fasudil-treated RA than in papaverine- or VG-treated RA. Histopathologically, RA graft diameter was markedly increased after fasudil injection, and the structure of the multiple elastic lamellae was intact. Blood pressure did not change significantly after drug injection in all groups.

Conclusions. Fasudil exhibited a very potent vasodilatory effect on the RA compared with conventional papaverine or VG, resulting in increased GFF. This agent is useful for dilating RA grafts in CABG.

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The potential of the radial artery (RA) as an arterial conduit in coronary artery bypass grafting (CABG) was first reported in 1973 [1, 2]. However, the use of the RA in CABG was soon abandoned because of vasospasm leading to early occlusion. Later, when long-term potency of some RA grafts began to be reported, this graft once again attracted attention and has increasingly been used in CABG. The RA graft is an attractive option because it can be harvested easily without complications, and endoscopic harvesting is also possible. Apart from easy handling, the RA also has other advantages such as being an arterial graft and providing an appropriate length for grafting. However, the RA is still not as widely used as the internal thoracic artery. The primary reasons are the high susceptibility of RA grafts to vasospasm during graft harvesting, which is evident even macroscopically, and the lack of evidence for long-term outcome.

Various vasodilators [3, 4] and harvesting techniques [5] have been used to prevent or resolve vasospasm of the internal thoracic artery graft, and application of these methods to RA graft harvesting has contributed to improved RA graft flow and patency. In this study, we investigated the effectiveness of a Rho kinase inhibitor, fasudil, which is a vasodilator with a new mechanism of action. Because of its potent vasodilating action, fasudil has been used clinically in the field of neurosurgery to prevent cerebral vasospasm, a serious complication secondary to intracranial hemorrhage [6]. Through attenuating coronary spasm, the potential of fasudil in the treatment of heart disease and arteriosclerosis is also anticipated [7]. Considering the clinical safety and the potent vasodilating action of this drug, we examined the usefulness of fasudil as a vasodilating agent for RA grafts as an alternative to conventionally used graft-dilating agents such as papaverine and verapamil-nitroglycerin (VG) solution.

Patients and Methods

Patients

Forty-five consecutive patients who underwent elective CABG using the RA conduit between June 2012 and January 2013 in our department were enrolled in this study. Patients who had a hemodialysis shunt in the forearm were excluded. The patients were randomly assigned, according to the agent used to dilate the RA

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graft, to the fasudil group (n = 15), the VG group (n = 15), and the papaverine group (n = 15) by means of a computerized randomization table. The trial was approved by the institutional ethics committee (No. 7513). Informed consent was obtained from each patient.

Protocol

With the patient under general anesthesia, the RA was isolated together with the accompanying vein by the semiskeletonizing technique using an electric scalpel at settings of blend 2 and 20 W. After administering heparin (150 U/kg), the graft was transected distally.

In each group, baseline graft free flow (GFF) of the RA was measured for 60 seconds. After 10 minutes, a graft-dilating agent was injected intraluminally into the RA graft. In the fasudil group, 2 mL of fasudil solution (Asahi Kasei Corp, Tokyo, Japan) diluted to 0.9 mg/mL (2.67 mmol/L) was injected. This concentration was determined according to basic research that we performed previously [8]. In the papaverine group, 2 mL of papaverine (0.4 mg/mL or 1.0 mmol/L) mixed with heparinized blood was injected. The concentrations of papaverine used varied widely from 30 μmol/L to 2.6 mmol/L. In the present study, we used the middle concentration of 1.0 mmol/L, which is also used in internal thoracic artery grafts [9, 10–14]. In the VG group, 2 mL of VG solution was injected. The VG solution was composed of 5 mg of verapamil hydrochloride, 2.5 mg of nitroglycerin, 500 units of heparin, and 0.2 mL of 8.4% $NaHCO_3$ in 300 mL of Ringer's solution. This solution gives a concentration of 30 μmol/L each of verapamil and nitroglycerin in an isotonic solution at pH 7.4. This concentration was determined based on a previous study using VG solution to prepare RAs for CABG [15]. Ten minutes after injection of the vasodilator agent, GFF of the RA graft was again measured for 60 seconds.

Thereafter, off-pump CABG was performed in all patients. The total numbers of anastomoses per patient ranged from 2 to 6 (mean, 3.4 ± 1.1). All patients had anastomosis of the left anterior descending coronary artery to the internal thoracic artery. In addition, they had 1 to 2 anastomoses of the RA (mean, 1.1 ± 0.3), and the target vessels were the first diagonal/obtuse marginal branch or right coronary artery.

Outcome Measures and Measurement Methods

GFF of the RA was measured by collecting free-flowing blood from the transected RA into a special tube and is expressed as milliliters per minute. During GFF measurement, mean arterial pressure was measured from the femoral artery and recorded.

Histopathologic Examination

Surplus RA tissue from 1 patient was examined histopathologically. Ring specimens of the RA graft stump were collected before and after fasudil injection to examine the vasodilating effect. Hematoxylin and eosin– and elastica van Gieson–stained sections were evaluated qualitatively for changes in the media and elastic fiber, as well as for the change in diameter.

Statistical Analysis

All statistical analyses were performed using SAS, version 9.1.3 (SAS Institute, Cary, NC). Continuous variables are expressed as mean ± standard deviation (except in Fig 1, in which data are expressed as mean ± standard error). The baseline characteristics and hospital outcomes for the 3 groups were compared using Fisher's exact test for categorical data or analysis of variance (ANOVA) for continuous data. The fasudil group, papaverine group, and VG group were compared with respect to pretreatment and posttreatment blood pressure and GFF of the RA graft using ANOVA. Statistical significance was defined as a p value less than 0.05.

Results

Demographic and Hemodynamic Data

The fasudil group (n = 15) comprised 12 men and 3 women aged 67.3 ± 9.7 years, whereas the papaverine group (n = 15) comprised 11 men and 4 women aged 66.2 ± 11.5 years, and the VG group (n = 15) comprised 13 men and 2 women aged 69.1 ± 10.1 years, with no significant differences among the 3 groups (Table 1). Other demographic data and risk factors of the 3 groups also did not differ significantly (Table 1).

There were no significant changes in mean arterial pressure among the 3 groups either before or after graft treatment (Table 2). No patient had perioperative

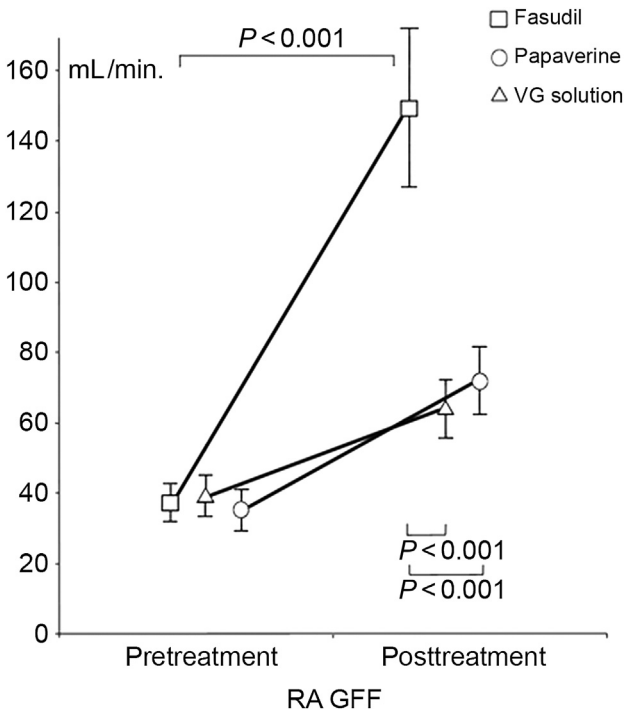

Fig 1. Change in graft free flow (GFF) (milliliters per minute) of radial artery (RA) graft before and after treatment with fasudil, papaverine, or verapamil-nitroglycerin (VG) solution. Data are expressed as mean (point) ± standard error (bar).

Table 1. Preoperative Patient Characteristics and Risk Factors

Variable	Fasudil (n = 15)	Papaverine (n = 15)	VG Solution (n = 15)	ANOVA
Age (y, mean ± SD)	67.3 ± 9.7	66.2 ± 11.5	69.1 ± 10.1	NS
Male sex, number (%)	12 (80)	11 (73)	12 (80)	NS
Diabetes mellitus, number (%)	5 (33)	6 (40)	6 (40)	NS
Hypertension, number (%)	5 (33)	6 (40)	5 (33)	NS
Hypercholesterolemia, number (%)	8 (53)	10 (67)	9 (60)	NS
Smoking, number (%)	3 (20)	3 (20)	4 (27)	NS
LVEF <35%, number (%)	6 (40)	5 (33)	6 (40)	NS
Preoperative renal failure, number	0	0	0	NS
Prior coronary surgery, number	0	0	0	NS
Left main coronary artery disease, number (%)	4 (27)	5 (33)	4 (27)	NS

ANOVA = analysis of variance; LVEF = left ventricular ejection fraction, NS = not significant; VG solution = verapamil-nitroglycerin.

myocardial infarction. There were no significant differences in the use of inotropic agents and postoperative drainage among the 3 groups. No serious complications such as pleural effusion were observed, and all patients were discharged after the postoperative observation period.

Effects of Fasudil, Papaverine, and VG

The GFF of the RA graft treated with fasudil increased significantly ($p = 0.001$) and markedly from 36.8 ± 24.0 mL/min at baseline to 148.0 ± 88.3 mL/min at 10 minutes after treatment (Fig 1). The GFF of the RA graft treated with papaverine increased significantly ($p < 0.001$) from 36.0 ± 19.0 mL/min at baseline to 72.3 ± 36.7 mL/min 10 minutes after treatment. The GFF of the RA graft treated with VG also increased significantly ($p < 0.001$) from 39.5 ± 23.3 mL/min to 64.3 ± 29.9 mL/min. Comparing fasudil-, papaverine- and VG-treated RA grafts, the posttreatment GFF was significantly higher in the fasudil group than in the other 2 groups (both, $p < 0.001$).

Graft angiography using 3-dimensional computed tomography was performed in all patients after operation. All the RA grafts in the 3 groups were patent.

Histopathologic Findings

The histopathologic findings of ring specimens collected from the RA stump from 1 patient before and after fasudil injection are shown in Fig 2. The internal diameter was increased after fasudil injection. Elastica van Gieson staining showed that the elastic lamella remained intact, and the smooth muscle–rich media became thinner after fasudil injection, suggesting relaxation.

Comment

To the best of our knowledge, this is the first study that demonstrates that the Rho kinase inhibitor fasudil is effective in preventing RA spasm, consequently increasing RA GFF. In the present study, fasudil treatment increased RA GFF strikingly by more than 400%. These results indicate a very potent vasodilatory effect of fasudil for the RA graft. Moreover, intraluminal administration of fasudil did not affect hemodynamic measurements or cause adverse effects, which is consistent with a previous study in patients with cerebral vasospasm after subarachnoid hemorrhage who received fasudil treatment [6]. In the present study, the RA conduits remained dilated during CABG after short-term fasudil treatment. None of the 15 patients who underwent grafting of fasudil-treated RAs exhibited myocardial ischemia.

The RA has been positioned as the third arterial graft of choice, after the internal thoracic artery and the gastroepiploic artery. However, the RA is also known to be very prone to spasm during the perioperative period, especially during the surgical procedure. This leads to a high rate of early occlusion. The evidence is provided by a report indicating that patency is maintained by administering a calcium antagonist during and after the operation [16].

The arteries in humans can be classified into 3 types according to their structure: type 1 (somatic), type 2 (splanchnic), and type 3 (limb). RA belongs to type 3 and has been reported to be more prone to spasm than the somatic-type arteries such as the internal thoracic artery [17, 18]. One reason is that the RA possesses a smooth muscle–rich medium. Adequate prevention of perioperative spasm will improve patency and prevent

Table 2. Comparison of Mean Blood Pressure (Mean ± SD) Before and After Treatment of Radial Artery Graft With Fasudil, Papaverine, or VG Solution

Time of Measurement	Fasudil (n = 15)	Papaverine (n = 15)	VG solution (n = 15)	*p* Value ANOVA
Blood pressure (mm Hg) (mean ± SD)				
Pretreatment	65.1 ± 9.9	65.0 ± 10.7	66.0 ± 8.8	0.492
Posttreatment	64.4 ± 9.3	68.1 ± 12.6	65.5 ± 9.9	

ANOVA = analysis of variance; VG solution = verapamil-nitroglycerin.

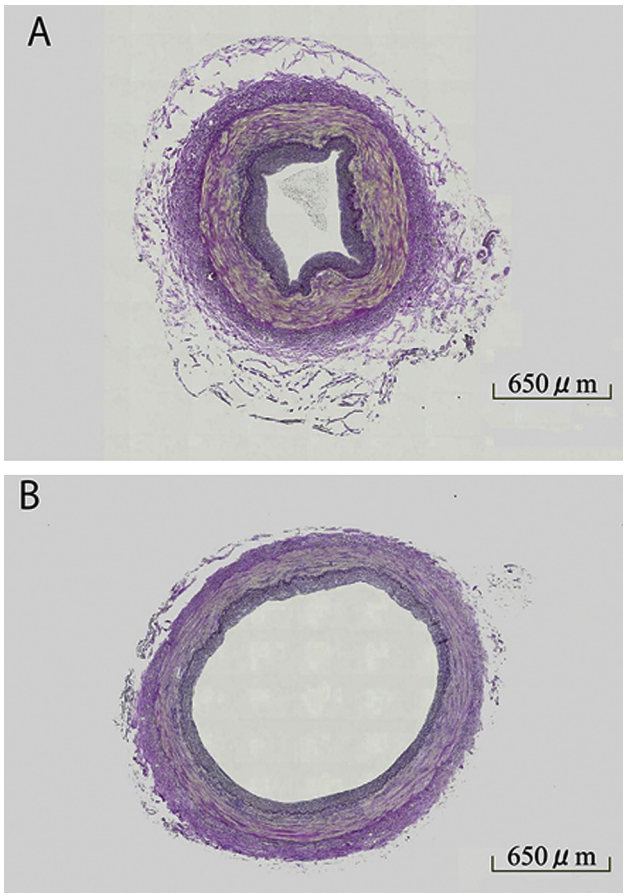

Fig 2. Histopathologic findings of radial artery (RA) specimen (A) before fasudil injection and (B) after fasudil injection (elastica van Gieson staining). The diameter of the radial artery increased markedly after fasudil infection.

perioperative hemodynamic deterioration, consequently improving long-term outcome. Therefore, appropriate intraoperative treatment is very important. Surgeons have attempted various methods to prevent spasm of the RA graft. One method is to modify the technique of harvesting the graft, such as by skeletonization using an ultrasonic scalpel. Another is the use of vasodilators. Many studies on smooth muscle relaxation with various drugs have been conducted using in vivo RA segments. These vasodilators can be classified as described in the following sections.

Nitrates and Nitrate Derivatives

This class of agents includes glycerin trinitrate, isosorbide dinitrate, sodium nitroprusside, and nicorandil. All have been shown to possess vasodilatory effects and to increase GFF, including that of RA grafts [19]. The increase is on the magnitude of 24 to 32 mL/min, and increases of more than 100% have not been reported. The vasodilatory effect of nitrates on RA segments has been reported by Chanda and coworkers [16] and He and associates [20].

Calcium Channel Blockers

This class of drugs is the most frequently used because these vasodilators act by selectively blocking L-type voltage-operated calcium channels on smooth muscle cell membranes, thereby inhibiting calcium influx and attenuating the contractile response [21]. The usefulness of verapamil has also been proved experimentally, but many studies combined it with nitrate. A cocktail of verapamil and nitroglycerin (VG solution) has been extensively studied. He and Yang [15] and Dogan and coworkers [22] reported good vasodilatory effects for the RA. Yoshizaki and associates [23] also reported VG solution to be a superior vasodilator based on postoperative imaging studies. The present study showed that intraluminal injection of VG solution into the RA graft significantly increased GFF, but the magnitude of increase was only moderate. A reason for this finding is the difference in treatment method used. He [24] immersed the RA grafts in the VG solution for 30 minutes as soon as they were dissected, whereas we injected VG solution intraluminally and waited for only 10 minutes. Our method probably did not allow maximal action of VG solution on the RA graft.

Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors have been used in recent years. Na and coworkers [25] observed an increase in GFF both in the RA and the internal thoracic artery, with an increase from 91 to 110 mL/min in the RA. The antispasmodic effect was also observed in segment specimens [26, 27], but superiority to the VG solution has not been reported. Papaverine is one of the most commonly used vasodilators for arterial grafts. It is a benzylisoquinoline alkaloid with nonselective smooth muscle relaxant properties [28]. Although papaverine is a low-cost drug exhibiting vasodilating effects for the internal thoracic artery, evaluation of its effect has been variable [29]. In addition, being an acidic solution, there is a risk of endothelial damage [30].

Although the drugs described have been shown to be effective to a certain extent, none of the reports indicated an increase in GFF by more than 100%. The VG solution is the most commonly used vasodilator [24], but the development of more effective and safe vasodilators for RA grafts has been awaited.

Rho kinase is an intracellular serine/threonine kinase identified in the mid-1990s as the target protein for the low-molecular-weight guanosine triphosphate (GTP)-binding protein "Rho" [31–33]. Rho kinase is closely related to many physiologic functions such as contraction, cell proliferation, cell migration, and induction of gene expression. Rho kinase is known to regulate vascular smooth muscle contraction and relaxation independent of the intracellular calcium ion concentration. Rho kinase is also implicated in endothelial dysfunction, which includes inhibition of nitric oxide synthase, upregulation of leukocyte adhesion molecule expression, and upregulation of proinflammatory cytokine expression [34]. Therefore fasudil might protect the endothelium from damage,

thereby preventing intimal proliferation, acceleration of atherosclerosis, and thrombosis, which likely improves the long-term patency of grafts. Our previous study [8] suggested that the antispastic effect of fasudil results from blockade of Rho-associated protein kinase because intraluminal fasudil injection into RA abolishes the increase in myosin phosphatase targeting subunit 1 phosphorylation at the Rho-associated protein kinase phosphorylation site Thr^{853} and consequently removes inhibition by myosin light chain phosphatase.

In patients with coronary vasospastic angina, selective injection of the Rho kinase inhibitor fasudil into the coronary artery inhibited acetylcholine-provoked coronary vasospasm, angina-related electrocardiographic changes, and chest pain [35]. Fasudil treatment markedly ameliorated intractable coronary vasospasm after CABG in patients who did not respond to maximum vasodilatory therapy [36]. With the objective of applying the potent vasodilatory effect of the Rho kinase inhibitor to CABG, we performed a study to investigate the in situ vasodilatory effect of fasudil on the human internal thoracic artery and showed a superior vasodilating effect of fasudil compared with papaverine [9]. In the present study, we found that fasudil also has a markedly more potent vasodilating effect on the RA compared with papaverine and VG solution.

The method of administering vasodilatory agents during CABG is an important issue. From the mechanism of action of the drug, 3 methods are plausible: (1) intraluminal injection, (2) topical application on the adventitia or covering with gauze soaked with the drug, and (3) systemic administration. For the RA, the drug and the administration method that provide maximum effectiveness remain unknown, and the exact mechanism is also unclear. In the present study, to exclude the effect of drug infiltration from outside and the effect of systemic administration, we injected a small volume (2 mL) of fasudil intraluminally. Because of the small volume, the drug is unlikely to circulate systemically. Hence, we evaluated only the effect of intraluminal administration. Studies on the effects of topical application and systemic administration are ongoing. Fasudil is a relatively low-cost drug and has a long history of clinical use. The performance of this drug in the neurosurgical field has been documented for more than 10 years [6]. Therefore, fasudil can be used without concern about safety.

CABG using an adequately dilated RA may yield good flow beginning immediately after operation. Because our studies have demonstrated that fasudil is a superior graft vasodilator for both the internal thoracic artery [9] and the RA, this agent may become the standard for arterial graft pretreatment in CABG.

Conclusions

Fasudil has very potent vasodilatory effects on the RA, resulting in significantly increased GFF. The vasodilatory effect is confirmed by histopathologic findings. Fasudil is a very effective drug for the pretreatment of the RA graft in CABG.

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