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Fasudil Is an Effective Graft Vasodilator for Gastroepiploic Artery in Coronary Artery Bypass Grafting

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Objective: The gastroepiploic artery (GEA) has been used as an alternative arterial in situ graft for coronary artery bypass grafting (CABG). However, because of the large individual differences and the spastic nature of the GEA, caution has to be exercised during harvesting. We evaluated the usefulness of fasudil, a Rho kinase inhibitor, as a vasodilator for right GEA (RGEA) graft after harvesting, compared with the conventional agents papaverine and verapamil-nitroglycerin.

Methods: Between June 2009 and January 2013, 30 patients with ischemic heart disease who underwent isolated CABG using RGEA graft were randomly assigned to fasudil (n = 10), papaverine (n = 10), or verapamil-nitroglycerin (n = 10) group. Fasudil (2.67 mmol/L), papaverine (1.0 mmol/L) mixed with heparinized blood, or verapamil-nitroglycerin (30 μmol/L each) was injected intraluminally into the RGEA graft after harvesting. Right GEA graft free flow (GFF), hemodynamic changes, and histopathology of RGEA were evaluated.

Results: Intraluminal injection of fasudil increased GFF significantly ($P < 0.001$) and markedly from 41.5 ± 31.5 mL/min at baseline to 149.3 ± 46.7 mL/min after injection. Papaverine increased GFF ($P < 0.001$) from 40.0 ± 35.8 to 64.9 ± 33.7 mL/min, and verapamil-nitroglycerin also increased GFF ($P < 0.001$) from 38.8 ± 32.1 to 79.0 ± 35.2 mL/min. The GFF was significantly higher ($P = 0.001$) in the fasudil group than in the other two groups. Histopathologically, fasudil treatment markedly increased the diameter of RGEA graft, while maintaining integrity of the multiple elastic lamellae. Blood pressure did not change significantly after drug injection in all groups.

Conclusions: Fasudil is more potent than papaverine or verapamil-nitroglycerin in increasing GFF of RGEA graft for CABG.

Key Words: Gastroepiploic artery graft, Fasudil, Coronary artery bypass grafting, Vasodilator.

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The gastroepiploic artery (GEA) has been used as an alternative arterial in situ graft for coronary artery bypass grafting (CABG). Since Suma et al[1] first reported the successful use of GEA graft in CABG, subsequent reports have also demonstrated good midterm and long-term outcome of GEA grafts. However, an issue of using the GEA graft is that it is prone to vasospasm after harvesting.[2,3] Graft spasm not only results in insufficient blood flow through the graft but also deteriorates the perioperative hemodynamics and may even lower the midterm and long-term patency rates.[3]

Vasodilating agents[4,5] and innovated harvesting techniques[6,7] have been used to prevent or resolve spasm of arterial graft during surgery to ensure sufficient blood flow. However, there are few reports on the use of conventional vasodilators such as papaverine, nitroglycerin, and verapamil (a calcium antagonist) in GEA grafts. Moreover, the effectiveness of these agents has not been established.

Fasudil is a Rho kinase inhibitor and a vasodilator with a new mechanism of action. Because of its potent vasodilating action, fasudil has been used clinically in neurosurgery to prevent cerebral vasospasm secondary to intracranial hemorrhage without serious adverse events.[8] The potential of fasudil in the treatment of heart disease and arteriosclerosis by attenuating coronary spasm has also been anticipated.[9] Considering the proven clinical safety and the potent in vivo vasodilating action of this drug, we examined the usefulness of fasudil as a vasodilating agent for GEA graft compared with conventionally used graft dilating agents such as papaverine and verapamil-nitroglycerin (VG) solution.

PATIENTS AND METHODS

Patients

Thirty consecutive patients who underwent elective CABG using the right GEA (RGEA) conduit in our department between June 2009 and January 2013 were enrolled in this study. Patients who had received previous abdominal surgery were excluded. The patients were assigned randomly according to a computerized randomization table to three groups according to the agent used to dilate the RGEA graft: fasudil group, papaverine group, and VG group. Informed consent was obtained from each patient.

Protocol

After a midline sternotomy, the internal thoracic artery was harvested. Then, the sternotomy was extended inferiorly for a further 5 cm. After opening the peritoneum, the RGEA was detached as a pedicle using a harmonic scalpel (Ethicon Inc, Somerville, NJ USA) according to the method reported previously.[6] Then skeletonization was conducted also using the

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TABLE 1. Comparison of Preoperative Patient Characteristics and Risk Factors in the Three Groups in Which Right Gastroepiploic Graft Was Treated With Fasudil, Papaverine, or VG

	Fasudil (n = 10)	Papaverine (n = 10)	VG Solution (n = 10)	*P* Value ANOVA
Age, mean ± SD, y	68.5 ± 7.2	67.8 ± 7.0	68.7 ± 5.2	NS
Male/female, n	8/2	9/1	8/2	NS
Diabetes mellitus, n (%)	4	4	3	NS
Hypertension, n (%)	3	4	4	NS
Hypercholesterolemia, n (%)	5	6	6	NS
Smoking, n (%)	2	3	2	NS
LVEF < 35%, n (%)	4	5	4	NS
Preoperative renal failure, n	0	0	0	NS
Previous coronary surgery, n	0	0	0	NS
Left main disease, n (%)	3	3	4	NS

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

harmonic scalpel. The GEA was harvested from the pylorus ring (proximal) until the superior part of the greater curvature of stomach (distal). After administering heparin (150 U/kg), graft free flow (GFF) was measured as described later.

In each group, baseline GFF of the RGEA graft was measured for 60 seconds immediately after harvesting. After 10 minutes, a graft dilating agent was injected intraluminally into the RGEA graft. In the fasudil group, 2 mL of fasudil solution (Asahi Kasei, Tokyo, Japan) diluted to 0.9 mg/mL (2.67 mmol/L) was injected. In the papaverine group, 2 mL of papaverine (0.4 mg/mL or 1.0 mmol/L) mixed with heparinized blood was injected. In the VG group, 2 mL of VG solution was injected. The VG solution consisted of 5 mg of verapamil hydrochloride, 2.5 mg of nitroglycerin, 500 U 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. Ten minutes after injection of the vasodilator, GFF of the RGEA graft was again measured for 60 seconds.

Off-pump CABG was performed in all patients. The total numbers of anastomosis per patient ranged from 2 to 5 (mean, 3.3 ± 0.8). All patients had anastomosis of the internal thoracic artery graft with the left anterior descending coronary artery. In addition, they had one anastomosis of the RGEA graft with the posterior descending branch of the right coronary artery.

Outcome Measure and Measurement Method

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

Histopathological Examination

Surplus RGEA tissue of one patient was examined histopathologically. Ring specimens of the RGEA graft stump were collected before and after fasudil injection. Hematoxylin and eosin– as well as Elastica van Gieson–stained sections were evaluated qualitatively for changes in wall structure and diameter.

Statistical Analysis

All statistical analyses were performed using SAS version 9.1.3 (Cary, NC USA). Continuous variables are expressed as mean ± SD unless stated otherwise. The baseline characteristics and risk factors of the three groups were compared using the Fisher exact test for categorical data or the analysis of variance (ANOVA) test for continuous data. The fasudil, papaverine, and VG groups were compared with respect to pretreatment and posttreatment blood pressure and GFF of the RGEA graft using ANOVA. Statistical significance was defined as a *P* value less than 0.05.

RESULTS

Background Clinic Characteristics and Perioperative Findings

The fasudil group (n = 10) comprised eight men and two women aged 68.5 ± 7.2 years, whereas the papaverine group (n = 10) comprised nine men and one woman aged 67.8 ± 7.0 years, and the VG group (n = 10) comprised eight men and two women aged 68.7 ± 5.2 years, with no significant differences among the three groups (Table 1). Other demographic data and risk factors of the three groups also did not differ significantly (Table 1). T1

There were no significant changes in mean arterial pressure among the three groups, both before and after graft treatment (Table 2). No patient had perioperative myocardial infarction. There were no significant differences in the use of inotropic agents and postoperative drainage among the three groups. No serious complications such as pleural effusion were observed, and all patients were discharged after the postoperative observation period. T2

Effects of Fasudil, Papaverine, and VG on Graft Flow

In the fasudil group, the GFF of the RGEA graft increased significantly ($P = 0.001$) and markedly from 41.5 ± 31.5 mL/min at baseline to 149.3 ± 46.7 mL/min at 10 minutes after treatment (Fig. 1). Treatment with papaverine increased the GFF of the RGEA graft significantly ($P < 0.001$) from 40.0 ± 35.8 to 64.9 ± 33.7 mL/min. Treatment with VG also increased the GFF of the RGEA graft significantly ($P < 0.001$) from 38.8 ± 32.1 to 79.0 ± 35.2 mL/min. The posttreatment GFF was F1

TABLE 2. Comparison of Mean Blood Pressure Before and After Treatment of Right Gastroepiploic Graft With Fasudil, Papaverine or VG Solution

	Fasudil (n = 10)	Papaverine (n = 10)	VG Solution (n = 10)	*P* Value ANOVA
Blood pressure, mean ± SD, mm Hg				
Pretreatment	72.1 ± 12.9	70.5 ± 16.9	70.2 ± 14.4	NS
Posttreatment	64.2 ± 8.0	67.5 ± 15.0	67.9 ± 9.7	

ANOVA, analysis of variance; NS, not significant; VG, verapamil-nitroglycerin.

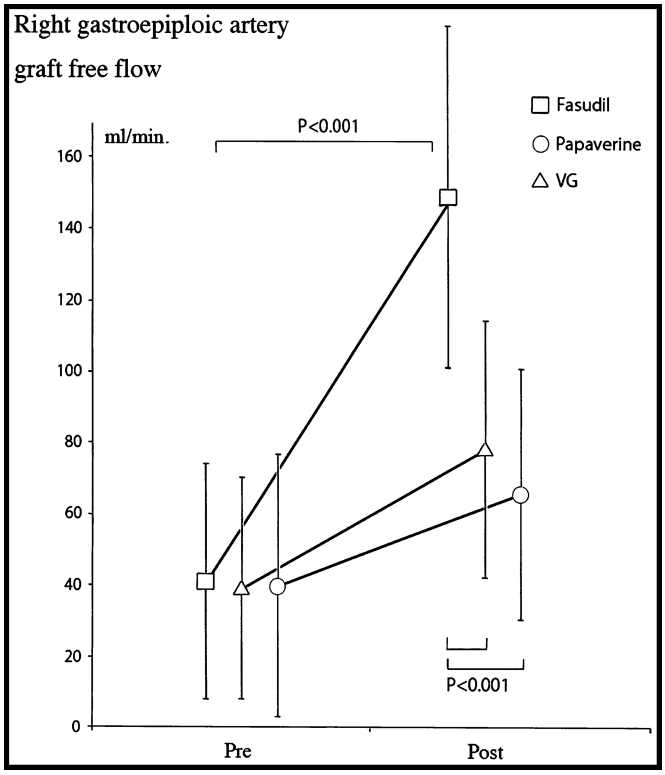

FIGURE 1. Change in graft free flow (mL/min) of right gastroepiploic graft before and after treatment with fasudil, papaverine, or VG solution. Data are expressed as mean (point) ± SE (bar).

significantly higher in fasudil-treated RGEA grafts than in papaverine- ($P < 0.001$) or VG-treated RGEA grafts ($P < 0.001$).

Graft angiography using three-dimensional computed tomography was performed in all patients 1 week after surgery. All the RGEA grafts in the three groups were patent.

Histopathological Findings

Ring specimens collected from the RGEA stump from one patient were examined histopathologically. The internal diameter of RGEA 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 (Fig. 2). F2

COMMENT

To the best of our knowledge, this report demonstrates for the first time that the Rho kinase inhibitor fasudil is highly effective in increasing RGEA GFF in patients undergoing CABG and that papaverine and VG solution, which are vasodilators conventionally used in radial artery grafts, are not as effective. The GFF of RGEA grafts increased by more than 260% after fasudil treatment compared with 60% to 100% after papaverine or VG treatment.

The internal thoracic artery graft remains the first choice for CABG. Bilateral internal thoracic arteries are used, and good long-term outcome has been reported. The GEA, being an in situ artery graft, is an attractive graft for CABG.[1] However, the GEA is characterized histologically by having a tunica media rich in smooth muscle, and spasm of the RGEA during harvesting is a problem. Surgeons have made various efforts to prevent graft spasm. An example is the skeletonization technique using an ultrasonic scalpel.[6] Treatment with drugs to increase graft flow has also been used. However, there are few reports regarding the effect of vasodilators on GEA GFF. The article by Chavanon et al[10] is the only report on the effect of topical application of vasodilators on the free flow of GEA graft. In that article, the authors reported an increase in mean GFF from 37 to 62 mL/min with papaverine and from 25 to 50 mL/min with glyceryl trinitrate. An in vitro study using porcine GEA segments examined the effects of papaverine and calcium antagonist on norepinephrine-induced GEA spasm, but human sample was not used, and flow was not determined in that study.[11]

The radial artery and the GEA are both muscular-type arteries, and both are prone to spasm when used in CABG. Unlike the GEA graft, the radial artery graft has been studied extensively regarding the effect of vasodilators for preventing spasm and increasing GFF. Phospodiesterase III inhibitors including papaverine have been shown to have vasodilatory

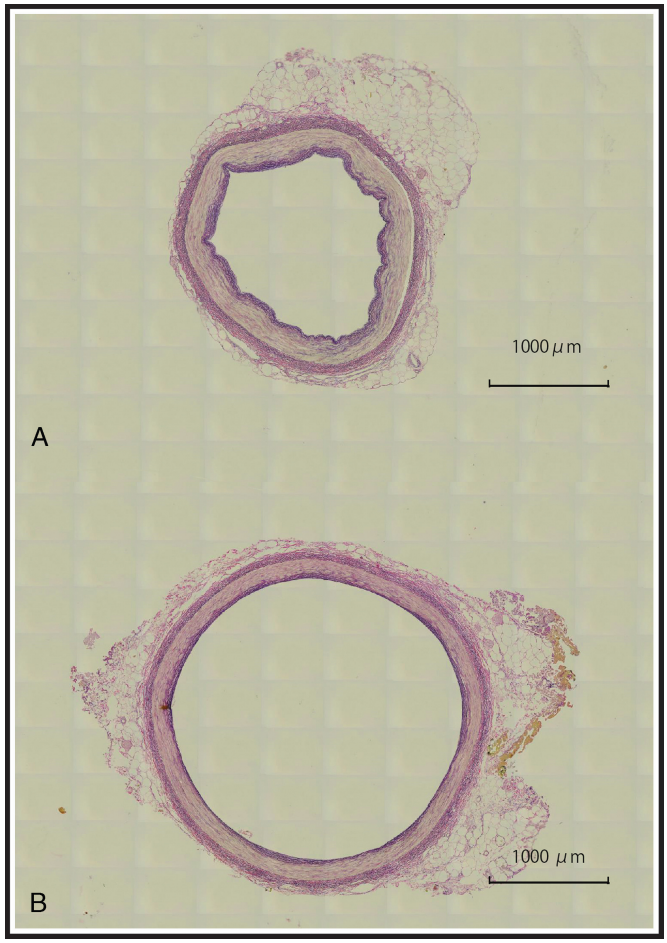

FIGURE 2. Histopathologic findings of right gastroepiploic graft specimen before fasudil injection (A) and after fasudil injection (B). The diameter of the graft increases markedly after fasudil infection. Elastica van Gieson staining.

Fig 2 A/C

effect on radial artery.[12] The nitrate derivatives including glycerin trinitrate, isosorbide dinitrate, sodium nitroprusside, and nicorandil possess vasodilatory effect. Nitroglycerin has been reported to be effective in preventing spasm of radial artery graft.[13] The increase in GFF is in the range of 24 to 32 mL/min, but an increase of more than 100% has not been reported.

Calcium channel blockers are the most frequently used vasodilator for radial artery. The usefulness of verapamil has also been proven experimentally, but many studies used a combination with nitrate. A cocktail of verapamil and nitroglycerin (VG solution) has been extensively studied. He and Yang[14] and Dogan et al[15] reported good vasodilatory effect for radial artery.

Our present study showed that intraluminal injection of VG solution into the RGEA graft significantly increased GFF, but the increase was moderate, with a mean increase of 40 mL/min or approximately twofold from baseline. The use of papaverine also increased RGEA GFF; again, the increase was moderate and not significantly different from that in the VG treatment. These results were similar to those that we reported previously for radial artery using the same method of GFF measurement.[16] These findings indicate that the conventionally used vasodilatory agents such as papaverine and VG are limited in their efficacy to increase GEA graft flow.

Rho kinase is an intracellular serine/threonine kinase identified in the mid-1990s as the target protein for the low-molecular-weight GTP-binding protein "Rho."[17–19] Rho kinase is involved in many physiological functions such as contraction, cell proliferation, cell migration, and gene induction. Rho kinase is known to regulate vascular smooth muscle contraction and relaxation independent of the intracellular calcium ion concentration. Rho kinase is also strongly associated with the pathogenesis of vascular diseases, suggesting a possible role of Rho kinase inhibitors in the treatment of these diseases.[9] 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 electrocardiography change, and chest pain.[20] In patients with intractable coronary vasospasm after CABG not responding to maximum vasodilatory therapy, fasudil treatment markedly ameliorated the conditions.[21] To apply the potent vasodilatory effect of the Rho kinase inhibitor to CABG, we previously investigated the vasodilatory effect of fasudil on human internal thoracic artery[22] and radial artery grafts[16] and showed the superior vasodilating effect of fasudil over papaverine and VG for both grafts. In the present study, we found that fasudil increased GEA GFF more than threefold, also significantly and markedly more potent than papaverine and VG.

Vasodilatory agents can be administered during CABG by the following methods: intraluminal injection, topical application on the adventitia (or covering with gauze soaked with the drug), and systemic administration. For GEA, the administration method that provides maximum effectiveness remains unknown. In the present study, we injected a small volume (2 mL) of fasudil intraluminally. Because of the small volume, the drug is unlikely to circulate systemically. This method allowed us to evaluate only the local effect of vasodilators on GEA, independent of other grafts and hemodynamic factors. With local application alone, fasudil demonstrates superior vasodilatory effect for internal thoracic artery,[22] radial artery,[16] and GEA, with no hemodynamic changes, no perioperative myocardial infarction, and no vasodilator-related complications. This agent may become the standard vasodilator for arterial graft pretreatment in CABG.

Fasudil is a relatively low-cost drug and has been used clinically in the neurosurgical field for more than 10 years.[8] Therefore, as a vasodilator, fasudil can be used locally and systemically without concern over safety. With proven efficacy for the three main grafts used in CABG, the effectiveness of systemic fasudil in preventing spasm and improving flow of all graft types would warrant further study.

CONCLUSIONS

Fasudil is more potent than papaverine or VG in increasing GFF of RGEA graft. Fasudil is a very effective drug for the pretreatment of RGEA graft in CABG.

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CLINICAL PERSPECTIVE

In this randomized clinical trial from Dr Watanabe and his colleagues, 30 patients undergoing isolated coronary artery bypass grafting using a right gastroepiploic artery (RGEA) were randomly assigned to having the conduit infused with fasudil, papaverine, or verapamil-nitroglycerin.

The RGEA graft free flow was increased in all groups but was significantly higher with fasudil compared with the other vasodilators. All the grafts in each group were patent at 1 week.

This is a well-designed study that demonstrates the physiological benefits of fasudil for RGEA vasodilatation. Whether this would translate into tangible clinical benefits, such as improved graft patency, will require further study.

AUTHOR QUERY

No query.