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

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Original Article

Potent vasodilatory effect of fasudil on radial artery graft in coronary artery bypass surgery

Running head: Fasudil potently dilates radial artery graft

Go Watanabe, MD, PhD, Shojiro Yamaguchi, MD, PhD, Takeshi Takagi, MD, PhD, Shigeyuki Tomita, MD, PhD, Pham Minh Tuan, MD.

Department of General and Cardiothoracic Surgery, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan

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Corresponding author: Go Watanabe, MD, PhD, Department of General and Cardiothoracic Surgery, Kanazawa University Graduate School of Medical Science, Kanazawa, 13-1 Takara-machi, Kanazawa 920-8640 Japan.
Tel: +81-76-265-2355; Fax: +81-76-222-6833; Email: watago6633@gmail.com

Abstract

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

Methods. Between June 2012 and January 2013, 45 patients with ischemic heart disease who underwent isolated CABG using RA were enrolled and randomly assigned to fasudil (n=15), papaverine (n=15), or verapamil-nitroglycerin (n=15) group. Fasudil (0.9 mg/dl), papaverine (0.4 mg/ml) mixed with heparinized blood, or verapamil-nitroglycerin was injected intraluminally into the RA graft after harvesting. Main outcome measures were RA graft free flow, hemodynamic changes, and histopathological examination of RA.

Results. In the fasudil group, graft free flow increased significantly (p<0.001) from 36.8±20.4 at baseline to 148.0±88.3 ml/min after injection. Graft free flow 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 verapamil-nitroglycerin group. The graft free flow was significantly higher (p=0.001) in fasudil-treated RA than in papaverine- or verapamil-nitroglycerin-treated RA. Histopathologically, RA graft diameter was markedly increased after fasudil injection, and the multiple elastic lamellae structure was intact. Blood pressure did not change significantly after drug injection in all groups.

Conclusion. Fasudil exhibited very potent vasodilatory effect on RA compared to conventional papaverine or verapamil-nitroglycerin, resulting in increased graft free flow. This agent is a useful for dilating RA graft in CABG.

Abstract word count: 249 words

Introduction

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 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 is 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 a graft of appropriate length. However, RA is still not as widely used as the internal thoracic artery. The primary reasons are the high susceptibility of RA graft 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 improve 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. Due to 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 graft, 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 graft into the fasudil group (n=15), VG group (n=15) and 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

Under general anesthesia, RA was isolated together with the accompanying vein by the semi-skeletonizing technique using an electric scalpel at settings of Blend 2 and 20 W. After administering heparin (150 unit/kg), the graft was transected distally.

In each group, baseline graft free flow (GFF) of the RA was measured for 60 seconds. After 10 min, a graft dilating agent was injected intraluminally into the RA graft. In the fasudil group, 2 ml of fasudil solution (Asahi Kasei, Japan) diluted to 0.9 mg/ml (2.67 mmol/L) was injected. This concentration was determined according to a 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 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 RA for CABG [15]. Ten minutes after injection of the vasodilator, GFF of the RA graft was again measured for 60 seconds.

Thereafter off-pump CABG was performed in all patients. The total numbers of

anastomosis per patient ranged from 2 to 6 (mean, 3.4±1.1). All patients had anastomosis of the left anterior descending coronary artery (LAD) with the internal thoracic artery. In addition, they had 1-2 anastomoses of the RA (mean 1.1±0.3), and the target vessels were first diagonal / obtuse marginal branch, or right coronary artery.

Outcome measures and measurement methods

Graft free flow of the RA was measured by collecting free flowing blood from the transected RA into a special tube and is expressed as mL/min. During GFF measurement, mean arterial pressure was measured from the femoral artery and recorded.

Histopathological examination

Surplus RA tissue of one 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 (HE) and Elastica van Gieson (EvG) stained sections were evaluated qualitatively for changes in the media and elastic fiber, as well as the change in diameter.

Statistical analysis

All statistical analyses were performed using SAS version 9.1.3 (Cary, NC). Continuous variables are expressed as mean±standard deviation. The baseline characteristics and hospital outcomes for the 3 groups were compared using the Fisher's exact test for categoric data or the ANOVA test 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, while 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 three groups (Table 1). Other demographic data and risk factors of the three groups also did not differ significantly (Table 1).

There were no significant changes in mean arterial pressure among 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 three 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 min 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 at 10 min 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 post-treatment GFF was significantly higher in the fasudil group than in the other two groups (both, $p < 0.001$).

Graft angiography using 3D-CT was performed in all patients after surgery. All the RA grafts in the three groups were patent.

Histopathological findings

The histopathological findings of ring specimens collected from the RA stump from one patient before and after fasudil injection are shown in Fig. 2. The internal diameter was increased after fasudil injection. EvG staining showed that the elastic lamella remained intact,

and the smooth muscle-rich media became thinner after fasudil injection, suggesting relaxation.

Comments

To the best of our knowledge, this is the first study that demonstrates that the Rho-kinase inhibitor fasudil is effective to prevent RA spasm and consequently increase RA GFF. In the present study, fasudil treatment increased RA GFF strikingly by over 400%. These results indicate a very potent vasodilatory effect of fasudil for the RA graft. Moreover, intraluminal administration of fasudil did not affect the hemodynamic parameters or cause adverse effects, which is consistent with previous report 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 RA exhibited myocardial ischemia.

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

The arteries in humans can be classified into three types according to the 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 compared to somatic type arteries such as the internal thoracic artery [17,18]. One of the reasons is that RA possesses a smooth muscle-rich media. Adequate prevention of perioperative spasm will improve the patency and prevent 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 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 follows.

Nitrates and nitrate derivatives. This class of agents includes glycerin trinitrate, isosorbide dinitrate, sodium nitroprusside and nicorandil. All have been shown to possess vasodilatory effect, and increase of GFF including that of RA graft has been reported [19]. The increase is in the magnitude of 24 to 32 ml/min, and increase of over 100% has not been reported. The vasodilatory effect of nitrates on RA segments has been reported by Chanda et al [16] and He et al [20].

Calcium channel blockers. This class of drugs is the most frequently used vasodilator, because they act by selectively blocking L type voltage-operated calcium channels on smooth muscle cell membrane, thereby inhibiting calcium influx and attenuating the contractile response [21]. 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 [15] and Dogan et al [22] reported good vasodilatory effect for RA. Yoshizaki et al [23] also reported that VG solution is 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 min as soon as they were dissected, while we injected VG solution intraluminally and waited for only 10 min. Our method probably did not allow maximal action of VG solution on the RA graft.

Phosphodiesterase inhibitors. PDE inhibitors have been used in recent years. Na et al [25] observed increase in GFF both in RA and internal thoracic artery, with an increase from 91 to 110 ml/min in RA. The anti-spasm effect was also observed in segment specimens [26,27], but superiority to VG solution has not been reported. Papaverine is one of the most commonly used vasodilators for arterial graft. It is a benzylisoquinonline alkaloid with non-selective smooth muscle relaxant properties [28]. Although papaverine is a low-cost drug exhibiting vasodilating effect for 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 above have been shown to be effective to certain extent, none of the reports indicated an increase in GFF by over 100%. The VG solution is the most commonly used vasodilator [24], but the development of more effective and safe vasodilator for RA graft 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 GTP-binding protein “Rho” [31-33]. Rho kinase is closely related to many physiological 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 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 is due to blockade of Rho-associated protein kinase (ROCK), because intraluminal fasudil injection into RA abolishes the increase in myosin phosphatase targeting subunit 1 (MYPT1) phosphorylation at the ROCK phosphorylation site Thr^{853}, and consequently deinhibits 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 ECG change and chest pain [35]. In patients with intractable coronary vasospasm after CABG not responding to maximum vasodilatory therapy, fasudil treatment markedly ameliorated the condition [36]. With the objective to apply the potent vasodilatory effect of Rho kinase inhibitor to CABG, we performed a study to investigate the in situ vasodilatory effect of fasudil on human internal thoracic artery, and showed superior vasodilating effect of fasudil compared to papaverine [9]. In the present study, we found that fasudil also has markedly more potent vasodilating effect on RA compared to papaverine and

VG solution.

The method of administering vasodilatory agent during CABG is an important issue. From the mechanism of action of the drug, three 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 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 over 10 years [6]. Therefore fasudil can be used without concern over safety.

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

Conclusion

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

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None

Disclosures

There is no conflict of interest**.**

Freedom of Investigation

The authors state that they had full control of the design of the study, methods used, outcome parameters, analysis of data and production of the written report.

Scientific Responsibility

Each author certifies that he or she has participated sufficiently in the work to take responsibility for a meaningful share of the content of the manuscript.

Others

The corresponding author has a graduate degree; and accepts responsibility for the integrity of the submitted work; and attests that no undisclosed authors contributed to the manuscript.

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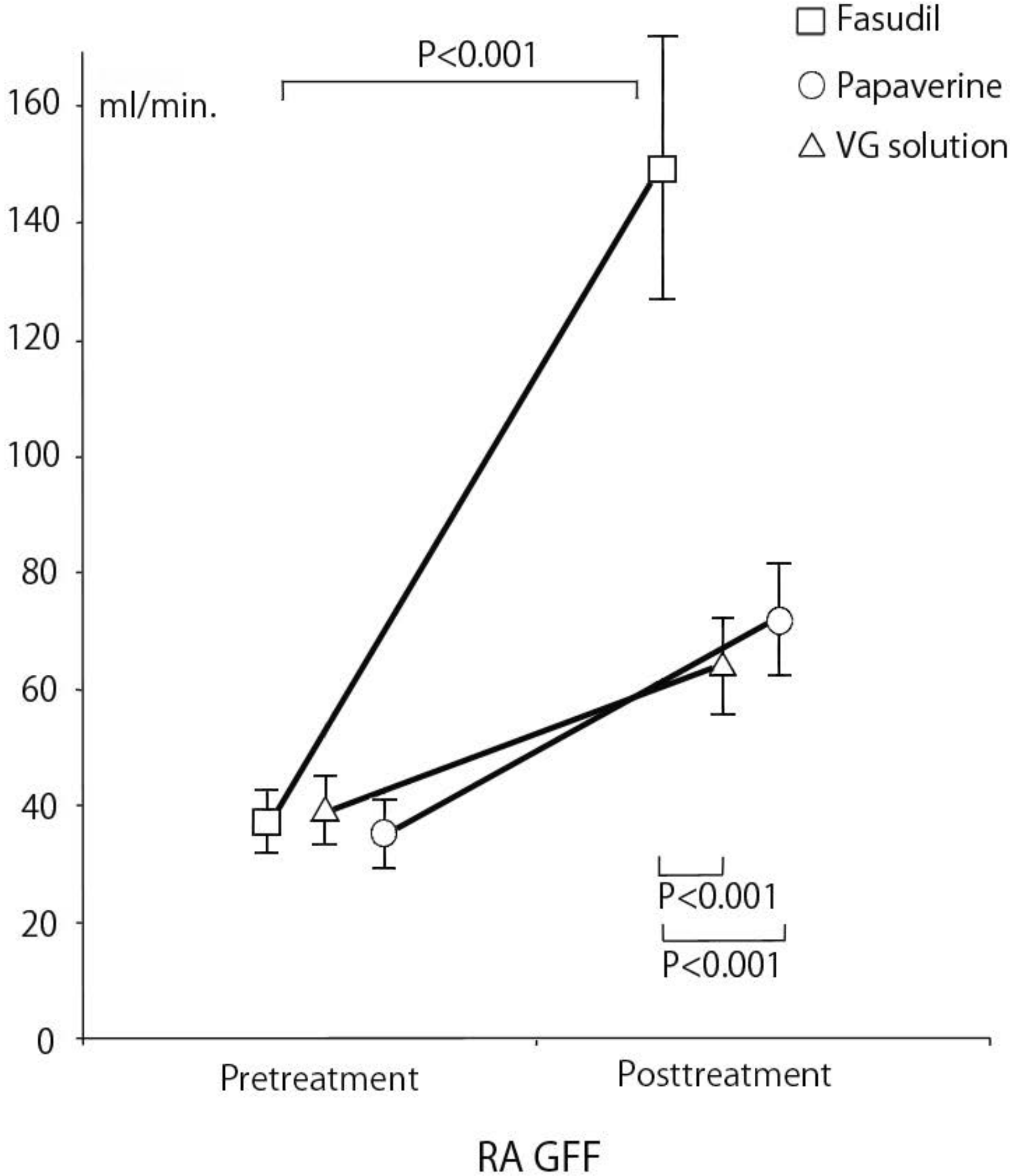
Figure Legends

Fig. 1. Change in graft free flow (mL/min) of radial artery graft before and after treatment with fasudil, papaverine or verapamil-nitroglycerin solution. Data are expressed as mean (point) ± standard ~~deviation~~ error (bar).

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


Fasudil
Papaverine
VG solution
P<0.001
160
ml/min.
140
120
100
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40
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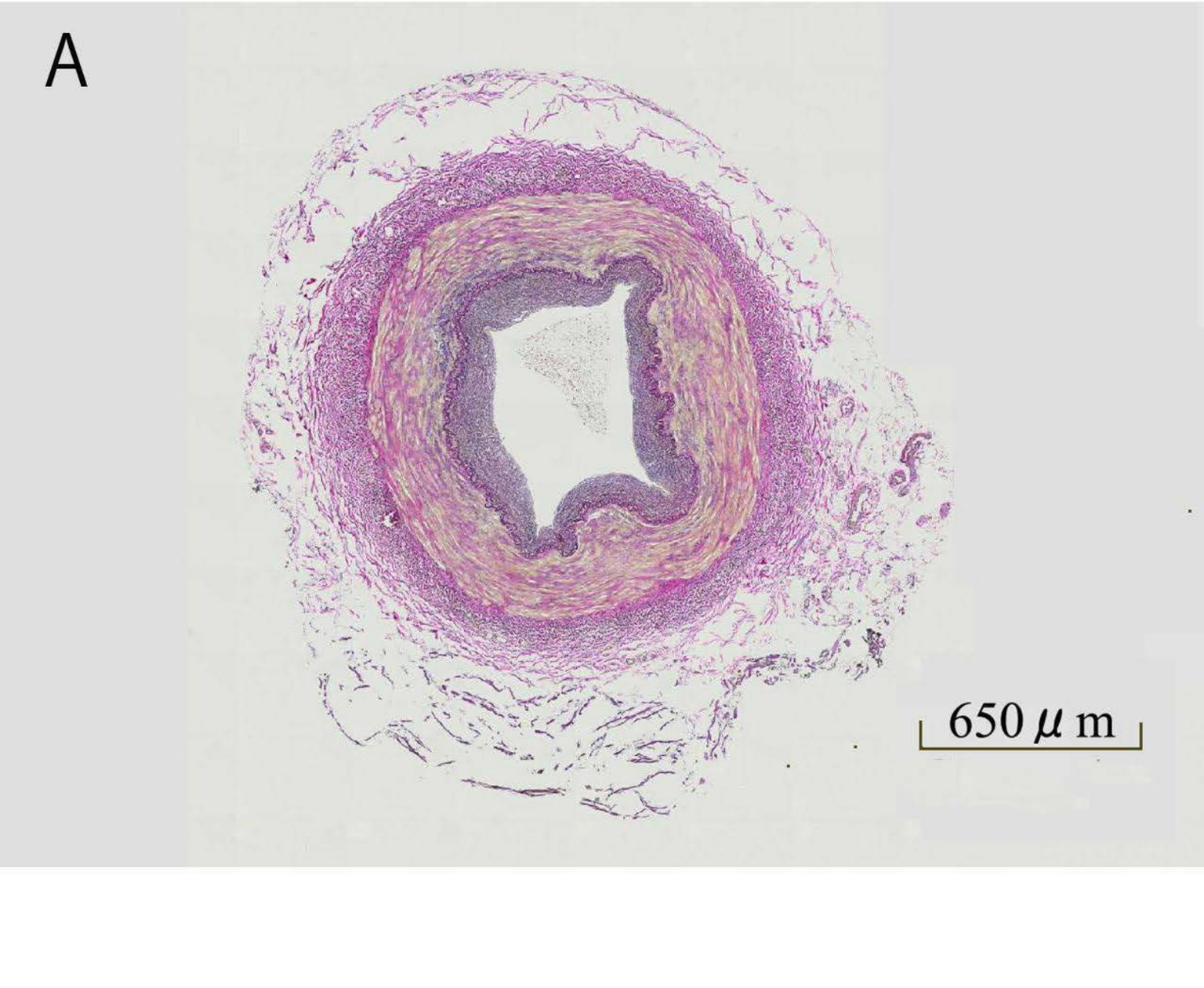
P<0.001
P<0.001
Pretreatment
Posttreatment
RA GFF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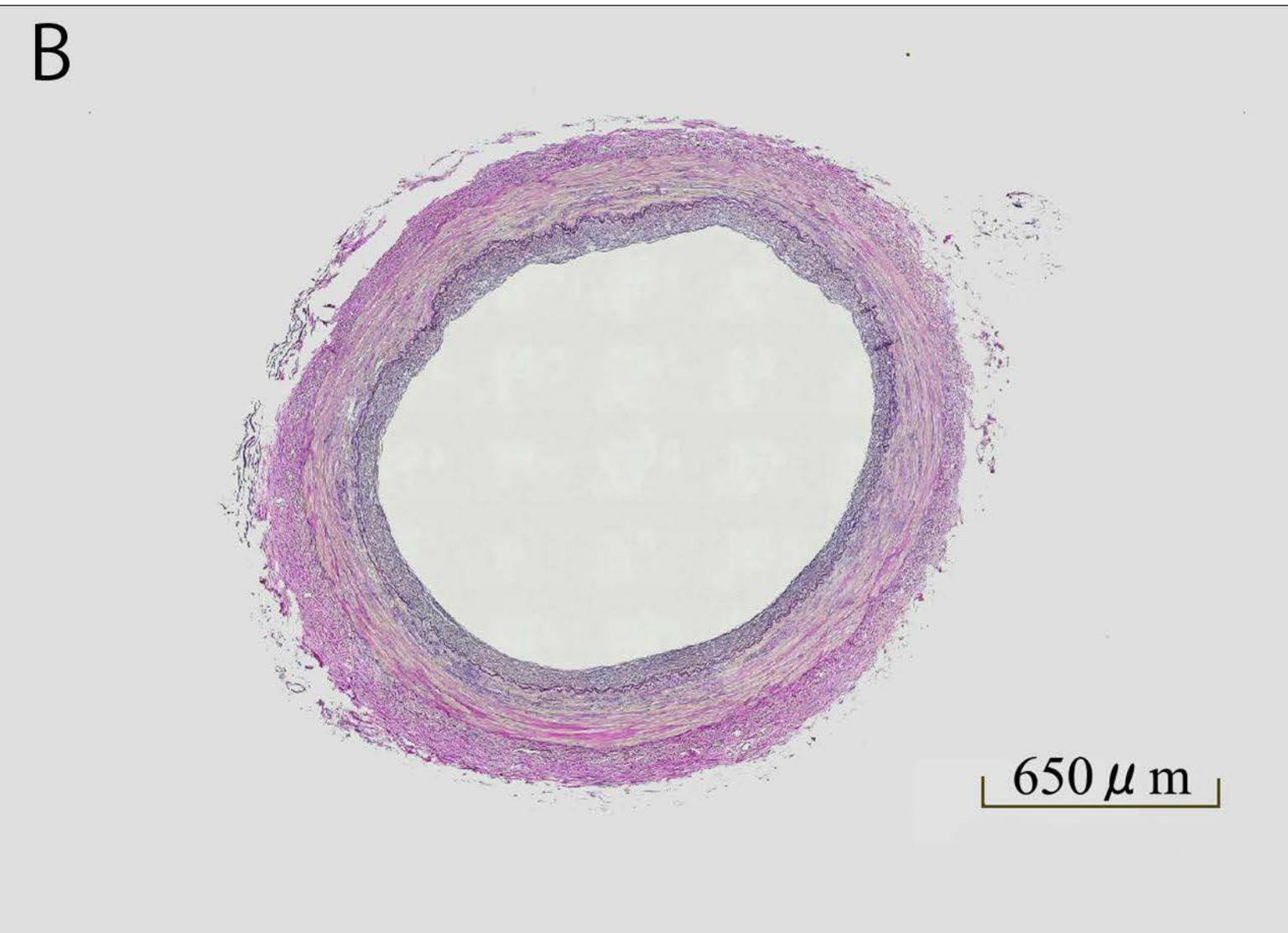
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Table 1. Preoperative patient characteristics and risk factors

	Fasudil (n=15)	Papaverine (n=15)	VG solution (n=15)	ANOVA
Age; years (mean±SD)	67.3±9.7	66.2±11.5	69.1±10.1	NS
Male; 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 disease; number (%)	4 (27%)	5 (33%)	4 (27%)	NS

VG solution: verapamil-nitroglycerin, LVEF: left ventricular ejection fraction, NS: not significant

Table 2. Comparison of mean blood pressure before and after treatment of radial artery graft with fasudil, papaverine or verapamil-nitroglycerin (VG solution)

	Fasudil (n = 15)	Papaverine (n = 15)	VG solution (n = 15)	p value ANOVA
Blood pressure (mmHg) (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	