

Fasudil is a superior vasodilator for the internal thoracic artery in coronary surgery

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Original Article

Fasudil is a superior graft vasodilator in coronary artery bypass surgery: internal thoracic artery

Running head: Fasudil as potent graft dilator in CABG

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Abstract

Background. Internal thoracic artery (ITA) is a very useful conduit for coronary artery bypass artery (CABG), with excellent long-term patency. With the purpose to dilate the ITA graft and increase graft free flow (GFF) intraoperatively, we evaluated the usefulness of intraluminal injection of fasudil, a Rho-kinase inhibitor, and compared with the conventional graft dilating agent papaverine.

Methods. Between June 2011 and January 2012, 30 patients with ischemic heart disease who underwent isolated CABG using ITA were enrolled. The patients were randomly assigned to two groups: fasudil group (n=15) in which fasudil solution 0.9 mg/dl was injected into ITA, and papaverine group (n=15) in which papaverine solution (0.4 mg/ml) mixed with heparinized blood was used. Outcome measures were left ITA GFF, heart rate and mean blood pressure during flow measurements, and histopathological examination of ITA.

Results. In the fasudil group, GFF increased significantly ($p<0.01$) from 19.7 ± 15.2 ml/min at baseline to 66.9 ± 31.7 ml/min after fasudil injection. In the papaverine group, GFF increased significantly ($p<0.01$) from 22.9 ± 17.3 ml/min at baseline to 44.8 ± 26.7 ml/min after papaverine injection. Blood pressure and heart rate did not change significantly after drug injection in both groups. The GFF was significantly higher ($p=0.038$) in fasudil-treated ITA than in papaverine-treated ITA. Histopathologically, the diameter of the ITA was markedly increased after fasudil injection. Elastica van Gieson staining showed that the multiple elastic lamellae structure was intact.

Conclusion. Fasudil exhibited very potent vasodilatory effect on ITA compared to conventional papaverine resulting in increased GFF. This agent is a useful graft dilating agent.

Introduction

The internal thoracic artery (ITA) graft is an indispensable conduit for coronary artery bypass grafting (CABG), because superior long-term patency is obtained with the ITA graft compared with the traditional saphenous vein and other grafts [1]. Although the ITA graft has the advantage of long-term patency, there are reported cases of reduced graft flow after left ITA–left anterior descending artery anastomosis caused by a narrow graft or spasm during graft harvest, leading to worsened hemodynamics [2]. Vasodilating drugs [3, 4] and harvesting techniques [5] have been used to prevent or relax spasm, which have contributed to improve the graft flow and increase the left ITA graft patency rate.

Fasudil is a Rho-kinase inhibitor and a vasodilator with a new mechanism of action. Due to its potent vasodilating action, fasudil has been used in various clinical fields. In the field of neurosurgery, fasudil is a very effective drug for the prevention of cerebral vasospasm, which is a serious complication secondary to intracranial hemorrhage.⁶ In cardiovascular field, fasudil attenuates coronary spasm, and its potential in the treatment of ischemic heart disease and arteriosclerosis is anticipated.⁷ Focusing on the potent vasodilating action of this drug and considering its clinical safety, we examined the usefulness of fasudil as a vasodilating agent for ITA graft and compared with the conventionally used papaverine.

Patients and Methods

Patients

Among the patients who underwent elective CABG in our department between June 2011 and January 2012, 30 consecutive patients using the left ITA conduit were enrolled in this study. Patients who had received radiotherapy in the left chest and patients who had a hemodialysis shunt in the forearm were excluded. All patients undergoing CABG during this period were eligible for entry into the trial. The trial was approved by the institutional ethics committee. Informed consent was obtained from each patient.

Patients were assigned randomly to two groups according to the agent used to dilate the ITA graft. In the fasudil group, fasudil solution (0.9 mg/ml) was injected into the ITA graft. In the papaverine group, conventional papaverine (0.4 mg/ml mixed with heparinized blood) was injected into the ITA graft.

Protocol

Under general anesthesia, a median sternotomy was performed, and a retractor for ITA harvest was placed. Using the Vallylab Force 2 (Tyco Healthcare co, USA) electro-scalpel at settings of Blend 2 and 20 Watts, the left ITA was isolated together with the internal thoracic vein using the semi-skeletonizing technique. Dissection was performed until the ITA origin from the subclavian artery at the proximal end, and until the bifurcation into the superior epigastric artery and musculophrenic artery at the distal end. After injecting heparin (150 unit/kg), the left ITA was transected just proximal to its bifurcation.

In both groups, baseline graft free flow (GFF) of the left ITA was measured for 60 seconds. After 10 min, 2 ml of fasudil solution (Asahi Kasei, Japan) diluted to 0.9 mg/ml was injected intraluminally into the ITA graft in the fasudil group, and 2 ml of papaverine (0.4 mg/ml mixed with heparinized blood) was injected into the ITA graft in the papaverine group. Ten minutes after injection of the vasodilator, GFF of the ITA graft was again measured for 60 seconds. Thereafter off-pump CABG was performed in all patients. The numbers of anastomosis ranged from 2 to 6 (mean, 3.2 ± 1.2). All these cases involved anastomosis of the left anterior descending coronary artery (LAD) with the left ITA.

Outcome measures and measurement methods

Graft free flow of the left ITA was measured by collecting free flowing blood from the transected ITA for 60 seconds into a special tube and expressed as ml/min. During GFF measurement, mean arterial pressure was recorded. Blood pressure was measured from the radial artery or femoral artery.

Histopathological examination

Surplus ITA tissue of one patient in the untreated group was examined histopathologically. Ring specimens of the left ITA 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 internal diameter.

Statistical analysis

All statistical analyses were performed using SPSS software (version 19.0.0.2; SPSS, Chicago, IL). All data are expressed as mean \pm standard deviation. The baseline characteristics and hospital outcomes for the two groups were compared using χ^2 test for categorical data, or unpaired t-test for continuous data. The fasudil group and papaverine group were compared with respect to pretreatment and posttreatment hemodynamic parameters and GFF of the left ITA graft using 2-way ANOVA. Statistical significance was defined as a *p* value less than 0.05.

Results

Demographic and hemodynamic data

The fasudil group (n =15) consisted of 12 men and 3 women with a mean age of 70.5 \pm 8.3 years old, while the papaverine group (n = 15) consisted of 13 men and 2 women with a mean age of 68.6 \pm 9.5 years, with no significant differences between two groups.

There were no significant changes in heart rate and mean arterial pressure between two groups both before and after graft treatment (Table 1). No patient had perioperative myocardial infarction. There were no significant differences in the use of inotropic agents and postoperative drainage between two groups. No serious complications such as pleural effusion were observed, and all patients were discharged after the postoperative observation period.

Effects of fasudil and papaverine

The GFF of the left ITA graft treated with fasudil increased markedly from 19.7 ± 15.2 ml/min at baseline to 66.9 ± 31.7 ml/min at 10 min after treatment, showing a significant increase ($p = 0.01$) (Fig. 1). The GFF of the left ITA graft treated with papaverine also increased significantly ($p = 0.05$) from 22.9 ± 17.3 ml/min at baseline to 44.8 ± 26.7 ml/min at 10 min after treatment. Comparing fasudil- and papaverine-treated left ITA grafts, the GFF was significantly higher in the fasudil group than in the papaverine group ($p = 0.038$).

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

Histopathological findings

We compared the histopathological findings of left ITA ring specimens collected from the same patient before and after fasudil injection (Fig. 2). The diameter of the ITA was markedly increased after fasudil injection. Elastica van Gieson staining showed that the structure of multiple elastic lamellae was intact. The smooth muscle-rich media became thinner after fasudil injection, suggesting relaxation.

Comments

In the present study, fasudil treatment of the ITA increased GFF by over 300%. This data greatly exceeds the maximum increase in GFF reported for papaverine (increase by 100%) [8], nitroglycerin and verapamil (GV) (86%) [9], and phosphodiesterase III inhibitor (PDE III) (59%) [10]. In the present study, there was a significant increase in GFF in papaverine-treated ITA grafts, showing the benefit of papaverine as a vasodilating agent. However, the post-treatment GFF in the papaverine group was significantly lower than in the fasudil group. To the best of our knowledge, this is the first study demonstrating that the Rho-kinase inhibitor fasudil is highly effective in dilating ITA with resultant increase in ITA graft free flow. Thus fasudil is an amazing vasodilating agent for ITA, with potency incomparably higher than the other agents. From the surgeon's view of the operative field under a 3.5 x magnifying lens, the

fasudil-treated ITA graft appears dilated and relaxed, with a thin wall. In fact, when pre- and post-fasudil-treated ring samples of the transected ITA from the same patient were examined histopathologically, the vascular wall was confirmed to be thin and dilated. In the surgical field, since the fasudil-treated ITA graft is thin due to the potent vasodilating effect, it probably requires more delicate handling than in conventional procedures.

Because of the good long-term patency rate, the ITA-LAD anastomosis is being used as the gold standard of CABG [1]. The good patency of the ITA led to the expectation that arterial grafts are superior, and other arterial conduits such as the radial artery (RA) and gastroepiploic artery (GEA) are also being used in CABG [11, 12]. However, the superiority of ITA remains unchanged. The characteristic of ITA which makes it an excellent graft is that it is an elastic type artery rich in elastic fiber in the media, compared with the other muscular type arteries such as the RA and GEA. Although the ITA, being an elastic type arterial graft, is expected to be less susceptible to graft spasm, report has indicated that spasm may occur during harvest or immediately after surgery, deteriorating perioperative hemodynamics [2]. Therefore appropriate intraoperative pretreatment of the ITA graft is essential to prevent or relax graft spasm.

Surgeons have developed various methods attempting to eliminate the negative effects of graft spasm. One of them is to modify the technique of harvesting the pedicle, such as using skeletonization with an ultrasonic scalpel⁵ and treatment with various anti-spastic agents [3, 4, 9]. We reviewed the effects of the conventionally used drugs reported by various investigators. Many anti-spastic agents have been reported, including papaverine, nitroglycerin, GV solution and phosphodiesterase (PDE) III inhibitor [3, 4, 8-10]. According to reports of quantitative evaluation of free flow of ITA treated by papaverine, Formica et al. [9] reported a 32% increase from 40 to 53 ml/min; Koramaz et al. [8] reported 100% increase from 32 to 64 ml/min; Nili et al. [3] reported 10% increase from 38.8 to 42.1 ml/min; and Takeuchi et al. [10] reported 8% increase from 37 to 40 ml/min. For verapamil, Nili et al. [3] reported 7.2% increase from 33.8 to 41.1 ml/min. For nitroglycerin, Nili et al. [3] reported 2% increase from 38.8 to 39.2 ml/min with no significant difference; and Takeuchi et al. [10]

reported 27% increase from 37.9 to 47.9 ml/min. Formica et al. [9] used glyceril-trinitrate/verapamil and showed an 86% increase in free flow from 31.6 to 58.8 ml/min. Recently, the vasodilatory effect of PDE III inhibitor has attracted attention, and experimental data have been reported [13, 14]. Takeuchi et al. [10] used PDE III inhibitor and measured the GFF of ITA. They reported 59% increase from 36 to 57 ml/min, and concluded the usefulness of this agent. Although PDE III, papaverine, GV and nitroglycerin alone have been shown to have some degrees of vasodilatory effect, none of the reports indicated an increase in graft flow by greater than 100%.

Rho kinase is an intracellular serine/threonine kinase identified in the mid-1990s as a target protein for the low molecular weight GTP-binding protein "Rho" [15, 16]. Rho kinase is closely associated with many physiological functions such as contraction, cell proliferation, cell migration, and induction of gene expression. It is known to regulate vascular smooth muscle contraction and relaxation independent of the intracellular calcium ion concentration. Rho kinase is closely involved in the pathogenesis of various diseases including cardiovascular disease, suggesting a possible role of Rho kinase inhibitor in the treatment of these diseases [7]. Selective injection of the Rho kinase inhibitor fasudil into the coronary artery inhibited acetylcholine-provoked coronary vasospasm, angina-related ECG change and chest pain [17, 18]. Fasudil treatment also markedly improves the conditions of patients with intractable coronary vasospasm not responding to maximum vasodilatory therapy immediately after CABG [19]. In the field of neurosurgery, fasudil has been shown to be useful in preventing cerebral vasospasm after cerebral hemorrhage. We focused on the application of the potent vasodilatory effect of Rho kinase inhibitor in coronary surgery, and performed a basic study to investigate the *in vivo* vasodilatory effect of the commercially available Rho kinase inhibitor fasudil in humans [20].

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 (infiltration from the intima to media and then to adventitia); (2) topical application on the adventitia or covering with gauze soaked with the drug (infiltration from the adventitia); and (3)

systemic administration. Conventional vasodilatory drugs are administered empirically by the first or second method, alone or in combination, depending on the surgeon. For ITA, 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. Our result thus showed that marked vasodilatation is achieved by intraluminal injection. This result is logical considering that the ITA has little vaso vasorum, and 80% of the blood in the arterial wall is directly supplied by the blood in the lumen. Studies on the effects of local application and systemic administration are ongoing. Fasudil is a relatively low cost drug and has a long history of clinical application. 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.

When a sufficiently dilated ITA graft is used in CABG, good flow can be expected after surgery. This technique can be recommended from the viewpoints of perioperative management and long-term graft patency, and may become the standard for arterial graft pretreatment.

Conclusion

In this study, fasudil exhibited very potent vasodilatory effect on ITA, resulting in markedly increased GFF. Dilatation of the ITA wall was histologically verified. Fasudil is a highly effective drug for the pretreatment of ITA graft.

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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.

References

1. Korkmaz AA, Onan B, Onan S, Ozkara A, Guden M, Bakay C. Combined internal mammary artery graft in coronary bypass: 18-year follow-up. *Ann Thorac Surg* 2009;87:e57-58.
2. Zünd G, Hauser M, Vogt P, Davis CP, Lachat M, Künzli A, et al. New approach to patency and flow assessment after left internal thoracic artery hypoperfusion syndrome with additional saphenous vein graft to the left anterior descending artery with phase-contrast magnetic resonance angiography. *J Thorac Cardiovasc Surg* 1997;114(3):428-433
3. Nili M, Stamler A, Sulkes J, Vidne BA. Preparation of the internal thoracic artery by vasodilator drugs: is it really necessary? A randomized double-blind placebo-controlled clinical study. *Euro J Cardiothorac Surg* 1999;16:560-563.
4. Sivalingam S, Levine A, Dunning J. What is the optimal vasodilator for preventing spasm in the left internal mammary artery during coronary arterial bypass grafting? *Interactive Cardiovasc Thoracic Surg* 2005;4:365-371.
5. Higami T, Yamashita T, Nohara H, Iwahashi K, Shida T, Ogawa K. Early results of coronary grafting using ultrasonically skeletonized internal thoracic arteries. *Ann Thorac Surg* 2001;71(4):1224-1248.
6. Iwabuchi S, Yokouchi T, Hayashi M, Uehara H, Ueda M, Samejima H. Intra-arterial administration of fasudil hydrochloride for vasospasm following subarachnoid hemorrhage - analysis of time-density curve with digital subtraction angiography. *Neurol Med Chir (Tokyo)*. 2006 ;46(11):535-539; discussion 540.
7. Shimokawa H, Takeshita A. Rho-Kinase is an important therapeutic target in cardiovascular medicine. *Arterioscler Thromb Vasc Biol* 2005;25:1767-1775.
8. Koramaz I, Ozkan M, Altun G, Guven KY, Kadioglu Duman M, Kalyoncu NI, et al. Effects of papaverine and carbon dioxide alone or in combination on the blood flow of internal thoracic artery. *J Thorac Cardiovasc Surg* 2006;132:1126-1130.
9. Formica F, Ferro O, Brustia M, Corti F, Colagrande L, Bosisio E, et al. Effects of

- papaverine and glycerilnitrate-verapamil solution as topical and intraluminal vasodilators for internal thoracic artery. *Ann Thorac Surg* 2006;81:120-124.
10. Takeuchi K, Sakamoto S, Nagayoshi Y, Nishizawa H, Matsubara J. Reactivity of the human internal thoracic artery to vasodilators in coronary artery bypass grafting. *Euro J Cardiothorac Surg* 2004;26:956-9.
 11. van Son JA, Smedts F, de Wilde PC, Pijls NH, Wong-Alcala L, Kubat K, et al. Histological study of the internal mammary artery with emphasis on its suitability as a coronary artery bypass graft. *Ann Thorac Surg*. 1993;55:106-113.
 12. Kamiya H, Watanabe G, Takemura H, Tomita S, Nagamine H, Kanamori T. Total arterial revascularization with composite skeletonized gastroepiploic artery graft in off-pump coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2004;127(4):1151-1157.
 13. He GW, Yang CQ. Inhibition of vasoconstriction by phosphodiesterase III inhibitor milrinone in human conduit arteries used as coronary bypass grafts. *J Cardiovasc Pharmacol* 1996;28:208-214.
 14. Huraux C, Makita T, Montes F, Szlam F, Levy JH. A comparative evaluation of the effects of multiple vasodilators on human internal mammary artery. *Anesthesiology* 1998;88:1654-1659.
 15. Matsui T, Amano M, Yamamoto T, Chihara K, Nakafuku M, Ito M, et al. Rho-associated kinase, a novel serine/threonine kinase, as a putative target for small GTP binding protein Rho. *EMBOJ* 1996;15:2208-2216.
 16. Ishizaki T, Maekawa M, Fujisawa K, Okawa K, Iwamatsu A, Fujita A, et al. The small GTP-binding protein Rho binds to and activates a 160 kDa Ser/Thr protein kinase homologous to myotonic dystrophy kinase. *EMBO J* 1996;15:1885-1893.
 17. Masumoto A, Mohri M, Shimokawa H, Urakami L, Usui M, Takeshita A. Suppression of coronary artery spasm by the rho-kinase inhibitor fasudil in patients with vasospastic angina. *Circulation* 2002;105:1545-1547.
 18. Kaski JC, Rosano GM, Collins P, Nihoyannopoulos P, Maseri A, Poole-Wilson PA. Cardiac syndrome X: clinical characteristics and left ventricular function. Long-term

follow-up study. *J Am Coll Cardiol* 1995;25:807-814.

19. Inokuchi K, Ito A, Fukumoto Y, Matoba T, Shiose A, Nishida T, et al. Usefulness of fasudil, a Rho-kinase inhibitor, to treat intractable severe coronary spasm after coronary artery bypass surgery. *J Cardiovasc Pharmacol* 2004;44:275-7.
20. Takagi T, Okamoto Y, Tomita S, Sato A, Yamaguchi S, Takuwa Y, Watanabe G. Intraradial administration of fasudil inhibits augmented Rho kinase activity to effectively dilate the spastic radial artery during coronary artery bypass grafting surgery. *J Thorac Cardiovasc Surg* 2011;142(2):e59-65.

Table 1. Hemodynamic parameters before and after left internal thoracic artery graft treatment

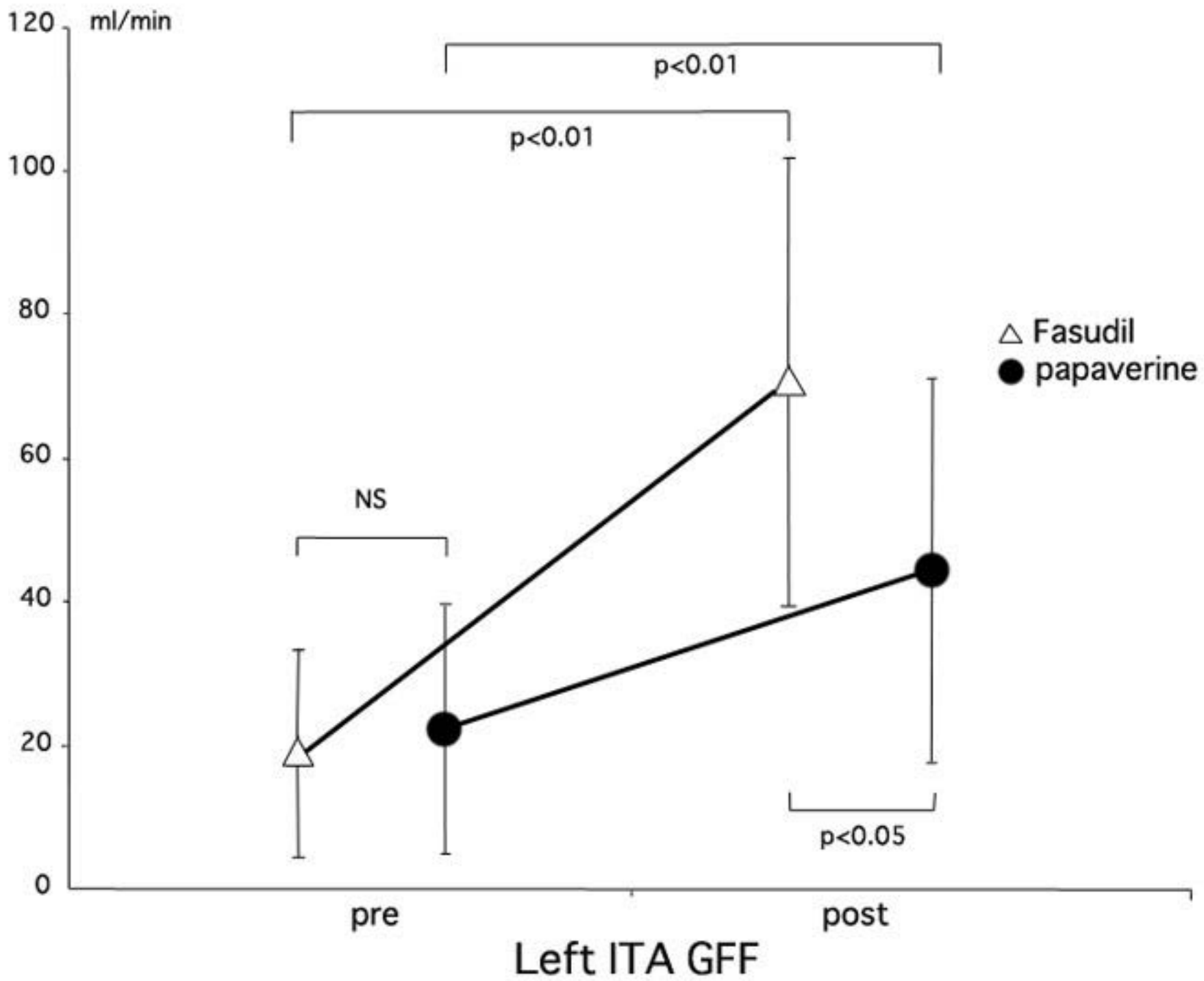
	Heart rate (/min)		Before vs. after treatment	Mean blood pressure (mmHg)		Before vs. after treatment
	Before treatment	After treatment		Before treatment	After treatment	
Fasudil group	75.6±12.9	76.2±13.9	NS	65.5±17.7	61.3±16.4	NS
Papaverine group	75.9±13.5	75.7±14.3	NS	67.4±12.9	64.3±9.8	NS
Fasudil vs. papaverine	NS	NS		NS	NS	

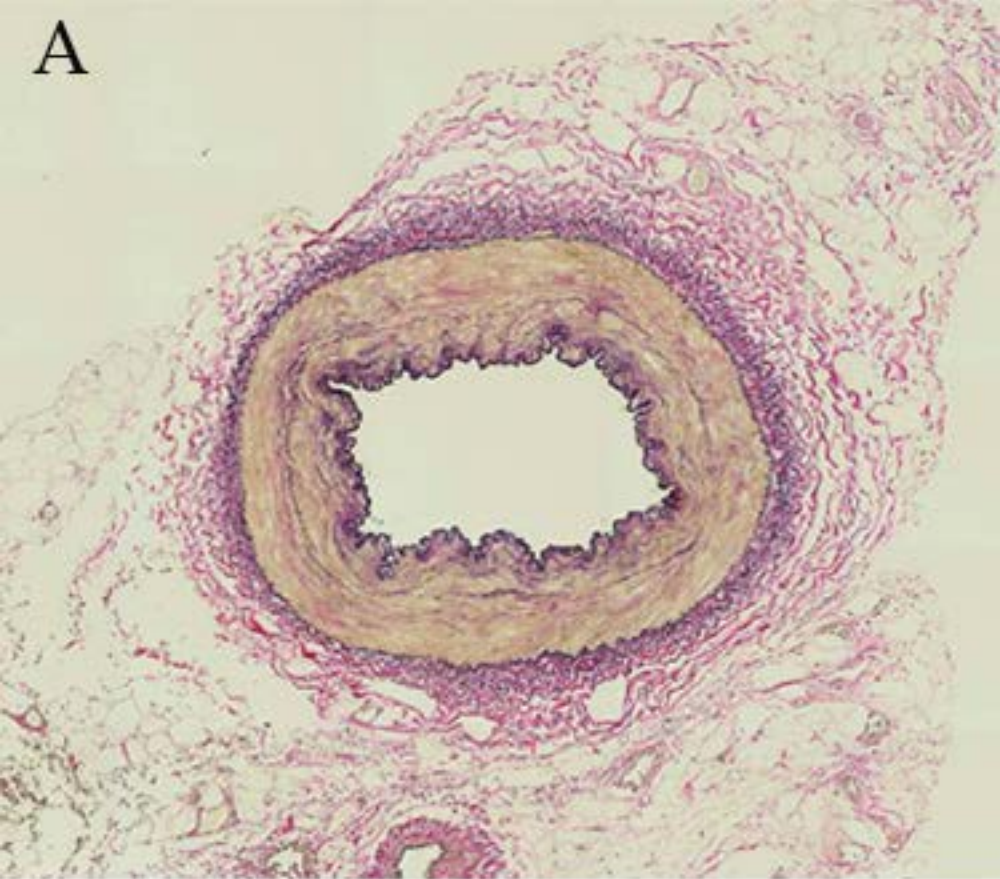
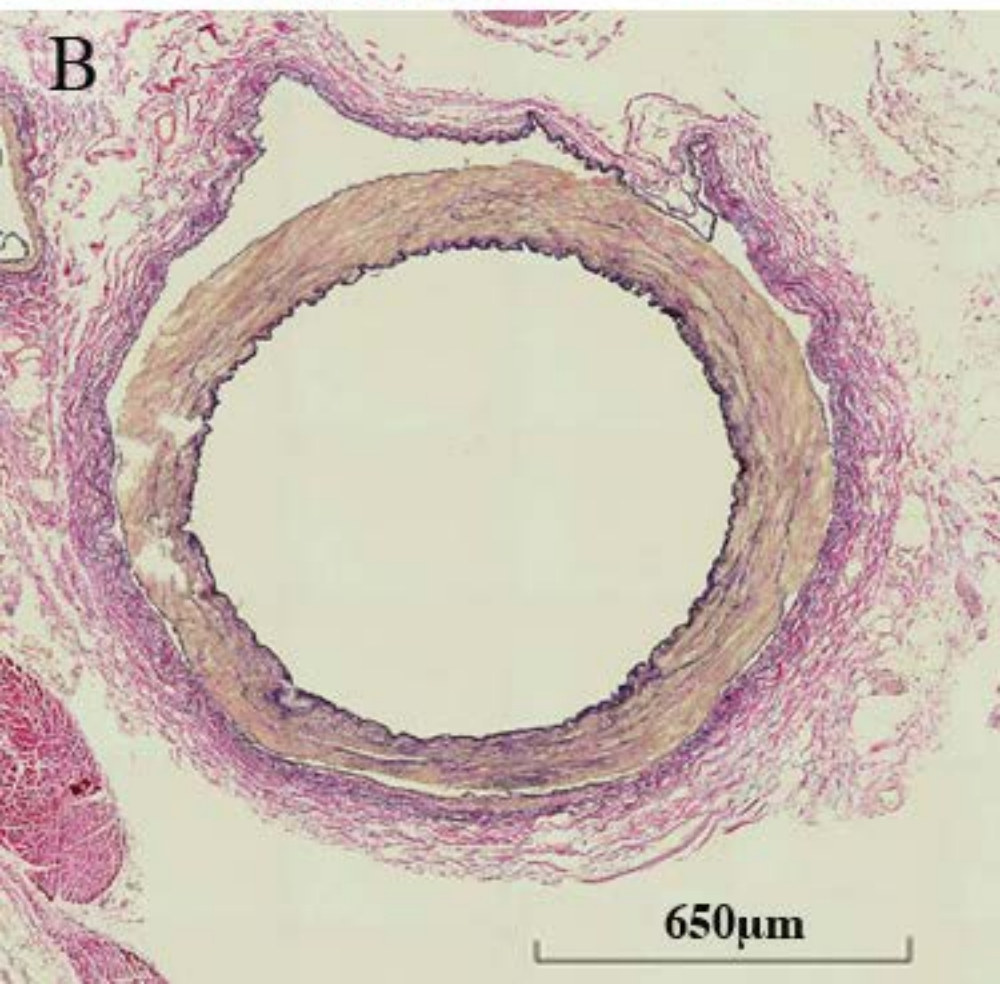
NS: not significant

Figure Legends

Fig. 1. Change in graft free flow (GFF; ml/min) of left internal thoracic artery (ITA) graft before and after treatment with fasudil or papaverine. NS: not significant.

Fig. 2. Histopathological findings of left internal thoracic artery (ITA) specimen before fasudil injection (A) and after fasudil injection (B). The diameter of the ITA increases markedly after fasudil injection. Elastica van Gieson staining.



A**B****650 μ m**