Reactivity of the human internal thoracic artery to vasodilators in coronary artery bypass grafting

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Abstract

Objective: The internal thoracic artery (ITA) is a useful conduit for coronary artery bypass grafting (CABG) and the patency rate is indispensable. Recently we have developed a method for increasing ITA blood flow during surgery by directly injecting phosphodiesterase III inhibitor (PDE III-I) into the left ITA (LITA) to prevent its contracture. In this study, we compared the reactivity of LITA blood flows before and after injection of four drugs: saline, papaverine hydrochloride, isosorbide dinitrate (ISDN), and PDE III-I. Method: 80 patients who were undergoing the first primary CABG, were randomly separated into four groups. Each group consisted of 20 patients. LITA graft free flow (GFF) and systemic mean blood pressure (MBP) were measured before and 1 min after direct intra LITA drug administration and blood vessel resistance (R) was calculated. Result: The saline group showed no significant changes in GFF, R value, and MBP. Significant increase in GFF was observed in the PDE III-I and ISDN groups. Except the saline group, each group exhibited a significant decrease in both the R value and MBP. A comparison of the change rate of MBP showed no significant differences among the four groups. The PDE III-I significantly increased the change rate of GFF and decreased the change rate of the R value, when compared to the saline and papaverine hydrochloride groups. The PDE III-I showed a tendency to increase the change rate of GFF and to decrease the change rate of the R value compared to the ISDN group. Conclusion: The results of this study suggested that the PDE III-I is the most effective for increasing the blood flow of a LITA graft for CABG during surgery.

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1. Introduction

The internal thoracic artery (ITA) graft is an indispensable arterial graft for coronary artery bypass grafting (CABG), because of its excellent patency rate compared with saphenous vein grafts (SVG) [1–5]. Vasospasm of the ITA decreased the blood flow volume and graft patency rate after the operation. It is reported that the prevention of spasm improved the patency rate [6,7]. The Phosphodiesterase III inhibitor (PDE III-I) is currently considered to be very effective to prevent vasospasm. The systemic administration of PDE III-I has been reported to increase graft blood flow [9,23–25]. A study on the direct injection into a graft is rare. In this study PDE III-I, papaverine hydrochloride and isosorbide dinitrate (ISDN) were applied into the ITA directly during surgery and a comparative study of the reaction of the ITA to the vasodilatation was performed. We did not applied sodium nitroprusside, because it is not always used in order to dilate ITA in CABG.

2. Patients and method

2.1. Patients

This investigation received local institutional review board approval, and each patient gave informed consent to participate in the protocol. At our institution, 151 CABG operation were performed between January 1999 and July 2001 and 80 patients of them were selected at random. All these cases involved anastomosis of the left anterior
descending artery (LAD) using a left ITA (LITA). Cases which involved intra aortic balloon pumping (IABP) or percutaneous cardiopulmonary support (PCPS) and emergency operation were excluded.

2.2. Operative technique

The radial artery pressure or the femoral artery pressure was monitored in all the cases for a mean systemic blood pressure (MBP). A median sternotomy was performed and the LITA was dissected and severed after systemic administration of Heparin. The arterial blood volume that flowed out from the proximal end of the severed LITA to a syringe was measured for 10 seconds, and it was named as graft free flow (GFF). MBP was recorded at the same time. Then, a drug to be tested (2 ml) was injected directly into the proximal segment of the severed LITA by 1 ml/s from the proximal end of the LITA, and the LITA was intercepted with a clip. Each of the 20 patients received 2 ml of saline (0.9% NaCl), papaverine hydrochloride (4 mg/ml), ISDN (0.5 mg/ml) or PDE III-I (1 mg/ml) (Fig. 1). One minute after injecting, GFF and MBP were measured again. From LITA GFF and MBP values before and 1 min after direct intraarterial drug administration, the blood vessel resistance (R) using the Poiseuille’s law was calculated. All measurements were performed only once at the time of the own beat.

2.3. Statistical analysis

All data was expressed as the mean ± standard deviation. The paired *t*-test was used for comparison between before and after each drug administration. A *p*-value of less than 0.05 was considered to be statistically significant.

Values of GFF, R, and MBP among four groups did not have a difference before each drug injection. Then, variations of GFF, MBP, and R after saline or papaverine hydrochloride or ISDN or PDE III-I were expressed as a percent change from baseline. GFF, R, and MBP percent change and mean age of each drug group were evaluated by one-way analysis of variance (ANOVA). In the case of significance, the Bonferroni test was then used to compare pre-injection data to values obtained following the application of saline, papaverine hydrochloride, ISDN and PDE III-I. A *p*-value of less than 0.05 was considered to be statistically significant.

3. Results

3.1. Changes before and after injection of each drug

3.1.1. Saline (group I)

There were 17 male and 3 female patients between 45 and 87 years of age (mean 63.4 ± 12.0). Saline treatment induced no significant decreases in LITA GFF (−2.7%), from 37.0 ± 13.9 to 36.0 ± 15.1 ml/min, and in MBP (−0.4%), from 72.2 ± 13.4 to 71.9 ± 13.2 mmHg. It showed no significant increase in R (9.1%), from 2.2 ± 0.7 to 2.4 ± 1.1 mmHg min/ml (Figs. 1 and 2).

3.1.2. Papaverine hydrochloride (group II)

There were 17 male and 3 female patients between 44 and 90 years of age (mean 66.8 ± 13.3). Papaverine hydrochloride treatment showed no significant increase in LITA GFF (8.1%), from 37.2 ± 17.0 to 40.2 ± 19.1 ml/min, a significant decrease in MBP (−6.4%), from 71.7 ± 11.1 to 67.1 ± 12.1 mmHg (p < 0.01), and a significant decrease in R (−16.7%), from 2.4 ± 1.3 to 2.0 ± 0.8 mmHg min/ml (p < 0.05) (Figs. 1 and 2).

3.1.3. ISDN (group III)

There were 13 male and 7 female patients between 47 and 80 years of age (mean 66.6 ± 10.9). ISDN treatment induced a significant increase in LITA GFF (26.4%), from 37.9 ± 16.4 to 47.9 ± 19.6 ml/min (p < 0.05), a significant decrease in MBP (−4.2%), from 69.1 ± 12.8 to 66.2 ± 11.1 mmHg (p < 0.05), and a significant decrease in R (−22.7%), from 2.2 ± 1.1 to 1.7 ± 0.9 mmHg min/ml (p < 0.05) (Figs. 1 and 2).

![Fig. 1. Change of graft free flow before and after injection of each drug. (mean ± SD, *p < 0.05, **p < 0.001) (group I: saline, group II: papaverine hydrochloride, group III: isosorbide dinitrate, group IV: phosphodiesterase III inhibitor).](https://academic.oup.com/ejcts/article/26/5/956/368357)

![Fig. 2. Change of blood vessel resistance before and after injection of each drug. (*p < 0.05, **p < 0.001).](https://academic.oup.com/ejcts/article/26/5/956/368357)
3.1.4. PDE III-I (group IV)

There were 19 male and 1 female patients between 48 and 88 years of age (mean 69.3 ± 9.6). PDE III-I treatment revealed a significant increase in LITA GFF (58.9%), from 36.0 ± 18.8 to 57.2 ± 18.3 ml/min (p < 0.0001), a significant decrease in MBP (−7.8%), from 69.3 ± 12.6 to 63.9 ± 11.7 mmHg (p < 0.05), and a significant decrease in R (−50.0%), from 2.6 ± 1.6 to 1.2 ± 0.5 mmHg min/ml (p < 0.001) (Figs. 1 and 2).

There was no significant difference in the mean age of each group. A comparison of the pre-injection data of GFF, MBP and R showed no significant difference among the four groups. Group IV significantly increased the change rate of GFF and significantly decreased the change rate of R compared with group I (GFF: p < 0.001, R: p < 0.0005) and group II (GFF: p < 0.01, R: p < 0.05). Group III significantly increased the change rate of GFF and significantly decreased the change rate of R compared with group I (p < 0.05). A comparison of the change rate of MBP showed no significant differences among the four groups.

We compared pathologically the diameter of LITA of one patient before and after injecting the PDEIII-I. After injecting the PDEIII-I the dilatation of the LITA was marked (Fig. 3).

Graft angiography was performed for all cases in the 1st month after surgery. All grafts in groups II and IV were patent. However, one graft in group III occluded.

4. Discussion

Thirty years or more have passed since the first CABG procedures, and the surgical technique and results are continually improving. SVG is manageable and has been used for many CABG cases [1]. As SVGs are often long and thick, it was thought that there would be adequate flow. However, sclerotic change seems to occur and long-term patency rates are not good [2–5]. The long-term patency of ITA graft is superior to SVG [2–5]. Loop and associates showed that patients who had only vein grafts had a 1.61 times greater risk of death throughout the 10 years, when compared with patients who received an ITA graft [2]. As well, patients who received only vein grafts had 1.41 times the risk of myocardial infarction, 2.00 times the risk of cardiac reoperation, as compared with patients who received ITA graft [2]. Thus, ITA graft has a high rate of long-term patency and that has become an indispensable arterial graft. Moreover, recently the necessity for artery graft, such as ITA, radial artery, inferior epigastric artery, and gastroepiploic artery, has been increasing [8]. If an arterial graft is compared to a vein graft, technical difficulty, vasospasm, and blood flow volume will pose a problem in the perioperative period. Several authors have suggested that spasm of the arterial graft can lead to perioperative hemodynamic disadvantage [6,7].

When using an arterial graft, various vasodilators are used and spasm is prevented to increase the amount of graft blood flow in the perioperative period. The quality of the LITA graft when vasodilators are used has been shown in other studies [9–14]. In case of only norepinephrine infusion cardiac output is increased, however, the risk of shrinking the LITA graft is high [9]. It is known from research that papaverine hydrochloride and ISDN are useful for LITA extension to increase blood flow. For this reason, they are used clinically [9–14].

The results of our study have shown that three kinds of vasodilators, papaverine hydrochloride, ISDN, and PDE III-I were used with saline as the control to LITA, and GFF of LITA increased. He and associates [16,19–21] showed that perioperative spasm of the ITA may be caused by potassium chloride(K+), thromboxane mimetic U46619, and so on. But vasodilators lowers the blood concentration of the constrictor agent and causes ITA relaxation [15–22]. Also in them, the arterial graft dilatation by PDE III-I is stronger than papaverine hydrochloride [23]. The results of our study have shown that PDE III-I made GFF of LITA increase most among all drugs used, and decreased R most.
The PDE III-I did not exhibit a significant difference to ISDN. However, it was thought that the PDE III-I was more useful than ISDN, because action time of the PDE III-I was longer than that of ISDN and the PDE III-I has positive inotropism. Although there are many experiments which show hemodynamic effects of the intravenous infusion of the PDE III-I [23–25], it is unknown whether PDE III-I is effective when it is injected directly into the ITA.

PDE III-I is found in vascular smooth muscle, and vasodilatation induced by this drug is likely mediated by increased availability of cyclic adenosine monophosphate (cAMP). The inotropic action of PDEIII-I has been attributed to inhibition of PDE III perpetuation of cAMP [18,24,25]. For this reason, it was thought that PDEIII-I acted on endothelium-independent and the LITA dilated. The results of this study are believed to result from the same effects which caused vasodilatation in vascular smooth muscles. In the future it would also be useful to examine the reaction of other grafts including radial artery to PDE III-I.

References