



Original Article

Use of nitroglycerin and verapamil solution by organ bath technique in preparation of left internal thoracic artery for coronary artery bypass surgery[☆]



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ABSTRACT

Background: The aim of this prospective study was to compare the effect of application of nitroglycerin and verapamil solution (GV) by organ bath technique with other methods of applications and solutions on the free blood flow of LITA. The technique was not described for in situ graft before.

Method: The patients were randomly assigned to four groups: group I (n_32, GV solution by organ bath technique), group II (n_30, papaverine solution by organ bath technique), group III (n_29, topical GV solution) or group IV (n_29, topical papaverine solution). In each patient, pedicled LITA was harvested; thereafter applied with the randomized different methods and solutions. The free flow from the distal end of the divided LITA was measured for 15 s under controlled hemodynamic conditions after harvesting (Flow 1). The flow of LITA was measured again just prior to anastomosing the conduit (Flow 2).

Result: The mean blood flow in LITA was 56.2 ± 5.0 ml/min before application of solutions. After application, the mean blood flow in group I: 102.3 ± 7.0 ml/min, in group II: 92.7 ± 3.4 ml/min, and in group III: 88.6 ± 2.2 ml/min and in group IV: 81.4 ± 2.1 . Proportional increases in blood flow observed in group I (82.6%) > group II (65.1%) > group III (57.6%) > group IV (44.8%) ($p < 0.05$).

Conclusions: GV solution by organ bath technique is effective and superior in comparison to use of papaverine using organ bath technique or topical spray of GV or papaverine solution.

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1. Introduction

Left internal thoracic artery (LITA) is the most widely used graft for anastomosis to left anterior descending artery (LAD), which is considered as gold standard in coronary artery bypass surgery (CABG).¹ ITA has anatomical features of a somatic artery and capable of undergoing severe spasm. It has been described in literature case reports that intractable spasm of ITA lead to transmural myocardial infarction and death.² Myocardial revascularization by CABG is a well-established surgical procedure and

yet spasm of conduits is still a debated issue by cardiac surgeons and pharmacologists. Actually, there is no a perfect vasodilator drug, because arterial spasm is often a multifactorial phenomenon modulated by different mechanism, such as mechanical stimuli, drugs, temperature, and endogenous catecholamine.⁵

In order to prevent LITA spasm, several vasodilatory agents, such as papaverine,^{7,13–15} calcium-channel blockers^{13,17} sodium nitroprusside,¹⁸ nitroglycerine,^{17,19} milrinone,^{19,20} and phenoxibenzamine,^{17,21} have been studied, compared, and used both topically and intraluminally to treat perioperative spasm of the arterial conduits. Papaverine is most commonly used agent,^{6,7} which initially was proposed to be injected intraluminally. Most surgeons use this agent topically due to known adverse effects of papaverine on endothelium because of acidic pH.^{14,22} Papaverine is the most commonly used agent for the prevention and treatment of conduit vasospasm. Glyceryl trinitrate or nitroglycerin- Verapamil (GV) solution has been an alternative to papaverine and has

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been used by cardiac surgeons mainly for radial artery but also for LITA as glyceryl-trinitrate has a rapid onset and verapamil has a longer duration of action than papaverine in causing relaxation of vascular smooth muscles.^{5,13,15,16}

Eleven randomized controlled trials and 2 multi-arm prospective cohort studies were found investigating the effects of topical, intraluminal and periarterial vasodilators.⁸ These studies compared mode of administration, concentration of the drug administered and the temperature of the drug administered. We did not come across any study describing the use of organ bath technique for the prevention of spasm of left internal thoracic artery before.

We have conducted a prospective randomized controlled trial to compare the effects of nitroglycerin & verapamil solution with papaverine by organ bath technique and also compared with topical spray of these agents on the free blood flow of left internal thoracic artery (LITA) prepared for coronary artery bypass grafting (CABG).

2. Materials & methods

2.1. Patient selection and data collection

The study consisted of 120 patients who underwent harvesting of LITA prepared for elective off pump CABG between August 2016 and December 2016 in Department of Cardiovascular & Thoracic Surgery, Lokmanya Tilak Municipal Medical College & Sion Hospital, and Mumbai, India. We routinely use off pump CABG. The surgery was done by a single surgeon. The surgeon was blinded for the vasodilating solutions. The study was approved by the local Ethics Research Committee and each patient included in the study gave a written consent.

All the patients were randomly assigned to one of the four groups: group I (n = 32), treatment with GV solution by organ bath technique; group II (n = 30), treatment with papaverine solution by organ bath technique; group III (n = 29), treatment with topical GV solution; group IV (n = 29), topical papaverine solution.

2.2. Surgical technique

All patients were anesthetized with standard general anesthesia using fentanyl and pancuronium. Continuous blood pressure monitoring via radial or femoral arterial lines, heart rate, and central venous pressure was constantly monitored. After median sternotomy, pedicled LITA was harvested from the subclavian vein to beyond LITA bifurcation by a single surgeon using low-power electrocautery. Major branches of LITA were ligated with hemoclips. LITA dissection time was recorded starting after opening the pleural space and tracing till the dissection was completed. The artery was divided distally following systemic administration of heparin.

After harvesting, the free flow from the distal divided end of the LITA was measured for 15 s in a heparin tinged open beaker under controlled hemodynamic conditions; free flow (ml) per minute was calculated accordingly (Flow 1). The measured blood was transfused back to the patient through central line. Afterward, following the randomization, LITA was treated with the appropriate solution and method.

The two solutions used in this study were: GV solution consisted of nitroglycerin 2.5 mg; verapamil 5 mg; 8.4% NaHCO₃, 0.2 ml; heparin, 500 units; and Ringer's lactate solution, 300 ml and the second solution was papaverine solution (1 mg/ml 0.9% normal saline). The two methods used for application of the solutions were: organ bath technique: the harvested graft was placed in a 20 cc syringe blocked with a tip cap containing either GV or papaverine solution. The syringe was placed in pleural cavity and the graft was allowed to dilate in solution bath (Fig. 1). The syringe was removed from the pleural cavity immediately prior to using it for anastomosis, topical method: The solution was sprayed onto the LITA pedicle throughout its whole length with 25 gauge needle attached to a syringe after harvesting. LITA pedicle was wrapped in the same topical solution-soaked gauze piece.

Just before the anastomosis, the flows of LITA were measured again (Flow 2). The flow rate before and after applications of solution were compared amongst all the groups and analyzed.

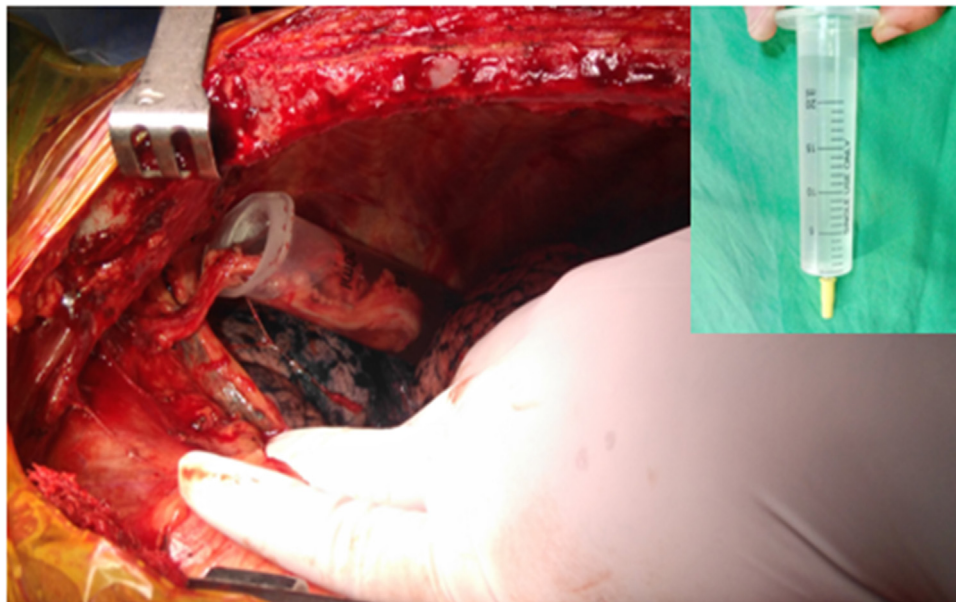


Fig. 1. LITA was placed in a 20 cc syringe with GV solution or papaverine and placed in the pleural cavity.

Table 1
Preoperative Data.

Variables	Group I (n = 32)	Group II (n = 30)	Group III (n = 29)	Group IV (n = 29)
Age	59.2 ± 10.3	60.1 ± 10.7	59.8 ± 9.0	60.3 ± 10.1
Sex (Male) n,%	23(71)	21(70)	20(68)	21(72)
Diabetes mellitus, n,%	22(68)	20(66)	20(68)	20(68)
Smoker, n,%	13(40)	11(36)	11(37)	10(34)
Hypertension	15(46)	13(43)	13(44)	14(48)
Dyslipidemia	21(65)	20(66)	20(68)	19(65)
BSA (m ²)	1.6 ± 0.15	1.7 ± 0.11	1.6 ± 0.13	1.6 ± 0.16
Ejection Fraction (%)	48.1 ± 13.3	49.3 ± 11.2	47.5 ± 13.1	48 ± 12.6

Table 2
Hemodynamic Data.

Variables	Group I	Group II	Group III	Group IV
HR 1	70.3 ± 10.2	69.1 ± 10.3	70.4 ± 10	70.3 ± 10.1
HR 2	70.5 ± 10.2	69.3 ± 10.3	71.1 ± 10.1	70.3 ± 10.2
MAP 1	71.8 ± 8.3	70.4 ± 9.1	70.9 ± 10.2	72 ± 8.5
MAP2	71.8 ± 8.3	70.8 ± 9.0	71.0 ± 9.8	72.1 ± 8.2
Time (min)	24.3 ± 6.1	25.5 ± 6.0	24.7 ± 5.8	24.4 ± 6.5
Time ^e	10.1 ± 1.8	9.8 ± 2.1	10.3 ± 1.4	10.0 ± 1.5

Data are presented as mean ± standard deviation of the mean. There were no statistically significant differences between the groups.

HR: heart rate.

MAP: mean arterial pressure.

Time: dissection time of left internal thoracic artery.

Time^e: interval between flow 1 and flow 2.

2.3. Statistical analysis

Patients were randomly assigned to four groups applying the method of block randomization. Statistical analyses were performed using the SPSS software package (SPSS for Windows, version 6.1; SPSS Inc, Chicago, IL, USA). Continuous variables are reported as mean ± standard deviation and compared using independent samples *t*-tests. Categorical variables were reported as frequency and percentage of total group and compared using Pearson's chi-squared test or Fisher's Exact test where applicable. A *p* value of less than 0.05 was considered to be statistically significant.

3. Result

The demographic and clinical profiles of the patients are shown in Table 1. There were no significant differences between the groups with respect to variables (*p* > 0.05). The time taken for LITA harvesting (Time^d) and the time interval between the flow 1 and flow 2 or time of exposure (Time^e) as shown in Table 2 were not significantly different among the four groups. The average time of exposure for in situ LITA graft in organ bath technique was 10 min. Heart rates (HR1 & HR2), mean arterial pressure (MAP1 & MAP2) at

Table 3
Flow rates obtained before and after application of solutions.

Measurement	Group I	Group II	Group III	Group IV
Flow 1 (ml/min)	56.1 ± 4.6	55.6 ± 5.1	56.3 ± 4.4	57.0 ± 4.1
Flow 2 (ml/min)	102.3 ± 7.0	92.7 ± 3.4	88.6 ± 2.2	81.4 ± 2.1

Data are presented as mean ± standard deviation of the mean.

Flow 1: flow before use of solution.

Flow 2: flow after use of solution.

the time of flow measurement were not significantly different between the groups as shown in Table 2.

The free flow (ml/min) of LITA before the application of solution i.e. flow1 as shown in Table 3 were not significantly different among the groups. The mean blood flow in LITA was 56.2 ± 5.0 ml/min before application of solutions. After application, the mean blood flow in group I: 102.3 ± 7.0 ml/min, in group II: 92.7 ± 3.4 ml/min, and in group III: 88.6 ± 2.2 ml/min, and in group IV: 81.4 ± 2.1. Proportional increases in blood flow observed in group I (82.6%) > group II (65.1%) > group III (57.6%) > group IV (44.8%) as shown in bars diagram (Fig. 2). When each solution was used topically, flow rate (flow2) was higher in group III as compared to group IV i.e. GV solution vs. papaverine solution but there was no statistically significant difference among groups, (*p* 0.17). When each solution was used by organ bath technique, a significant difference was observed among groups. The flow 2 in group I and in group II was significantly higher than flow in group III and group IV (*p* 0.01), whereas flow2 in group I was higher than flow2 in group II, but they did not reach statistical significance (*P* 0.13). There were no intra-op ischemic events in any patients. There was no in-hospital mortality.

4. Discussion

ITA spasm is a complication that many preclude use of graft intraoperatively and has the potential to cause myocardial ischemia or infarction postoperatively when spasm develops in peri-operative period.^{3,4} ITA, however, is susceptible to vasospasm during and after mobilization, which is a common arterial response to low blood flow and operative handling.^{2,7}

There are more than hundred reports in literature dedicated to pharmacological prevention of ITA spasm.⁹ However until now there is no consensus regarding drug, its dosage and route of administration. The question remains unanswered though whether prevention is required in general.¹⁰ There are no previous studies describing the organ bath technique as a method of application for prevention of intraoperative ITA spasm and its comparison with other methods. The organ bath technique is mainly used for preventing radial artery spasm as described in previous studies.^{11,12}

Green introduced papaverine to cardiac surgery in 1971.⁷ Since then, many cardiac surgeons have used this drug to treat the spasm both of ITA and vein grafts.⁹ This vasodilator can be used topically and intraluminally, but its solution is acid (pH 4.4–4.8)¹³ when used in surgery. Acid solutions can cause damage to endothelium.^{14,15} Due to this deleterious effect of papaverine, many cardiac surgeons were using other antispasmodic agents as an alternative to papaverine. The valid alternative to papaverine is GV solution as it has a pH of 7.4, because of NaHCO₃ in the mixture. Second, the GV solution is suitable for all arterial

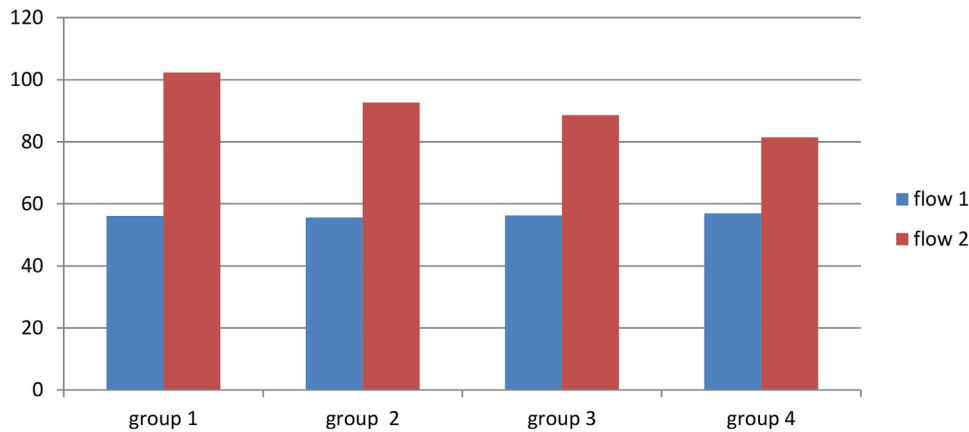


Fig. 2. Comparison between the flow (ml/min) before and after use of solutions in group I, II, III, IV respectively.

conduits and third, that should prevent spasm conduit in the early postoperative hours.^{12,13,15,16}

The results of our study show the difference of two vasodilators in terms of type of solution and route of administration. We never used the vasodilatory solution via intraluminal method due to its deleterious effect on LITA. Nitroglycerin has a more rapid onset and verapamil has a longer action than papaverine, we are encouraged to continue to use the GV solution. As previously described, mechanical spasm during ITA harvesting represents one of the most important constrictor stimuli. In accordance with our results, we have shown that when the antispasmodic agent is topically delivered there is not any significant difference among the two groups i.e. group III & group IV. On the other hand, when the vasodilator agent was administered by organ bath technique, we observed a dramatic increase of free flow in both the group I (GV solution by organ bath technique) and the group II (Papaverine solution by organ bath technique). The blood vessel resistance after organ bath technique had a significant reduction in the groups treated with the antispasmodic agents. The major reason that could explain the low ITA flow, after topical application of vasodilator, is LITA harvesting with its own pedicle (about 2 cm wide). Probably, both papaverine and GV solution did not work as topical vasodilators in the presence of a thick tissue around LITA and no uniform exposure to the solution. We routinely harvest LITA with its pedicle in our institution, and we have never tried to compare the flow with skeletonized LITA.²³ Using organ bath technique, LITA is uniformly exposed to the vasodilator solution throughout the exposure time. Based on our results, papaverine and GV solutions could be used to treat LITA spasm, effectively by organ bath technique. The method of delivery is easy and also low cost compare to papaverine solution.

5. Limitations of the study

Our study has few limitations. The study cohort was small. The pedicled LITA was harvested in the entire patients. So skeletonized LITA was not included and compared. We used a system to check the free blood flow in an open beaker in 15 s and flow per minute was calculated accordingly. By using more sophisticated systems like transit time Doppler flow-evaluation, better measurements could possibly be obtained. The study cohort was small. We did not compare the ITA flow to the postoperative patency of LITA using post-operative coronary angiograms.

6. Conclusion

In conclusion, GV solution used as an organ bath technique for LITA preparation may provide better flow when compared to papaverine solution and both the solutions provide superior LITA flow when used in a syringe bath as compared to topical spray when the conduit is harvested as a pedicle.

Disclaimers

None declared.

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References

1. Tector AJ, Schmahl TM, Canino VR. The internal mammary artery graft: the best choice for bypass of the diseased left anterior descending coronary artery. *Circulation*. 1983;68:II214–217.
2. Stone GW, Hartzler GO. Spontaneous reversible spasm in an internal mammary artery graft causing acute myocardial infarction. *Am J Cardiol*. 1989;64:822–823.
3. Sarabu MR, McClung JA, Fass A, Reed GE. Early postoperative spasm in left internal mammary artery bypass grafts. *Ann Thorac Surg*. 1987;44:199–200.
4. Kong B, Kopelman H, Segal BL, Iskandrian AS. Angiographic demonstration of spasm in a left internal mammary artery used as a bypass to the left anterior descending coronary artery. *Am J Cardiol*. 1988;61:1363.
5. Formica Francesco, Ferro Orazio, Brustia Matteo, 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.
6. Mills NL, Ochsner JL. Preparations of internal mammary arteries for coronary bypass with intraluminal papaverine. *J Cardiovasc Surg (Torino)*. 1975;16:632–633.
7. Green GE. Rate of blood flow from the internal mammary artery. *Surgery*. 1971;70:809–813.
8. Sivalingam Sivakumar, Levine Adrian, Dunning Joel. What is the optimal vasodilator for preventing spasm in the left internal mammary artery during coronary arterial bypass grafting? *Interact Cardiovasc Thorac Surg*. 2005;4:365–371.
9. Ziadinov E, Al-Kemyani N, Al-Sabti H. Management of internal mammary artery spasm. *J Cardiol Clin Res*. 2014;2(2):1028.
10. 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. *Eur J Cardiothorac Surg*. 1999;16:560–563.
11. Arif Tarhan Ibrahim, Kehlibar Tamer, Arslan Yucetin, et al. Effects of normothermic organ bath and verapamil–nitroglycerin solution alone or in combination on the blood flow of radial artery. *Eur J Cardiothorac Surg*. 2007;32:617–622.

12. He Guo-Wei. Verapamil plus nitroglycerin solution maximally preserves endothelial function of the radial artery: comparison with papaverine solution. *J Thorac Cardiovasc Surg.* 1998;115(June (6)):1321–1327.
13. He GW, Buxton B, Rosenfeldt F, Angus JA, Tatoulis J. Pharmacological dilatation of the internal thoracic artery during coronary artery bypass surgery. *J Thorac Cardiovasc Surg.* 1994;107:1440–1444.
14. Mayranpaa M, Simpanen J, Hess MW, Werkalla K, Kovanen PT. Arterial endothelial denudation by intraluminal use of papaverine-NaCl solution in coronary bypass surgery. *Eur J Cardiothorac Surg.* 2004;25:560–566.
15. Rosenfeldt FL, He GW, Buxton B, Angus JA. Pharmacology of coronary artery bypass. *Ann Thorac Surg.* 1999;67:878–888.
16. He GW, Yang CQ. Use of verapamil and nitroglycerin solution in preparation of radial artery for coronary grafting. *Ann Thorac Surg.* 1996;61:610–614.
17. Mussa S, Guzik TJ, Black E, Dip MA, Cannon KM, Taggart DP. Comparative efficacies and durations of action of phenoxybenzamine, verapamil/nitroglycerin solution, and papaverine as topical antispasmodics for radial coronary bypass grafting. *J Thorac Cardiovasc Surg.* 2003;126:1798–1805.
18. Sassoon L, Cohen AJ, Hauptman E, Schanchner A. Effect of topical vasodilators on internal mammary arteries. *Ann Thorac Surg.* 1995;59:494–496.
19. Zabeeda D, Medalion B, Jakobshvilli S, Ezra S, Schachner A, Cohen AJ. Comparison of systemic vasodilators: effects on flow in internal mammary and radial arteries. *Ann Thorac Surg.* 2001;71:138–141.
20. Lobato E, Janelle GM, Urdaneta F, Martin TD. Comparison of milrinone versus nitroglycerin, alone and in combination, on grafted internal mammary artery flow after cardiopulmonary bypass: effect of alpha-adrenergic stimulation. *J Cardiothorac Vasc Anesth.* 2001;15:723–727.
21. Dipp MA, Nye PCG, Taggart DP. Phenoxybenzamine is more effective and less harmful than papaverine in the prevention of radial artery vasospasm. *Eur J Cardiothorac Surg.* 2001;19:482–486.
22. Gao YJ, Stead S, Lee RMKW. Papaverine induces apoptosis in vascular endothelial and smooth muscle cells. *Life Sci.* 2002;70:2675–2685.
23. Türk Tamer, Tiryakioglu Osman, Vural Ahmet Hakan, Ata Yusuf, Selimoglu Özer, Yavuz Senol. Effect of skeletonization on flow and length of internal thoracic artery. *Turkish J Thorac Cardiovasc Surg.* 2005;13:112–114.