# Comparison of the Pretreatment Effects of Mixed Vasodilators (3-D Solution) on Radial and Internal Thoracic Arteries by Using a 3-Dimensional Anaglyph Electron Microscope Technique



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# ABSTRACT

**Objective.** Currently, internal thoracic arteries (ITA) and radial arteries (RA) are the first choice of conduits for coronary artery bypass grafts (CABG). Because the perioperative vasospasm continues to be a major problem, a number of pharmacologic agents such as papaverine, calcium receptor blockers, nitroglycerine, and phenoxybenzamine have been suggested as topical antispasmodics that may be used in the pre- and postoperative periods. In the present study, we investigated the quantitative efficacies of the mixed solution, which included verapamil, nitroglycerin, and papaverine, on RA and ITA using a scanning electron microscope with a 3-dimensional anaglyph technique.

**Methods.** Diameter changes of RA and ITA in response to clinically important vasodilators were measured on 40 RA and 40 ITA rings from patients who had been subjected to coronary artery bypass procedure after 20 minutes of ex vivo incubation with verapamil (45  $\mu$ g/L), nitroglycerin (45  $\mu$ g/L), papaverine solution (266  $\mu$ mol/L or 0.1  $\mu$ g/mL), and 30 mL autologous heparinized whole blood (individual patient's blood obtained before cardiopulmonary bypass contained100 IU of heparin per kg of patient weight). The pretreatment action was assessed by measuring the response to vasodilators.

**Results.** In all cases, we did not observe graft vasospasm in any of the conduits during the intraoperative period between postanastomosis and sternal closure. In the postoperative period, we did not record any evidence of ischemic change in patients' electrocardiographic and myocardial enzyme analyses. None of the cases required inotropic support after the operation. The diameters of the pretreated RA and ITA were: minimum, 2.1 mm; maximum, 4.0 mm; and mean value,  $2.80 \pm 0.46$  mm. The diameters of the pretreated ITA were: minimum, 1.2 mm; maximum, 2.5 mm; and mean value,  $1.76 \pm 0.35$  mm. Incubated arterial segment diameters for the RA were: minimum, 2.8 mm; maximum, 5.2 mm; and mean value,  $3.95 \pm 0.65$  mm. These values for the ITA were: minimum, 1.5 mm; maximum, 3.9 mm; and mean value, 2.37  $\pm$  0.50 mm. These findings were statistically significant for both arterial grafts (*P* <.05).

**Conclusions.** According to our study findings, the mixed solution demonstrates a broad range of efficacy. We conclude that the described vasodilator solution with heparinized autologous blood seems to be very effective and may be used as a pretreatment agent in CABG conduits. Although papaverine has the shortest duration of action, its efficiency is increased by verapamil and nitroglycerin, in our opinion. To the best of our knowledge, high-quality imaging of CABG conduits with the 3-D anaglyph technique using a scanning electron microscope was a first in the literature. This technical approach may be used for confirming the ultrastructural anatomy and the quantitative vasodilator effects of arterial conduits. We believe that valuable anatomo-pathologic details of the CABG conduit can be obtained by this technique.

#### INTRODUCTION

Since the reintroduction of the radial artery (RA) as an arterial bypass conduit in coronary artery bypass grafting (CABG) by Acar et al [1992], it has been increasingly used in a number of centers. The improved results were achieved by careful harvesting and the use of calcium channel blockers to prevent graft vasospasm. Despite surgical practice and antivasoconstrictors, a 4% incidence of vasospasm is still reported in RA grafts, which therefore represents an important and unresolved problem [He 1997]. Histologic investigation has shown that the RA is a class muscular artery with a greater propensity for vasospasm [van Son 1990]. Surgical damage during graft harvesting and preparation can adversely effect endothelial function, which may result in graft vasoconstriction and finally lead to early graft failure. Until now, no optimal solution has been described. We therefore investigated the effect of mixed storage solutions that included verapamil (Abbott Laboratories, Abbott Park, IL, USA), papaverine (Sigma, St. Louis, MO, USA), and nitroglycerine (Schwarz Pharma, Monheim, Germany) in heparinized 30 cc of autologous blood within terms of human RA and internal thoracic artery (ITA) diameter in CABG patients.

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Table 1.	Clinical	Profile	of the	Overall	Patients	(n =	= 40)	)
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Age, y	59 ± 3
Male, %	65
Diabetes mellitus, %	35
Hypertension, %	63
Smoking history, %	64
Hypercholesterolemia, %	75
Beta-blocker usage, %	100
Aspirin usage, %	100

# METHODS

RA (n = 40) and ITA (n = 40) specimens were obtained after receiving informed consent from 40 patients undergoing CABG. Patient demographic characteristics, risk factors for atherosclerosis, and preoperative medications are shown in Table 1. A total of 40 RA and 40 ITA segments were carefully dissected free of their adnexae and cut into vascular rings from the distal end of the arterial grafts, each measuring 2 mm in length, to be included in the control group. During the operation, the ITA was treated by injection of the mixed solution, and tepid rinsing solution was sprayed during the anastomosis. The RA was harvested with the accompanying venae comitantes and intact connective tissue, and a 0.5 cm to 1 cm segment was obtained from the distal end and placed immediately in a mixed vasodilator solution that included verapamil (45  $\mu$ g/L), nitroglycerin solution (45 µg/L), papaverine (266 µmol/L or 0.1 mg/mL), and 30 mL autologous heparinized whole blood (this solution was named the 3-D vasodilator solution, after the initials of Dr. Dogan, Dr. Demircin, and Dr. Duman). Individual blood samples containing 100 IU of heparin were obtained from each patient before cardiopulmonary bypass (CPB). The specimen was fixed in 2.5% glutaraldehyde for 24 hours, washed in phosphate buffer (pH: 7.4), postfixed in 1% osmium tetroxide in phosphate buffer (pH: 7.4), and dehydrated in increasing concentrations of alcohol. After dehydration, the specimens underwent drying to a critical point and were mounted on metal stubs with double-sided adhesive tape. Then the samples were sputtered with 150-Å thick layer of gold in a Bio-Rad sputter apparatus (Munich, Germany). The images were taken as stereopairs by a Jeol SEM ASID-10 electron microscope (Tokyo, Japan). The measurement of each arterial diameter was obtained by "ImageJ 1.32," a software program developed by the National Library. The studies of arterial diameter were performed by mounting vascular rings on stainless steel hooks in a warm 50 mL mixed solution chamber (37°C). A total of 80 vessel rings, 40 RA and 40 ITA, were rinsed in the described solution for 20 minutes and then transferred to the electron microscope laboratory in a glutaraldehyde solution as we have described. All vasodilator responses were measured under scanning electron microscope (SEM) (Figures 1 and 2) and the high-quality images were provided by the 3-D anaglyph technique (Figures 3 and 4). The mixed solution consisted of verapamil, nitroglycerine (30 µmol/L), and papaverine (266 µmol/L). The remaining arterial rings (40 RA and 40 ITA) were left untreated to be included in the control.



Figure 1. Scanning electron microscope images of the radial artery.

## Statistical Analysis

Vasodilator responses were expressed as a percentage of the initial response in individual rings. Data are shown as mean  $\pm$  standard deviation. Dose-response diameters were compared with control values by means of a SEM examination. For investigation of statistical significance, a paired sample Student *t* test was used. Also, to compare the arterial responses to the vasodilator solution correlation analyses were used. The arterial diameter increments were compared by percentages. P <.05 was accepted as statistically significant.

#### RESULTS

#### Efficacy of Vasodilator Activity

All patients weaned from CPB uneventfully. CPB and aortic cross-clamping times were not significant. Patients' electrocardiographies were normal. There were no electro-



Figure 2. Scanning electron microscope images of the internal thoracic artery. E indicates endothelial layer; L, lumen; A, adventitia.



Figure 3. 3-D anaglyph image of the internal thoracic artery treated with the solution. Two sections were prepared after slicing the rings horizontally. This image should be viewed with anaglyph glasses for at least 30 to 45 sec.

cardiographic postoperative changes such as a new Q wave and/or ST elevation. No patient required positive inotropic support after weaning from CPB or in the intensive care unit (ICU). In ICU, all patients weaned from respirator in the first day after the operation. In the ICU and clinical follow-up, we did not see any change in a patient's elecrocardiography with 12 leads, and ventricular arrhytmias or high levels of myocardial enzymes were not detected postoperatively. We therefore assessed that graft vasospasm did not occur in our cases. There was no evidence of peri- or postoperative myocardial infarction, and there was no extended hospitalization in the ICU postoperatively. Because angiography is a very invasive procedure, especially in the early postoperative period, we did not perform coronary angiography in our cases.

The response to vasodilator effect was measured serially in each ring. Pretreated RA ring diameters were: minimum, 2.1 mm; maximum, 4.0 mm; and mean value ( $\pm$  standard deviation), 2.8  $\pm$  0.6 mm. Posttreated RA ring diameters were: minimum, 2.9 mm; maximum, 5.1 mm; and mean value, 3.95  $\pm$  06. The pre- and posttreated arterial rings are



Figure 4. 3-D anaglyph image of the radial artery treated with the solution. Two sections were prepared after slicing the rings horizon-tally. This image should be viewed with anaglyph glasses for at least 30 to 45 sec.

summarized in Table 2. During calculation of the caliber of RA grafts, it was seen that the mean pretreated RA diameter was 4.34 mm<sup>2</sup>, whereas posttreated RA diameter was 6.20 mm<sup>2</sup>. When we compared pre- and posttreated RA diameter size it was statistically significant (2-tailed test: P < .05).

Pretreated ITA diameters were: minimum, 1.1 mm; maximum, 2.5 mm; and mean value,  $1.75 \pm 02$  mm. Posttreated ITA diameters were: minimum, 1.6 mm; maximum, 3.9 mm; and mean value (± standard deviation),  $2.37 \pm 0.4$  mm (Table 2). These results were statistically significant (2-tailed test: P < .05). The calculation of ITA diameters were 2.74 mm<sup>2</sup> and 3.72 mm<sup>2</sup> for the pre- and posttreated periods, respectively. This level was significant.

We also evaluated the increment percentage of arterial grafts. Increment percentages of the arterial diameters are presented in Table 3 and Figure 5. Whereas in 12 cases the increment of the RA diameter was between 0% to 25%, in 13 cases this level was between 26% to 50%. In 10 cases, this increment value was between 51% to 75%. In the remaining 5 cases, the increment of RA diameter was between 76% to 100%. For ITA, the increment level was between 0% to 25%

	Radial Arteries with	Radial Arteries with	Internal Thoracic Arteries with	Internal Thoracic Arteries with
Patients	Pretreatment	Posttreatment	Pretreatment	Posttreatment
1	2.1	4.2	1.2	1.6
2	2.2	3.3	1.1	1.5
3	2.4	3.9	1.5	2
4	1.9	3.5	2	3.1
5	2.5	5	2.1	2.2
6	2.2	2.9	1.9	2.1
7	2.1	2.8	1.6	1.7
8	2.7	3.6	1.5	1.9
9	3.1	4	1.1	1.6
10	2.8	3.7	1.8	1.9
11	2.7	4.3	1.6	2.3
12	2.4	4.6	1.8	2.2
13	2.9	3.6	1.3	2
14	2.8	3.5	1.5	2.1
15	2.4	3.1	1.7	1.9
16	2.2	2.9	1.9	2.1
17	2.1	4.2	1.8	2.7
18	2.3	4	1.5	2.1
19	3.1	4.9	1.6	2.6
20	3.2	4.9	1.4	2.8
21	2.9	4.7	1.9	2.7
22	2.5	3.9	2.1	2.6
23	3.2	3.5	2	3.1
24	3.3	3.9	2.3	3.9
25	4	4.7	2.5	3.5
26	3.5	3.8	2.1	2.4
27	3.2	3.5	2	2.6
28	3.1	3.9	2.4	2.9
29	2.9	4.7	1.9	2
30	3.1	5.2	1.8	2.2
31	3.3	4.9	1.7	1.9
32	2.9	3.9	1.5	1.8
33	3.2	3.8	1.4	1.6
34	2.9	3.5	1.3	2.7
35	3	3.6	1.9	3
36	3.3	3.7	2.1	2.9
37	2.8	2.9	2.3	2.9
38	2.6	3.7	2.1	3.1
39	3.1	4.8	1.5	2.4
40	3.4	4.5	1.6	2.5

Table 2. Radial and Internal Thoracic Artery Rings with Pretreatment and Posttreatment

in 15 cases. Also, in 15 cases the increment percentage was calculated between 26% to 50%, and in 8 cases it was measured between 51% to 75%. In addition, this level was observed as 100% in the remaining 2 patients. Overall, 25 cases (10 ITA and 15 RA rings) manifested an increment of arterial ring diameter more than 50% when compared to pretreated ring diameters. In comparison, the increment percentage was 100% in 7 cases (5 RA and 2 ITA) (see Figure 5).

According to our results, the mixed solution significantly increased the diameter of both graft rings. T-test results for RA were  $2.8075 \pm 0.468$  and  $3.9500 \pm 0.643$ . The correlation analysis result for RA was 0.396. T-test results for ITA were

1.7575  $\pm$  0.3500 and 2.3775  $\pm$  0.557. The correlation for ITA was 0.711. These values were statistically significant (P < .05). Thus, incubation of vessel rings with mixed solution significantly increased the vessels' ring diameters in both arteries. These findings suggest that the defined solution has a specific property for vessel dilatation. Figure 6 and Figure 7 show the arterial vasodilatation due to storage solution. When the vessel ring area was calculated, we thought that this solution had provided a significantly effective area in both arterial grafts. The calculated ITA diameters were 2.74 mm<sup>2</sup> and 3.72 mm<sup>2</sup> for the pre- and posttreated period, respectively. This level was also significant (P < .05).

D		Dedial			- I Th
Grafts as	Percentages				
Table 3.	The Diameter	Increment	of the	Treated	Arterial

Percentage,	Radial	Internal Thoracio		
%	Artery, n	Artery, n		
0-25	12	15		
26-50	13	15		
51-75	10	8		
76-100	5	2		

In addition, ultrastructural analyses showed that there were no atherosclerotic changes in RA and ITA. Both transmission electron microscope and SEM demonstrated a normal intimal and medial layer in all arterial rings. There was no evidence of intimal and medial thickening and/or intimal deposits. In all arterial lumens, a smooth and regular cellular formation was seen.

## DISCUSSION

As we know, in most of the cases undergoing CABG, 3 or more grafts are used. Thus, the RA has become the conduit of choice for the third arterial graft because it can be harvested easily and safely and reaches most of the coronary target comfortably. Moreover, it can be used as free or composite grafts [Reyes 1995]. However, for both grafts of ITA and RA, vasospasm continues to be a major problem in the perioperative and/or postoperative period [Chester 1972]. The RA is a thick-walled, predominantly muscular artery with a



Figure 5. The increment of vessel rings for the internal thoracic artery and the radial artery in percentages. Both arterial graft diameters were significantly increased. In total, 10 internal thoracic artery and 15 radial artery ring diameter increments were more than 50%. In 7 cases, the increment percent was 100%.

mean medial width of 500  $\mu$ m, compared with 300  $\mu$ m for the more elastic ITA [van Son 1990], and it has also a greater contractility than the ITA [Chardigny 1993; Chester 1998]. Many studies have demonstrated that substances such as postoperative norepinephrine cause severe vasoconstriction in RA and ITA [Taylor 1979; Minami 1990]. In addition, the



#### Radial Artery Treated

Figure 6. The comparison of untreated and treated radial artery graft diameters. Pretreated radial artery ring diameter calculations were: minimum, 2.1 mm; maximum, 4.0 mm; and mean value,  $2.8 \pm 0.6$  mm. The diameters with posttreatment were calculated as: minimum, 2.9 mm; maximum, 5.1 mm; and mean value,  $3.95 \pm 0.6$  mm. Horizontal and vertical lines symbolize the number of radial arterial rings and arterial diameters, respectively. In 3 cases (horizontal lines), ring diameters were increased to 2.9 mm. In 5 cases, the increase was to 3.5 mm. Based on these measurements, the mixed dilator agent seems to be significantly effective.



Figure 7. The comparison of internal thoracic artery (ITA) diameters with pretreatment and posttreatment. Pretreated ITA ring diameters were as follows: minimum, 1.1 mm; maximum, 2.5 mm; and mean value,  $1.75 \pm 02$  mm. ITA diameters with posttreatment were as follows: minimum, 1.6; maximum, 3.9; and mean value (± standard deviation),  $2.37 \pm 0.4$  mm. The 2-tailed test was statistically significant (*P* < 0.05). Horizontal and vertical lines symbolize the number of ITA rings and those rings' diameters, respectively. In 3 cases (horizontal lines), ring diameters were increased to 1.60 mm. In 4 cases, the increase was to 1.9 mm. Based on our findings, the mixed dilator agent was determined to be significantly effective for the ITA graft, as well as the radial artery.

authors have proposed that arterial spasm is not solely a function of the muscular wall but that an enhanced reactivity for vasoactive mediators is of key importance as well [Chardigny 1993]. As a result, several topical and systemic pharmacologic agents have been used to reduce the spasm of the arterial bypass conduits. Ideally, antispasmodic preparations should prevent vasoconstriction in response to relevant contractile stimuli for a prolonged postoperative period without damaging the arterial endothelial cells while avoiding any major systemic hemodynamic effect. To prevent vasospasm, certain topical agents are used because they are cost effective, are easily administered during surgery, and do not have a systemic hemodynamic effect. However, because repeated topical application is not possible after surgery, its duration of action is a main problem in many vasodilators. Papaverine [He 1993], verapamil, nitroglycerin solution [He 1994], and phenoxybenzamine are clinically used as topical arterial antispasmodics [Dipp 2001; Harrison 2001; Velez 2001]. Although a verapamil and nitroglycerin combined solution has been used in preparation of the RA for coronary grafting by He et al [Dipp 2001], to date, the cumulative effects of the mixed vasodilator agents (constituted of 3 vasodilators), have not been investigated. To the best of our knowledge, the calculation and comparison of arterial diameter by 3-D anaglyph techniques (DAC technique; Dogan-Aldur-Celik) following the pretreatment of arterial conduits has not been reported in the literature yet. Many factors in open heart surgery affect the postoperative vasoconstrictor response. CPB and surgical stress cause elevations in plasma levels of epinephrine, and those elevations remain at least for 1 day after surgery [Minami 1990]. In addition, epinephrine or

arterial antinet solution introglycerine solution applied to RA rings preconstricted by potassium chloride [He 1996] and reported that its effect persisted for at least 24 hours in RA segments stored for 24 hours at 4°C. Our study confirms that additional papaverine solution may be of more additive effect in these operations. We did not investigate the arterial ring segment response against vasocontrictors, but we decided that the vasodilator effect of this solution against vasocontrictors such as adrenaline, thromboxane, and/or angiotensine should be investigated in

the near future.

On the other hand, longer exposure to vasodilators is often impractical in the operating room. Pretreatment of bypass grafts for 45 minutes has been recommended by He et al, however, in the present study, results showed that 20-minute arterial segment exposure to the mixed vasodilator agent is enough.

norepinephrine infusion may be used in a state of low cardiac

output, further increasing the circulating levels of this vaso-

constrictor. Previous investigations have also shown that

angiotensin II levels, a strong vasoconstrictor agent, are increased after CPB [Taylor 1979]. Although the plasma lev-

els of dopamine are not consistently elevated after CPB, the

agent may be administered intravenously as a pressor follow-

ing CABG surgery. The conduit vasospasm resulting from

over-excreation of these vasoconstrictors may be seen after

CABG surgery. Thus, surgeons should prevent the arterial

glycerine (a nitric oxide donor with a short half-life) was

first suggested by He et al [He 1993; Dipp 2001] for saphenous

vein and ITA conduit preparation. The authors subsequently

demonstrated vasodilatation in response to verapamile-

Vasodilator solution, a mixture of verapamil and nitro-

vasoconstrictor effect in the pre- and postoperative period.

In recent years there has been considerable interest in the use of phenoxybenzamine as a topical antispasmodic for RA conduit preparation. It is a nonselective  $\alpha$ -adrenoceptor antagonist with a long duration of action. Taggart et al initially reported the efficacy of phenoxybenzamine versus epinephrine-mediated vasoconstriction in the RA [Taggart 2000]. In another study, the efficacy of phenoxybenzamine in preventing norepinephrine-mediated vasoconstriction has been clearly demonstrated by Harrison et al [2001]. Recent contributions to the literature suggest reductions in terms of dose and treatment period and indicate the ex vivo phenoxybenzamine duration of action in preventing catecholamine-mediated vasoconstriction as varying between 18 to 48 hours.

#### Study Limitations

The main limitation of our study is that the in vitro vasoconstrictor response of the arterial grafts and the time of mixed solution's vasodilatator effect have not been investigated.

## CONCLUSION

The following are the most important findings in this study. To provide a larger luminal area on arterial grafts during anastomosis, a mixed vasodilator solution should be kept in mind for preventing vasoconstriction. We suggest that the mixed vasodilator drug may be used safely, easily, and effectively in CABG cases. For the first time, we presented the details of vascular anatomy and compared the effects of vasodilator solution in CABG conduits using a 3-D electron microscopeic examination.

The etiology of coronary bypass arterial conduit vasospasm is likely to be multifactorial, resulting from a combination of surgical injury during the graft harvesting, exposure to circulating internal vasoactive mediators during the operation, and preexisting endothelial and medial smooth muscle dysfunction in those with vascular disease. None of the topical antispasmodic agents solely match all the necessary criteria for preventing the arterial graft vasospasm in clinical practice. In light of the findings of the present study, the mixed solution seems to be substantially effective against a broad range of vasoconstrictors, but we have no information about the duration of action limits. Its prolonged duration of action makes it a useful agent in the immediate postoperative period following CABG. In our opinion, papaverine, which solely exhibits the shortest duration of action and limited efficacy against relevant vasoconstrictors, is not a useful topical antispasmodic as a single vasodilator. A combination of different vasodilators may be more suitable to inhibit the vasospasm and may reduce the likelihood of early graft failure. The nature of more vasodilator characteristics of RA and ITA support the need for a more active synergist pharmacological intervention to relieve spasm following the CABG operation. In addition, highquality images of the CABG conduit using a 3-D anaglyph technique was employed in this study. This technical approach may present a certain advantage for confirming the ultrastructural anatomy of CABG conduits.

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