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Effects of Pretreatment with Different Topical Vasodilators on Blood Flow in the Internal Mammary Artery: A Prospective Randomized Study

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ABSTRACT

Background. This study was conducted to investigate how brief pretreatments with 4 different vasodilators applied topically at normal body temperature affect blood flow in the internal mammary artery.

Methods. One hundred patients who had an internal mammary artery mobilized as a pedicle for coronary artery bypass grafting were randomly assigned to one of 5 groups of equal size (20 subjects in each). Each group of pedicles was treated with a different topical solution: normal saline (control), nitroglycerin, diltiazem, papaverine, or adenosine. Internal mammary artery flow and hemodynamic measurements were recorded immediately after harvesting and after 5 minutes of immersion in a tube filled with test solution (50 mL at 37°C). Results for each study variable were compared within and between groups, and posttreatment-to-pretreatment ratios were also calculated and compared.

Results. All 4 vasodilator groups showed a significant increase in internal mammary artery flow rate from pretreatment to posttreatment, whereas the saline group did not. There were no significant differences among the 5 groups' pretreatment flow rates ($P = .526$) or posttreatment flow rates ($P = .194$). The mean ratio values (posttreatment-to-pretreatment) for flow rate were 1.08 ± 0.17 in the saline group, 1.74 ± 0.17 with nitroglycerin, 1.77 ± 0.49 with diltiazem, 1.82 ± 0.59 with papaverine, and 1.57 ± 0.54 with adenosine. Post hoc analysis revealed that the mean ratio values for flow rate in the 4 vasodilator groups were significantly higher than the corresponding ratio in the saline group.

Conclusions. Brief treatment of the internal mammary artery with topical vasodilators at normal body temperature significantly increases blood flow in this vessel. The data from this study are particularly valuable in relation to off-pump surgery, in which this vessel is usually anastomosed soon after it is harvested.

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INTRODUCTION

Today, the internal mammary artery (IMA) is the conduit of choice for coronary artery bypass grafting (CABG). Extensive research has revealed that IMA grafts yield longer patency and longer survival time than saphenous grafts [Lytle 1985; Loop 1986; Hennessy 1998]. This has led to attempts at bilateral IMA grafting for myocardial revascularization, and studies indicate that this method extends patient survival and reduces the need for cardiac reintervention [Tatoulis 1999; Rizzoli 2002]. One major drawback to using IMAs for CABG is that this vessel tends to spasm. IMA spasm has been reported to cause perioperative mortality and morbidity [Sarabu 1987; Jones 1989; Van Son 1990; Rosenfeldt 1999]. Although the mechanism of IMA graft spasm is still unclear, it is widely attributed to mechanical manipulation and other physical factors, such as diathermy during surgical harvesting [Jett 1992; Frierson 1993; Canzer 1994].

Currently, a variety of topical vasodilator agents are used to prevent IMA spasm during harvesting, and these agents are applied prior to use in CABG. However, there is still debate about which topical vasodilator solution is best for treating IMA grafts before anastomosis in CABG [Mills 1989; Cooper 1992; Sasson 1995; Nili 1999]. There is also no consensus on the optimal temperature or duration of exposure when applying topical vasodilator solutions to this vessel. In most studies that have assessed effects of these agents on free IMA blood flow, the mean interval from pretreatment to posttreatment flow measurements has been longer than 30 minutes, and in many cases the posttreatment measurements have been recorded during cardiopulmonary bypass (CPB) [Dregelid 1993, 1995; Sasson 1995; Nili 1999; Vilandt 1999; Girard 2004]. In most previous works on this topic, topical vasodilator solutions have been applied at room temperature (18-22°C) [Cooper 1992; Sasson 1995; Nili 1999; Vilandt 1999; Formica 2006]. These conditions do not reflect the situation with off-pump surgery (ie, CABG without CPB). An off-pump technique

Table 1. Treatment Group Results for the Clinical and Hemodynamic Variables*

	Group S (n = 20)	Group N (n = 20)	Group D (n = 20)	Group P (n = 20)	Group A (n = 20)	*P*†
Age, y	56.5 ± 10.3	63.5 ± 10.8	59.5 ± 10.8	60 ± 11.3	60 ± 10.4	.38
Sex, female/male	4/16	5/15	4/16	6/14	3/17	.82
Body surface area, m^2	1.82 ± 0.13	1.83 ± 0.13	1.79 ± 0.15	1.75 ± 0.13	1.84 ± 0.13	.28
Pretreatment MAP, mmHg	69.3 ± 9.6	66.6 ± 7.9	67.8 ± 7.2	67 ± 8.9	69.8 ± 7.5	.86
Posttreatment MAP, mmHg	68.7 ± 9.1	64 ± 8.8	69 ± 8.6	66.4 ± 8	68.1 ± 10.3	.38
P	.59	.12	.48	.68	.98	
MAP ratio	0.99 ± 0.08	0.97 ± 0.11	1.06 ± 0.2	1 ± 0.11	1.01 ± 0.17	.41
Pretreatment HR, beats/min	76.2 ± 11.4	69.2 ± 12.7	68.3 ± 14.1	65.6 ± 16.5	69.8 ± 11.8	.16
Posttreatment HR, beats/min	78.8 ± 14.5	70.6 ± 11.9	70.4 ± 14.5	66.7 ± 14.7	70 ± 11.2	.08
P	.13	.14	.1	.54	.58	
HR ratio	1.04 ± 0.09	1.03 ± 0.06	1.03 ± 0.08	1.03 ± 0.12	1.03 ± 0.13	.99
Pretreatment CVP, mmHg	8.1 ± 3.4	9.6 ± 2.9	7.7 ± 3.8	8.4 ± 3.1	6.9 ± 2.7	.1
Posttreatment CVP, mmHg	8 ± 3.4	9.4 ± 2.7	7.5 ± 3.6	8.7 ± 2.8	7.3 ± 2.8	.19
P	.86	.42	.72	.25	.13	
CVP ratio	1.01 ± 0.14	0.99 ± 0.15	1.13 ± 0.3	1.07 ± 0.17	1.09 ± 0.2	.16

*Results for male versus females patients were compared using χ^2. Each pretreatment and posttreatment pair of results was compared using the Student *t* test. S indicates saline; N, nitroglycerin; D, diltiazem; P, papaverine; A, adenosine; MAP, mean arterial pressure; ratio, posttreatment-to-pretreatment ratio; HR, heart rate; CVP, central venous pressure.

†Results for the 5 treatment groups were compared using 1-way analysis of variance.

provides only a short window of time to treat the IMA with a topical vasodilator; therefore, a rapid vasodilation response is required. Also, it is best to maintain normal body temperature during off-pump surgery, and the pharmacologic action of vasodilators is greater at warm temperatures.

The aim of this prospective randomized trial was to assess how brief pretreatment with different vasodilators applied topically at normal body temperature affects blood flow in the IMA.

MATERIALS AND METHODS

The subjects were 100 patients who underwent IMA harvesting in preparation for elective, first-time CABG. The protocol was approved by our institution's ethics committee, and informed consent was obtained from all participants. The subjects were 78 men and 22 women with a mean age of 59.8 ± 10.7 years (range, 30-74 years) and a mean body surface area of 1.81 ± 0.15 m^2. Individuals who required emergent CABG, patients who were older than 75 years, and those who had poor left ventricular function (ejection fraction ≤40%), serum creatinine ≥2 mg/dL, or pulmonary or liver disease were excluded from the study. Hemodynamically unstable patients who required pharmacologic inotropic support at the time of IMA blood flow measurement were also excluded intraoperatively.

The IMA was harvested as a pedicle that extended from the level of the subclavian vein to just beyond the site of bifurcation. The artery was dissected with diathermy, and hemoclips were used to occlude side branches. Before the distal end was cut, a dose of heparin (2-4 mg/kg) was administered, and the activated clotting time was checked repeatedly. Once testing revealed an activated clotting time longer than 250 seconds, the IMA was severed 1 to 2 mm proximal to its bifurcation. After the vessel was cut, it was allowed to bleed freely for 30 seconds and the blood flow rate in milliliters per minute was determined. This was defined as the "pretreatment flow rate." Hemodynamic parameters (mean arterial pressure [MAP], heart rate [HR], and central venous pressure [CVP]) were also recorded at this pretreatment time point.

Once the pretreatment flow rate was determined, patients were randomly assigned to 5 groups of equal size (20 patients in each) using a random numbers table. Each group of pedicles was treated with a different solution: 0.9% normal saline (controls, or group S); 0.01 mg/mL nitroglycerin solution (group N); 0.25 mg/mL diltiazem solution (group D); 0.6 mg/mL papaverine solution (group P); 0.05 mg/mL adenosine solution (group A). All concentrations were selected based on routine use in clinical practice, and all solutions were at normal body temperature (37°C) when applied.

After it was established which topical treatment would be administered, a technician prepared the solution. With the patient's pretreatment flow rate already recorded, a clip was applied to the distal end of the IMA. The pedicle was then gently manipulated into a tube that contained 50 mL of the test solution. The tube was oriented vertically (perpendicular to the operating table) inside the thoracic cavity, with the mouth of the tube located just below the level of the sternum. This allowed the IMA to be completely immersed in solution. After 5 minutes of immersion, the pedicle was carefully removed from the tube and then severed a few millimeters proximal to the clip. A second blood flow measurement, the "posttreatment flow rate," was then recorded using the method detailed above. MAP, HR, and CVP were also noted at this time point.

Table 2. Pretreatment and Posttreatment Internal Mammary Artery (IMA) Flow Rates and Posttreatment-to-Pretreatment Ratios for Each Solution Tested*

	Pretreatment, mL/min	Posttreatment, mL/min	*P*	IMA Flow Ratio
Group S	43.2 ± 22.4	46.8 ± 25.2	.25	1.08 ± 0.17
Group N	38.5 ± 16.9	65 ± 31.1	.0001	1.74 ± 0.17
Group D	37.2 ± 14.1	64.2 ± 24.8	.0001	1.77 ± 0.49
Group P	34.6 ± 7	62.8 ± 22.2	.0001	1.82 ± 0.59
Group A	38.4 ± 12.7	60.6 ± 30.3	.0001	1.57 ± 0.54
	P = .526†	*P* = .194†		*P* = .0001†

*Each pretreatment and posttreatment pair of results was compared using the Student *t* test. S indicates saline; N, nitroglycerin; D, diltiazem; P, papaverine; A, adenosine; ratio, posttreatment-to-pretreatment ratio.

†Group results were compared using 1-way analysis of variance.

The surgeon who dissected the IMA and recorded the pretreatment and posttreatment flow rates was blinded to the topical solution applied. A posttreatment-to-pretreatment ratio was calculated for each variable (flow rate and hemodynamic parameters).

Statistical analyses were performed using the SPSS software package (SPSS for Windows, version 13.0; SPSS, Chicago, IL, USA). Data are presented as mean ± standard deviation. Normality of distribution and homogeneity of variance were assessed using the Shapiro-Wilk test. Within each group, the pretreatment and posttreatment findings for each variable were compared using the Student t test. Differences among and between groups were compared using 1-way analysis of variance or χ^2 testing, as appropriate. Post hoc least significant difference analysis was used to compare the groups' posttreatment-to-pretreatment ratio values. Any *P* value less than .05 was considered statistically significant.

RESULTS

The results for the demographic features and hemodynamic variables in the 5 treatment groups are shown in Table 1. There were no statistically significant differences among the groups with respect to mean age, mean body surface area, or sex distribution. Within each group, there was no significant change in mean MAP, mean HR, or mean CVP from pretreatment to posttreatment. Comparisons also revealed no significant differences among the 5 groups with respect to the means for pretreatment hemodynamic variables (HR, CVP, MAP) or the corresponding posttreatment means. Comparisons of the groups' mean ratio values (posttreatment-to-pretreatment ratios) for MAP, HR, and CVP, respectively, also revealed no significant differences.

The groups' pretreatment and posttreatment IMA blood flow rates and posttreatment-to-pretreatment ratios for IMA flow are shown in Table 2. Each of the groups treated with a vasodilator agent showed a significant increase in flow rate from pretreatment to posttreatment, whereas the control group (normal saline) did not. There were no significant differences among the groups' pretreatment flow rates (*P* = .526) or posttreatment flow rates (*P* = .194). The mean ratios for IMA flow rate were 1.08 ± 0.17 in group S, 1.74 ± 0.17 in group N, 1.77 ± 0.49 in group D, 1.82 ± 0.59 in group P, and 1.57 ± 0.54 in group A. One-way analysis of variance identified a significant difference among these values (*P* = .0001). Post hoc analysis revealed that the mean ratios for IMA flow rate in the 4 vasodilator groups were significantly higher than the corresponding control group mean (Table 3).

DISCUSSION

This prospective randomized study looked at how brief treatment with 4 separate vasodilator agents (nitroglycerin, diltiazem, papaverine, and adenosine) applied at normal body temperature affects IMA blood flow. Identical application of normal saline was used as the control. The data revealed that, for each vasodilator tested, 5 minutes of IMA immersion increased blood flow to a significantly greater extent than was observed with normal saline. Statistical analysis of the mean posttreatment-to-pretreatment ratios for IMA flow rate revealed no significant differences among the degrees of

Table 3. Comparisons of the Groups' Posttreatment-to-Pretreatment Ratios for Internal Mammary Artery (IMA) Free-Flow Rate*

	IMA Flow Ratio	*P*
S versus N	1.08 ± 0.17 versus 1.74 ± 0.17	.0001
S versus D	1.08 ± 0.17 versus 1.77 ± 0.49	.0001
S versus P	1.08 ± 0.17 versus 1.82 ± 0.59	.0001
S versus A	1.08 ± 0.17 versus 1.57 ± 0.54	.003
N versus D	1.74 ± 0.17 versus 1.77 ± 0.49	.858
N versus P	1.74 ± 0.17 versus 1.82 ± 0.59	.592
N versus A	1.74 ± 0.17 versus 1.57 ± 0.54	.31
D versus P	1.77 ± 0.49 versus 1.82 ± 0.59	.72
D versus A	1.77 ± 0.49 versus 1.57 ± 0.54	.233
P versus A	1.82 ± 0.59 versus 1.57 ± 0.54	.122

*All values compared using post hoc least significant difference analysis. S indicates saline group; N, nitroglycerin group; D, diltiazem group; P, papaverine group; A, adenosine group.

vasodilation achieved with these 4 agents; however, the mean ratios for the papaverine, nitroglycerin, and diltiazem groups were all higher than the corresponding value in the adenosine group.

Many surgeons use systemic, topical, perivascular (pedicle injection), or intraluminal vasodilators to prevent or treat IMA spasm before this vessel is anastomosed to a coronary artery. To date, there is still no consensus on which is the best topical vasodilator for treating IMA grafts prior to use in CABG. Numerous studies have attempted to assess how topical vasodilator solutions affect free blood flow in the IMA. However, most of these have focused only on topical, perivascular, or intraluminal application of papaverine [Mills 1989; Dregelid 1993, 1995; Hausmann 1996; Bilgen 1996; Vilandt 1999; Girard 2004; Formica 2006], and a few have clinically compared the effects of topical nitroglycerin solutions on free blood flow in the IMA [Cooper 1992; Sasson 1995; Nili 1999]. Sasson and colleagues evaluated the effects of topical papaverine, nitroglycerin, and sodium nitroprusside, and found no significant advantages over topical application of normal saline [Sasson 1995]. Nili and coworkers investigated the effects of these same topical vasodilator drugs and topical verapamil on the IMA, and found no significant benefits over normal saline [Nili 1999]. Formica and associates observed that topical administration of nitroglycerin/verapamil solution and papaverine solution did not achieve optimal free IMA flow [Formica 2006]. In contrast, Cooper and associates studied the efficacy of papaverine, nifedipine, nitroglycerin, and sodium nitroprusside as topical vasodilators, and reported that all these agents increased IMA flow to a significantly greater degree than normal saline [Cooper 1992]. To our knowledge, no formal study has yet evaluated how topical application of other vasodilators (including diltiazem and adenosine) affects IMA flow.

Some previous investigators have attempted to assess topical vasodilator effects on IMA blood flow by comparing flow rates before and after CPB [Nili 1999; Vilandt 1999; Girard 2004]. Furthermore, numerous studies have featured very long topical vasodilator exposure times, some exceeding 30 minutes [Dregelid 1993, 1995; Sasson 1995; Nili 1999; Vilandt 1999; Girard 2004]. During CPB, blood flow through the IMA is not physiological because CPB provides nonpulsatile flow. Also, CPB triggers a systemic inflammatory response in which increased circulating vasoactive substances alter vascular tone. Furthermore, body temperature is often reduced during CPB, and this could modify IMA response to vasodilators that are tested. For these various reasons, results from research involving CPB cannot be extrapolated to off-pump surgery, which provides limited time to treat the IMA with topical vasodilator solution, and during which normal body temperature is preserved. It is important to note that in most previous studies vasodilators have been topically applied by covering the IMA with a drug-soaked sponge [Mills 1989; Cooper 1992; Dregelid 1995; Sasson 1995; Hausmann 1996; Bilgen 1996; Formica 2006]. In contrast, we completely submerged the IMA in a tube that contained vasodilator solution at 37°C. The aim was to ensure homogeneous and consistent distribution of each vasodilator agent tested, and to keep the IMA at normal body temperature during flow measurements. Previous studies have investigated intraluminal or perivascular delivery of different solutions to prevent or treat IMA spasm. Although intraluminal papaverine administration provides greatest IMA flow compared to perivascular injection or topical exposure, it carries a considerable risk of intimal or medial injury [Mills 1989; Dregelid 1995]. Few studies have indicated that perivascular papaverine injection into the pedicle of the IMA increases blood flow to a significantly greater degree than topical exposure and avoids any risk of intimal injury [Hausmann 1996; Girard 2004]. Injection of the topical solution into the pedicle of the IMA may allow better adventitial exposure of the vasodilator agent than topical therapy, but this method is not applicable when the IMA is harvested as a skeletonized vessel.

In off-pump surgery, whenever possible the left IMA is grafted onto the left anterior descending coronary artery as the first step. This is preferred because less displacement of the heart is needed to expose this major coronary vessel, and because it allows immediate perfusion of a large portion of myocardium without proximal anastomosis [Magee 2003]. This means that, during off-pump CABG, the IMA is often anastomosed very soon after it is harvested. Studies have demonstrated that at least 35 to 40 minutes are needed for a harvested IMA to relax naturally (spontaneously) [Cooper 1992; Bilgen 1996; Vilandt 1999]. However, in off-pump surgery it is essential to rapidly vasodilate the IMA to counteract the spasm that occurs during harvesting. Considering this requirement, the relatively short operative time, and ethical issues, we decided to test using brief vasodilator exposure (5 minutes), and therefore a short interval between pretreatment and posttreatment measurements. Although the short duration of exposure likely resulted in submaximal vasodilator effect, we found the IMA flow response to be satisfactory. When the IMA pedicles were exposed to papaverine solution at 37°C for 5 minutes, IMA flow increased 1.82-fold on average. We observed only slightly lesser degrees of flow increase with diltiazem and nitroglycerin, and considerably less effect (1.57-fold) with adenosine.

In our study, brief immersion of IMA pedicles in normal saline solution did not increase flow in the vessel. This indicates that the IMA does not undergo substantial spontaneous dilatation in the first 5 minutes after harvesting. Results from studies that have looked at spontaneous IMA vasodilatation after harvesting are conflicting. Some investigators have observed no spontaneous relaxation between the time of IMA mobilization and the start of CPB [Cooper 1992; Bilgen 1996; Formica 2006]. Two other reports have indicated that IMA spasm attenuates and flow increases with time, and that application of various topical vasodilators provides no significant advantage over normal saline [Sasson 1995; Nili 1999]. The discrepancy between these results may be related to time intervals between the 2 sets of flow measurements (ie, the pretreatment and posttreatment time points that were chosen). The studies that revealed no spontaneous attenuation of IMA spasm featured shorter time intervals (14 to 18 minutes) [Cooper 1992; Bilgen 1996; Formica 2006], whereas the other investigations featured longer ones (37-75 minutes) [Sasson 1995; Nili 1999; Vilandt 1999]. Longer time between flow measurements could allow greater opportunity for spontaneous relaxation of the IMA.

Another important aspect of our study was the temperature of the solutions that were tested. Most topical vasodilator solutions are used at room temperature (18-20°C), whether for off-pump CABG or other operations [Cooper 1992; Sasson 1995; Nili 1999; Vilandt 1999; Formica 2006]. As noted, normal body temperature is preserved during off-pump surgery. We believe that, when the circulating blood is at normal temperature, applying a topical vasodilator solution that is at room temperature could attenuate the effect of the solution. Therefore, for our investigation, we heated all test solutions to 37°C before application. Bilgen and colleagues demonstrated that the vasodilatory action of normothermic topical papaverine on IMAs is superior to that of room-temperature topical papaverine [Bilgen 1996]. They stated that this could likely be explained by decreased enzyme activity at lower temperatures.

In conclusion, when a harvested IMA is immersed for just 5 minutes in any one of the topical solutions we tested at normal body temperature, vessel spasm is reduced and blood flow increases. Papaverine is the topical vasodilator most widely used for preventing and treating arterial graft spasm. Of the 4 vasodilator agents we assessed in this study, papaverine had the most pronounced vasodilatory effect on harvested IMAs. Topical nitroglycerin and diltiazem also had satisfactory effects on IMA free flow. Immersion in adenosine solution had a less pronounced vasodilatory effect than papaverine, nitroglycerin, or diltiazem. The methodology of our study involved short-term (5 minutes) exposure to each agent at 37°C, and these features make our results relevant to off-pump surgery.

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