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Topical Vasodilators for Preventing Radial Artery Spasm during Harvesting for Coronary Revascularization: Comparison of 4 Agents

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ABSTRACT

Background. There is still controversy about which vasodilator solution is best for storing radial artery (RA) conduits prior to coronary artery bypass grafting. The aim of this pilot study was to investigate how 4 different topical vasodilators applied during RA harvesting affect blood flow with the vessel in situ.

Materials and Methods. The subjects were 85 patients who underwent RA harvesting in preparation for coronary artery bypass grafting. Each case was assigned to 1 of 5 groups (17 RAs each) that were treated with different solutions: normal saline (control), nitroglycerin, diltiazem, papaverine, and adenosine. Standard clinical concentrations were used. The RA was partially harvested (pedicle attached proximally) and flow rates and hemodynamic parameters (mean arterial pressure, heart rate, central venous pressure) were recorded at 2 time points: (1) pretreatment and (2) after 5 minutes of immersion in 60 mL of treatment solution. Results were compared within and between groups, and post-treatment-to-pretreatment ratios were calculated for each variable.

Results. There were no significant differences among the groups' mean pretreatment flow rates (P = .979) or mean posttreatment flow rates (P = .069). All except the diltiazem group showed a significant rise in mean flow rate from pretreatment to posttreatment. The mean posttreatment-to-pretreatment ratios for RA flow rate were 1.28 ± 0.39 in the saline group, 1.85 ± 0.72 in the nitroglycerin group, 1.31 ± 0.48 in the diltiazem group, 1.37 ± 0.64 in the papaverine group, and 1.23 ± 0.42 in the adenosine group. Only the mean flow ratio in the nitroglycerin group was significantly higher than that in the saline group (P = .003). The mean flow ratios in the other vasodilator groups were not statistically different from the flow ratio in the saline group.

Conclusions. These preliminary results indicate that topical application of nitroglycerin solution effectively prevents perioperative spasm of the RA in patients undergoing coronary artery bypass surgery. The authors recommend this solution for preparation and storage of RA grafts. Randomized controlled trials with power analysis will give more definitive information.

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INTRODUCTION

One major drawback to using arterial grafts for coronary artery bypass grafting (CABG) is that these vessels tend to spasm. This is particularly true with the radial artery (RA), and perioperative spasm of this vessel can be devastating. Earlier reports identified RA spasm as the main cause of early graft failure in patients undergoing multivessel CABG [Carpentier 1973; Fisk 1976; Gabe 2001], but this situation has changed with medical advancements. Today, the risk of RA spasm during coronary revascularization is much lower than it once was, owing to more careful surgical techniques that focus on minimal touch and to pharmacologic dilation with topical and systemic vasodilators.

Previous authors have documented the effects of various systemic vasodilators on RA spasm in vivo [Acar 1992; Shapira 2000; Gabe 2001; Zabeeda 2001; Affleck 2004]. As well, in vitro studies on experimental models with human or canine RA segments have shown that some agents can inhibit or relax chemically induced muscle contraction in the RA wall [He 1996; Tatoulis 1999; Bond 2000; Chanda 2000; Medina 2000; Chong 2001; Velez 2001; Conant 2003]. However, it is still not clear which topical vasodilator solution is optimal for treating and storing human RA grafts prior to use in CABG. To date, no investigation has clinically compared the effects of topical vasodilator solutions on free blood flow in the RA in situ. The aim of this pilot study was to assess how pretreatment with different topical vasodilators affects flow in the RA during harvesting of this vessel for CABG.

MATERIALS AND METHODS

The study involved 85 patients who underwent RA harvesting in preparation for elective, first-time CABG between July 2004 and August 2005. The protocol was approved by

our institution's ethics committee and informed consent was obtained from all patients. The subjects were 69 men and 16 women, with a mean age of 55.7 ± 9.3 years (range, 31-73 years). The mean body surface area for the group was 1.8 ± 0.2 m^2 (range, 1.4-2.3 m^2). Patients who were older than 75 years, and those who had left ventricular dysfunction (ejection fraction ≤40%), serum creatinine ≥2 mg/dL, or pulmonary or liver disease were excluded from the study. Individuals who required emergent CABG were also excluded.

Before RA harvesting, each patient underwent the modified Allen's test to confirm adequate collateral circulation to the hand via the ulnar artery. For this, the examiner used his fingers to occlude both the ulnar artery and the RA at the wrist. He then asked the patient to slowly open and close the hand several times, forming a tight fist and then releasing. After several clenches, the patient was asked to slowly open the hand and extend the fingers fully. The examiner then released the ulnar artery and observed. A hyperemic response in the thenar eminence and thumb within 10 seconds was considered to indicate satisfactory collateral circulation by the ulnar artery. A plethysmographic pulse test was also done in the operating room before induction of anesthesia. For this, a pulse oxymeter sensor was placed on the index finger and the examiner occluded both the ulnar artery and the RA at the wrist until pulse waves disappeared from the oxymeter screen. Reappearance of pulse waves on the screen within 10 seconds of releasing the ulnar artery was taken to signal adequate collateral circulation in the hand.

The RA was "partially harvested" as a pedicle that extended from the brachial fossa to the wrist. The artery was dissected with diathermy, and hemoclips were used to occlude side branches. Before the distal end of the RA was cut, a dose of heparin (2-4 mg/kg) was administered and activated clotting time was monitored. Once testing revealed activated clotting time longer than 250 seconds, the RA was severed 2 cm above the wrist joint to preserve collateral circulation. After the vessel was severed, it was allowed to bleed freely for 30 seconds in situ, 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, each patient was assigned to 1 of 5 groups (17 RAs per group) that were treated with different solutions: 0.9% normal saline (controls, or NS group), 0.1 mg/mL nitroglycerin solution (NTG group), 0.25 mg/mL diltiazem solution (DIL group), 0.6 mg/mL papaverine solution (PPV group), and 0.05 mg/mL adenosine solution (ADE group). All concentrations were selected based on routine use in clinical practice, and all solutions were at 37°C when applied.

Once 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 RA. The pedicle was then gently manipulated (using fine tissue forceps and grasping only the surrounding adipose tissue or satellite veins) into a tube that contained 60 mL of the vasodilator solution. The tube was suspended vertically beside the patient's elbow so that the RA was completely immersed. After 5 minutes of immersion, the pedicle was carefully removed from the tube (using the same manipulation technique specified above) 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.

The surgeon who dissected the RA and recorded the pretreatment and posttreatment flow rates was blinded to the topical solution applied. A posttreatment-to-pretreatment ratio (Po:Pr) was calculated for each variable (flow rate and hemodynamic parameters). All measurements were recorded with the patient in supine position. If necessary, certain management strategies (volume replacement, Trendelenburg position) were used to maintain sufficient blood pressure during operation. However, none of the patients required intervention for blood pressure regulation within 10 minutes before flow measurements were recorded.

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 tested 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 (ANOVA) or χ^2 testing, as appropriate. Post hoc least significant difference analysis was used to compare the groups' Po:Pr 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 HR, pretreatment CVP, posttreatment HR, or posttreatment CVP. There was also no significant difference among the group means for pretreatment MAP, but the NS group (controls) had a significantly higher mean posttreatment MAP than the other 4 groups (*P* = .01).

The Figure shows comparisons of the pretreatment and posttreatment RA blood flow rates in the 5 groups. There was no significant difference among the groups' pretreatment flow rates (*P* = .979), and also no significant difference among the groups' posttreatment flow rates (*P* = .069). All groups except the DIL group showed a significant rise in flow rate from pretreatment to posttreatment. The respective mean pretreatment and posttreatment RA flow rates in each group were as follows: 75.6 ± 61.2 and 89.8 ± 64.7 mL/min in the NS group (*P* = .016); 83.2 ± 57.4 and 149.8 ± 99.6 mL/min in

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

	NS Group, n = 17	NTG Group, n = 17	DIL Group, n = 17	PPV Group, n = 17	ADE Group, n = 17	*P*
Age, y	56 ± 10.6	56.5 ± 9.1	54.9 ± 7.3	54.4 ± 11.3	55.7 ± 9.3	.952
Sex, female/male	4/13	4/15	3/14	3/14	4/13	.981
Body surface area, kg/m^2	1.8 ± 0.2	1.8 ± 0.1	1.8 ± 0.1	1.8 ± 0.1	1.8 ± 0.2	.971
Pretreatment MAP, mmHg	72.8 ± 15.1	69.2 ± 9.6	68.1 ± 9.5	67.5 ± 6.8	66.1 ± 10.2	.422
Posttreatment MAP, mmHg	75.9 ± 10.8	70.7 ± 9.3	67.8 ± 9.9	69.6 ± 6.3	64.4 ± 9.7	.01
P	.288	.122	.879	.18	.504	
Pretreatment HR, beats/min	68 ± 15.2	72.3 ± 11.4	67.4 ± 13.5	70.6 ± 15.3	68.3 ± 15.8	.84
Posttreatment HR, beats/min	69.5 ± 12.9	71.3 ± 11.3	78.8 ± 13.8	67.8 ± 13.1	67.9 ± 15.9	.943
P	.399	.669	.395	.11	.743	
Pretreatment CVP, mmHg	9.4 ± 3.7	9.6 ± 3.4	8.8 ± 2.7	8.5 ± 4.2	7.59 ± 3.7	.465
Posttreatment CVP, mmHg	9.1 ± 3.8	9.9 ± 3.7	9.1 ± 2.8	8.4 ± 3.8	8.2 ± 3.8	.654
P	.428	.415	.524	.627	.083	

*Each pretreatment and posttreatment pair of results were compared using the Student *t* test. Results for the 5 treatment groups were compared using 1-way analysis of variance. Results for male versus female patients were compared using the χ^2 test. NS indicates normal saline; NTG, nitroglycerin; DIL, diltiazem; PPV, papaverine; ADE, adenosine; MAP, mean arterial pressure; HR, heart rate; CVP, central venous pressure.

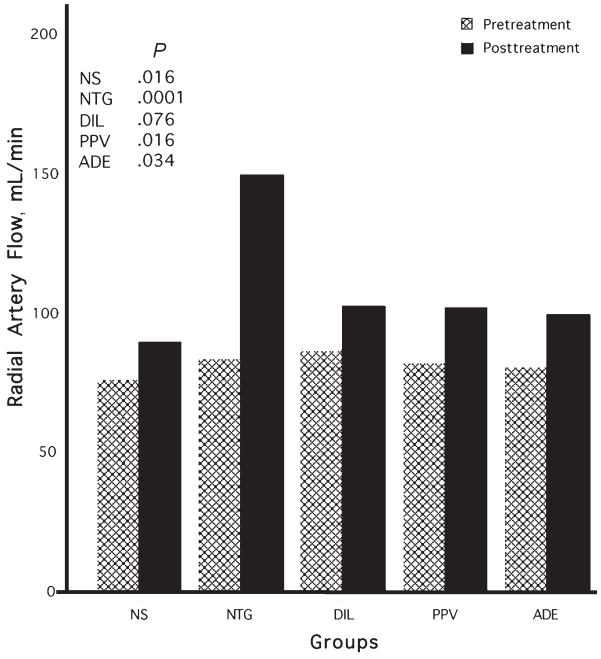
the NTG group (*P* = .0001); 86.3 ± 48.5 and 102.2 ± 47.9 mL/min in the DIL group (*P* = .076); 81.6 ± 36.8 and 102.1 ± 42 mL/min in the PPV group (*P* = .016); and 80.1 ± 35.8 and 99.4 ± 50.4 mL/min in the ADE group (*P* = .034).

Comparisons of the groups' mean Po:Pr values for MAP, HR, and CVP revealed no significant differences (Table 2). The mean Po:Pr values for RA flow rate were 1.28 ± 0.39 in the NS group, 1.86 ± 0.72 in the NTG group, 1.31 ± 0.48 in the DIL group, 1.37 ± 0.64 in the PPV group, and 1.23 ± 0.42 in the ADE group. One-way ANOVA identified a significant difference among these ratios (*P* = .008). Post hoc analysis revealed that the mean Po:Pr values for RA flow rate in the DIL, PAP, and ADE groups were not significantly different from the corresponding ratio in the NS group (*P* = .843, .627, and .809 for DIL, PAP, and ADE, respectively). The mean Po:Pr for flow rate in the NTG group was significantly higher than that in the NS group (*P* = .003) (Table 3).

DISCUSSION

Currently, the internal mammary artery (IMA) is the conduit of choice for CABG. However, the RA is gaining popularity as an arterial conduit for use in conjunction with the IMA during this procedure. The wall of the RA features a higher density of myocytes than the wall of the IMA, and endothelial regulation of vascular smooth muscle is less pronounced in the RA than in the IMA [Cable 1999]. Perioperative prophylaxis against RA spasm is essential when this vessel is used for CABG because RA spasm is more intense and more difficult to reverse than spasm in other arterial grafts. Spasm of an RA graft can reduce luminal blood flow after coronary revascularization, thereby limiting graft function. Like all other types of arterial grafts, the RA begins to spasm during harvesting, mostly due to mechanical manipulation and other physical factors such as diathermy. Success with the RA as a graft for CABG depends on the steps that are taken to minimize or prevent perioperative spasm. Minimal-touch harvesting is essential, and pharmacologic strategies to maintain maximal patency during harvesting and storage prior to grafting are also critical steps.

It is common for an RA graft to be treated and stored in solution for several minutes before it is anastomosed to a



The pretreatment and posttreatment radial artery flow rates (mL/min) for each solution tested. Each pretreatment and posttreatment pair of results were compared using the Student t test. ADE indicates adenosine; DIL, diltiazem; NS, normal saline; NTG, nitroglycerin; PPV, papaverine.

Table 2. Posttreatment-to-Pretreatment Ratios (Po:Pr) for the Hemodynamic Variables and Radial Artery (RA) Free-Flow Rate*

	NS Group, n = 17	NTG Group, n = 17	DIL Group, n = 17	PPV Group, n = 17	ADE Group, n = 17	*P*
Po:Pr, MAP	1.07 ± 0.19	1.04 ± 0.11	1.01 ± 0.14	1.03 ± 0.09	0.99 ± 0.16	.481
Po:Pr, HR	1.04 ± 0.12	0.99 ± 0.12	1.04 ± 0.11	0.97 ± 0.08	1.01 ± 0.07	.225
Po:Pr, CVP	0.98 ± 0.17	1.04 ± 0.17	1.04 ± 0.21	1.01 ± 0.17	1.11 ± 0.32	.555
Po:Pr, RA flow	1.28 ± 0.39	1.86 ± 0.72	1.31 ± 0.48	1.37 ± 0.64	1.23 ± 0.42	.008

*Group results were compared using 1-way analysis of variance. NS indicates normal saline; NTG, nitroglycerin; DIL, diltiazem; PPV, papaverine; ADE, adenosine; MAP, mean arterial pressure; HR, heart rate; CVP, central venous pressure.

coronary artery. Various solutions are used to store vascular grafts prior to CABG. Virtually all existing knowledge about these storage solutions has come from research on how different vasodilators affect RA segments in vitro [He 1996; Tatoulis 1999; Bond 2000; Chanda 2000; Medina 2000; Chong 2001; Velez 2001; Conant 2003]. Our preliminary study is the first to have compared the clinical effects of topical vasodilator solutions on blood flow rates in RAs in situ. Current recommendations about storage solutions for preventing RA spasm during CABG are based on results from in vitro studies. Our data reflect the clinical setting more closely in that we measured RA flow rates directly with the vessel partially harvested but still in situ, as opposed to testing RA rings in organ baths. We found that, even when an RA pedicle was immersed in saline solution alone, within 5 minutes the spasm attenuated and flow increased 1.28-fold on average.

Papaverine is a nonspecific vasodilator substance that relaxes vascular smooth muscle through multiple mechanisms, predominantly by inhibiting phosphodiesterase. We observed only a limited increase in RA flow when papaverine was applied. This was somewhat surprising because at most cardiac centers it is common practice to use papaverine solution to prevent spasm in RA bypass conduits [He 1998; Barner 1999; Bond 2000; Shapira 2000; Chong 2001]. In fact, there is no clear evidence to indicate that topical treatment of RA grafts with papaverine before CABG attenuates vasospasm. In vitro findings have been inconsistent. Conant et al tested human RA rings in the laboratory and observed that pretreatment with papaverine solution (0.6 mg/mL) for 5 minutes resulted in significantly reduced vasoconstrictive responses to norepinephrine, vasopressin, angiotensin II, potassium chloride, and endothelin-1 [Conant 2003]. In contrast, Velez and colleagues compared findings in 2 sets of canine RA rings, one pretreated with papaverine solution at a concentration of 10^{-6} M (30 minutes of immersion) and one untreated [Velez 2001]. They found that the treated set showed no significant attenuation of vasoconstrictor response to either norepinephrine or phenylephrine. Although papaverine has been proposed as a satisfactory topical vasodilator for preventing RA spasm [Shapira 2000], our clinical data from in situ RAs indicate that 5 minutes of immersion in a standard concentration of papaverine offers no advantage over normal saline for storing harvested RAs.

To date, no in vivo or in vitro research has been done on adenosine as a storage solution for RA bypass conduits. Two in vitro studies have assessed responses to adenosine in IMA segments with vasoconstriction induced by U46619 (a substance that mimics thromboxane) and norepinephrine [Luscher 1988; Tanaka 2004]. The results indicate that adenosine causes only mild, concentration-dependent relaxation of contracted IMA segments in these settings. Our finding that 5 minutes of immersion in 0.05 mg/mL adenosine has minimal dilatory effect on RAs in situ is in line with this.

Like papaverine, the calcium-channel antagonist diltiazem is widely used to prevent RA spasm during or after CABG [Acar 1992]. However, in vitro research on human RA segments has revealed that this agent has little or no inhibitory effect on spasm induced by various vasoconstrictive substances. Bond et al assessed how diltiazem affected human RA rings that were exposed to endothelin and norepinephrine [Bond 2000]. They observed no significant attenuation of wall contraction in either of these settings. Cable and colleagues found that diltiazem did not attenuate vasoconstriction in human RA rings that were treated with norepinephrine or potassium chloride [Cable 1998]. In our study of RAs in situ, statistical comparison of the groups' Po:Pr values for flow rate revealed that the anti-spasm effects of the papaverine, diltiazem, and adenosine storage solutions were not significantly different from the effect achieved with normal saline (the control solution).

Our results for nitroglycerin solution identified this agent as superior to normal saline and the 3 other vasodilators that were tested. Five minutes of immersion in 0.1 mg/mL nitroglycerin increased blood flow in RAs in situ to a significantly greater extent than was observed with all 4 of the other

Table 3. Results for Comparisons of the Groups' Posttreatment-to-Pretreatment Ratios (Po:Pr) for Radial Artery (RA) Free-Flow Rate*

	Po:Pr, RA flow	*P*
NS versus NTG	1.28 ± 0.39 versus 1.86 ± 0.72	.003
NS versus DIL	1.28 ± 0.39 versus 1.31 ± 0.48	.843
NS versus PPV	1.28 ± 0.39 versus 1.37 ± 0.64	.627
NS versus ADE	1.28 ± 0.39 versus 1.23 ± 0.42	.809
NTG versus DIL	1.86 ± 0.72 versus 1.31 ± 0.48	.005
NTG versus PPV	1.86 ± 0.72 versus 1.37 ± 0.64	.011
NTG versus ADE	1.86 ± 0.72 versus 1.23 ± 0.42	.001
DIL versus PPV	1.31 ± 0.48 versus 1.37 ± 0.64	.773
DIL versus ADE	1.31 ± 0.48 versus 1.23 ± 0.42	.661
PPV versus ADE	1.37 ± 0.64 versus 1.23 ± 0.42	.468

*All values compared using post hoc least significant difference analysis. NS indicates normal saline group; NTG, nitroglycerin group; DIL, diltiazem group; PPV, papaverine group; ADE, adenosine group.

solutions evaluated (mean Po:Pr for flow rate in the NTG group, 1.86; $P = .008$). This is in accordance with previous in vitro research on the impact of nitroglycerin on RA-ring spasm induced by various vasoconstrictors. Chanda and Canver investigated the vasodilative effect of nitroglycerin in human RA, IMA, and saphenous vein rings that were exposed to a mixture of endothelin-1, norepinephrine, angiotensin II, and 5-hydroxytryptamine [Chanda 2001]. When the tissues were bathed in nitroglycerin solution (2×10^{-8} mol/L), the authors noted reversal of vasospasm in 82.7% of the RA rings, 53.6% of the IMA rings, and 47.3% of the saphenous vein rings. Shapira et al examined the vasodilator effects of diltiazem and nitroglycerin, respectively, on RAs in vitro and in vivo [Shapira 1999]. They observed that nitroglycerin significantly inhibited spasm in RA rings that were vasoconstricted by U46619, whereas diltiazem did not. In the same study, in vivo ultrasound findings in patients undergoing CABG revealed that intravenous injection of nitroglycerin increased RA diameter by 22%, and this was significantly greater than the 3% increase noted with diltiazem. A later investigation by Shapira et al extended the observations from the above research to other aspects of the clinical setting [Shapira 2000]. The results showed that systemic nitroglycerin infusion (0.1 mg kg^{-1} min^{-1}) was superior to diltiazem infusion (0.1 mg kg^{-1} min^{-1}) with respect to drug side effects and hospital costs in this patient group. However, our study differs from these in vivo reports with respect to the route of vasodilator administration; we applied vasodilator solutions topically, not systemically. He and Yang conducted in vitro research on human RA rings constricted with U46619, and found that immersion in a nitroglycerin bath resulted in 6.2-fold more relaxation than immersion in a sodium nitroprusside bath [He 1999].

Blood flow rate is an important indicator of flow capacity in coronary bypass grafts. As noted, our investigation differs from previous in vivo research on RA blood flow. Distinct from the vessel diameter work by Shapira et al, Zabeeda and coworkers published the first in vivo study of the specific effects of systemic vasodilators on flow rates in RAs in situ [Zabeeda 2001]. In contrast, we assessed the effects of topical solutions on blood flow in RAs in situ. In their unique investigation, Zabeeda et al found that a 10-minute infusion of nitroglycerin (0.5-3 μg kg^{-1} min^{-1}) caused significant vasodilation and increased blood flow in the RA. Our findings are in accord with this. Of the 4 topical vasodilator solutions we tested, nitroglycerin was the only one that significantly inhibited vasospasm of the RA in situ. As detailed above, we observed a significantly greater increase in flow rate with nitroglycerin than with normal saline or the other 3 vasodilators that were tested. Two reports have documented in vivo research on the flow reserve of the RA, but in both cases the RA flow measurements were made after the RA was end-to-side anastomosed to an in situ IMA (forming a T-graft). Specifically, Affleck et al demonstrated the flow dynamics of T-grafts but did not assess how vasodilators affected flow rate [Affleck 2004]. Locker and coworkers found that 8 to 15 minutes of topical treatment with the a-antagonist Regitine (phentolamine methansulphonic, 0.07 mg/mL; Promedico, Petah Tikra, Israel) significantly increased RA flow rates when this vessel was part of a T-graft, but they did not assess flow in RAs in situ [Locker 2002].

In conclusion, it is obviously best to prevent RA spasm during preparation for coronary revascularization rather than attempt treatment after it has occurred. As well, it is important to recognize that no vasodilator applied topically or systemically will be effective in every situation. Our comparison of the 4 topical vasodilator agents in this pilot study (papaverine, diltiazem, adenosine, and nitroglycerin) identified nitroglycerin as the most potent vasodilator of partially harvested RAs in situ. We suggest that topical application of 0.1 mg/mL nitroglycerin solution (5 minutes minimum) during harvesting is an effective way to prevent RA vasospasm in patients who are undergoing coronary revascularization with RA conduits. We also recommend this as a storage solution for RA grafts that will be used in CABG. To follow our preliminary investigation, randomized controlled trials with suitable power analysis would be valuable.

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