The Heart Surgery Forum #2006-1211
10 (3), 2007 [Epub March 2007]
doi: 10.1532/HSF98.20061211 Online address: http://cardenjennings.metapress.com

Normothermia is the Key for the Treatment of Internal Thoracic Artery Spasm

Dr. Tarhan

Ibrahim Arif Tarhan, Tamer Kehlibar, Mehmet Yilmaz, Yucesin Arslan, Mert Dumantepe, Kazim Berkoz, Cansin Pancaroglu, Azmi Özler

Department of Cardiovascular Surgery, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turkey

ABSTRACT

Background. Free flow of the internal thoracic artery decreases commonly after harvesting because of spasm. Tissue heat loss is inevitable during surgery. The aim of this study was to compare the internal thoracic artery pedicle rewarming method with topical papaverine applications in different thermal conditions.

Methods. Patients (n = 120) were organized in to 6 equally sized groups. The effects of topical papaverine application at room temperature, topical heated papaverine (at 37°C) application, internal thoracic artery pedicle storage in normothermic conditions, pedicle storage in normothermic conditions combined with topical papaverine application, and pedicle storage in normothermic conditions combined with topical heated papaverine application were investigated. In the control group, no treatment was applied and the pedicle was stored in room temperature conditions. We measured internal thoracic artery free flows at 3 stages: at the initiation of harvesting, after total harvesting, and after antispasmodic treatment. Durations of the stages were recorded. At each stage hemodynamic parameters, tissue and core temperatures were also monitored.

Results. Internal thoracic artery pedicle temperature significantly decreased simultaneously with the free flow after the harvesting procedure. Recovery of the physiologic temperature state, provided by storing the internal thoracic artery pedicle in normothermic conditions, improved the flow and increased the efficiency of topically applied papaverine on the vasospasm of the internal thoracic artery.

Conclusion. Topical application of heated papaverine itself does not warm pedicle tissue, but papaverine efficiency increases when the pedicle is stored in normothermic conditions. Preserving internal thoracic artery pedicles in normothermic conditions can be the preferred treatment for spasms.

Received December 14, 2006; received in revised form February 14, 2007; accepted February 14, 2007.

Correspondence: Tamer Kehlibar, Inonu cad. Mehpare sok. No: 17/13 Kozyatagi, Kadikoy, Istanbul, Turkey; 90-216-3499120; 90-216-4675621; fax: 90-216-5652130 (e-mail: tamerkehlibar@gmail.com).

INTRODUCTION

Arterial grafts are indispensable in coronary artery bypass procedures. The internal thoracic artery (ITA) is accepted as the gold standard graft choice in coronary bypass surgery. ITA vasospasm reduces ITA flow and is a general problem that can occur after harvesting of the pedicle. It may contribute to myocardial ischemia and early postoperative morbidity and mortality [Jones 1989].

Arterial spasm subsequent to the harvesting procedure seems to be an extremely complex phenomenon, depending on an unsteady balance between several relaxing and constrictor factors. Miscellaneous factors have been accused of causing vasospasm [Rosenfeldt 1999]. Moderate hypothermia is one of the major factors, but its role has not been investigated adequately. It has been stated that moderate hypothermia can induce vasoconstriction by various neurohumoral mechanisms [Yamamoto 1989; Harker 1990; Harker 1991; Yamamoto 1992]. In our former study, we demostrated that heat loss in the operating room and peripheral cooling by redistribution of heat can induce vasospasm [Tarhan 2006a].

In the studies concerning graft spasm and antispasmodic procedures, the roles of the decrease in local tissue temperature and core cooling are disregarded. After a review of the medical literature, it can be noticed that almost all arterial graft studies have focused on using various pharmacological agents in different ways [Cooper 1992; He 1994; Sasson 1995; Rosenfeldt 1999; Yavuz 2001; Girard 2004; Formica 2006]. There is not a perfect vasodilator that authors agree on [Rosenfeldt 1999]. Surgeons continue to search for the appropriate antispasmodic agent and application method. The aim of this study was to compare ITA pedicle rewarming methods with topical papaverine applications in varied thermal conditions.

MATERIALS AND METHODS

After obtaining informed consent from patients and approval from the ethics commitee, we organized 120 consecutively randomized patients whose left ITA were used as a conduit for elective first-time myocardial revascularization in to 6 equally sized groups. The effects of ITA pedicle storage in room temperature conditions (group C, n = 20), topical standard papaverine application at room temperature (group P, n = 20), topical heated papaverine (at 37°C) application (group HP, n = 20), ITA pedicle storage in normothermic conditions (group N, n = 20), and pedicle storage in normothermic conditions combined with application of topical standard papaverine at room temperature (group NP, n = 20) or with heated papaverine at 37°C (group HNP, n = 20) were investigated.

Patients who had any of the following criteria were not included in this study: age over 70 years, peripheral arterial disease, chronic renal disease, diabetes mellitus, low cardiac ejection fraction, perioperative vasoactive agent utilization, and excessive delays during anesthesia preparation process. We also excluded patients whose ITA harvesting durations lasted more than 30 minutes. We stopped the medications, which have vasodilator activity, on the last day before surgery.

Time of patients' entrance to the operation room was recorded. In anesthesia induction, pancuronium (0.1 mg/kg), fentanyl (10 μ/kg), and propofol (2 mg/kg) were used. The operating room temperature was kept at 24°C during the anesthesia preparation process, it was then lowered to 20°C, as generally accepted for the initiation of the surgery. A microprocessor-controlled heating blanket system (Blanketrol II Hyper-Hypothermia System; Cincinnati Sub-Zero Products, Cincinnati, OH, USA) was used for preserving the total body temperature.

Surgical Technique

ITA harvesting was performed by 4 staff surgeons using the standard pedicle-style procedure of a distal bifurcation into the superior epigastric and muscular phrenic arteries to the subclavian artery. After the sternotomy, 1 cc intravenous heparin was administered. Low diathermy (15 milliAmpere) and small-sized metal ligature clips were used during the harvesting procedure. ITA harvesting was started from the distal portion prior to bifurcation into the superior epigastric and musculo-phrenic branches. After harvesting a 2-cm long distal segment of ITA, we divided it from the distal tip and preharvesting free flow was measured. Flow was determined using fine-scale injectors to measure the amount of blood freely expelled from the tip of the bleeding artery during a 15-second period. The amount was multiplied 4 times to calculate the flow per minute. Then jetting artery tip was closed with a metal clip. Five minutes after systemic heparin treatment and after harvesting of the pedicle from the thoracic wall was completed, we removed the clip at the tip of ITA and measured postharvesting flow with the same method.

Spasmolytic Treatments

We performed appropriate treatment processes in the groups after postharvesting flow measurement. Two major manipulations were used in the study; first was the standard or heated papaverine application and the second was the pedicle storage in room temperature conditions or normothermic conditions. These 2 manipulations were combined in different configurations and these configurations were compared with each other in the 6 groups. We applied papaverine in 4 groups by injecting 10 mg of papaverine hydrochloride (1 mg/mL 0.9% saline) into the perivascular tissue and spraying another 10 mg of papaverine hydrochloride over the pedicle with a fine needle. Papaverine was applied at room temperature (20°C) in groups P and NP, whereas heated papaverine (at 37°C) was applied in groups HP and NHP.

The ITA pedicle was stored in a gauze pack soaked with normal saline solution at room temperature just after postharvesting flow measurement in group C and after papaverine application in groups P and HP. No manipulations were done except storing pedicles in wet gauze at room temperature in group C. In groups N, NP, and NHP, the ITA pedicle was stored in a gauze pack soaked with normal saline solution at 37°C and the gauze pack was irrigated with normal saline solution at 37°C regularly every 3 minutes. In group N, only the normothermic storage method was performed.

The ITA package was stored inside the left thorax cavity to keep the pedicle temperature more stable during the procedure until the final measurements. After a treatment period, final (posttreatment) flow was recorded. At the 3 stages, free flows were measured and esophageal and ITA pedicle tissue temperatures, hemodynamic parameters, and time of the measurements were recorded.

To monitor tissue temperature, a myocardial temperature probe (REF 81-030418, De Royal, Powell, TN, USA) was inserted in the perivascular fatty tissue of the ITA and a general-purpose temperature probe (REF 81-020409, De Royal) was used for measuring esophageal temperature.

Statistical Analysis

All statistical procedures were performed using the program GraphPad InStat version 3.06 (San Diego, CA, USA). All values are expressed as mean ± standard deviation. To compare the flows, the mean arterial pressure, the esophageal temperature, the pedicle temperature, the heart rate values, and the central venous pressure measurements, analysis of variance was used in each group. The comparison of the measurements between the groups was made by 1-way analysis of variance and Tukey's multicomparison tests. Gaussian distributions were tested using the Kolmogorov method and Smirnov assumption test. Kruskal-Wallis and Dunn's multiple comparison tests were performed whenever the normality test failed. A P value less than .05 was considered significant. Nonsignificant results were evaluated as mean differences in 95% confidence interval (CI) for clinical significance.

RESULTS

Clinical characteristics and hemodynamic data of the patients are presented in Table 1. ITA pedicle tissue temperature and flow data are shown in the Figure. There was no significant difference between body surface areas or patient ages in the 6 groups. When the hemodynamic parameters were compared, there were no significant differences between and within the groups. Periods between the patients' entrance to the operating room and the first measurements, ITA harvesting periods, and the treatment times were not statistically different.

Table 1. Demographic, Hemodynamic, and Time Interval Data*

	Group C	Group P	Group HP	Group N	Group NP	Group NHP
Treatment	No Treatment	Papaverine at Room Temperature	Heated Papaverine (37°C)	Normothermic Pedicle Rewarming Procedure	Normothermic Pedicle Rewarming Procedure after Papaverine at Room Temperature	Normothermic Pedicle Rewarming Procedure after Heated Papaverine
Male/female, n	14/6	15/5	17/3	12/8	10/10	15/5
Age, y (range)	59.8 ± 6.7 (46-70)	58.9 ± 7.5 (44-70)	59.6 ± 5.5 (49-69)	58.1 ± 7 (45-70)	59 ± 8	58 ± 8 (44-70)
BSA, m^2 (range)	1.83 ± 0.09 (1.64-2.05)	1.87 ± 0.08 (1.67-2.02)	1.84 ± 0.1 (1.65-2.06)	1.86 ± 0.08 (1.7-2.01)	1.82 ± 0.09 (1.61-2.02)	1.84 ± 0.11 (1.58-2.06)
HR_1, beats/min	76.3 ± 8.8	75.4 ± 8.5	76.2 ± 6.8	76.5 ± 8.6	77.6 ± 8.8	77.7 ± 6.1
HR_2, beats/min	76.6 ± 7.8	76 ± 7.8	76.9 ± 6.3	77.2 ± 8	77.5 ± 9.2	78.2 ± 6.1
HR_3, beats/min	77.4 ± 8.8	76.4 ± 7.6	76.2 ± 6.7	77.6 ± 7.3	77.4 ± 8.7	77.3 ± 5.8
MAP_1, mmHg	77.3 ± 3.8	78.1 ± 4.4	76 ± 3.6	75.1 ± 3.7	75.9 ± 4.3	75.8 ± 3.3
MAP_2, mmHg	77.7 ± 4.8	78 ± 3.7	76.3 ± 3.7	75.2 ± 3.9	76.6 ± 3.9	75.9 ± 2.7
MAP_3, mmHg	77.5 ± 3.8	78.7 ± 3.5	76.6 ± 3.6	75.3 ± 3	77.2 ± 3.8	76.5 ± 2.7
CVP_1, mmHg	4.2 ± 2.2	3.8 ± 1.8	3.8 ± 1.9	3.6 ± 1.8	3.8 ± 1.6	4.1 ± 2
CVP_2, mmHg	4 ± 1.2	3.8 ± 1.5	3.6 ± 1.8	3.5 ± 1.6	3.6 ± 1.2	4 ± 1.9
CVP_3, mmHg	4.3 ± 1.4	4.3 ± 1.3	3.7 ± 1.3	3.7 ± 1.6	3.7 ± 1.6	4.3 ± 1.3
t_1, min	49.7 ± 4.8	50.6 ± 4.4	48 ± 3.1	49.7 ± 3.5	48.8 ± 3.9	47.3 ± 2.2
t_2, min	12.75 ± 3.6	13.2 ± 3.1	12.9 ± 3.2	13.2 ± 2.6	13.1 ± 2.6	13.7 ± 2.7
t_3, min	17.7 ± 2	18.1 ± 1.9	17.2 ± 1.8	17.6 ± 1.9	18.1 ± 1.7	17.3 ± 2.5

*Data are presented as mean ± standard deviation unless otherwise indicated. BSA indicates body surface area; HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; t_1, time period between the patients' entrance to the operating room and the initial flow measurements after the minimal distal harvesting of the internal thoracic artery (ITA); t_2, time period between initial measurements and second measurements that were after the total harvesting of the ITA; t_3, time period between the second measurements and third measurements that were performed at the end of a waiting period after the treatment of the ITA pedicle.

Second and third esophageal temperature values decreased slightly in all groups, but were not different significantly between groups. Third esophageal temperatures remained over 35°C in all groups. First ITA pedicle tissue temperatures were nearly the same in the 6 groups, but they all showed a significant decrease in the second measurements ($P < .01$). There was not a significant difference between these decreased second measurements of the groups. The significant decrease continued in the third measurements in groups C, P, and HP, while heat loss was recovered in the pedicle rewarming procedure groups (Table 2).

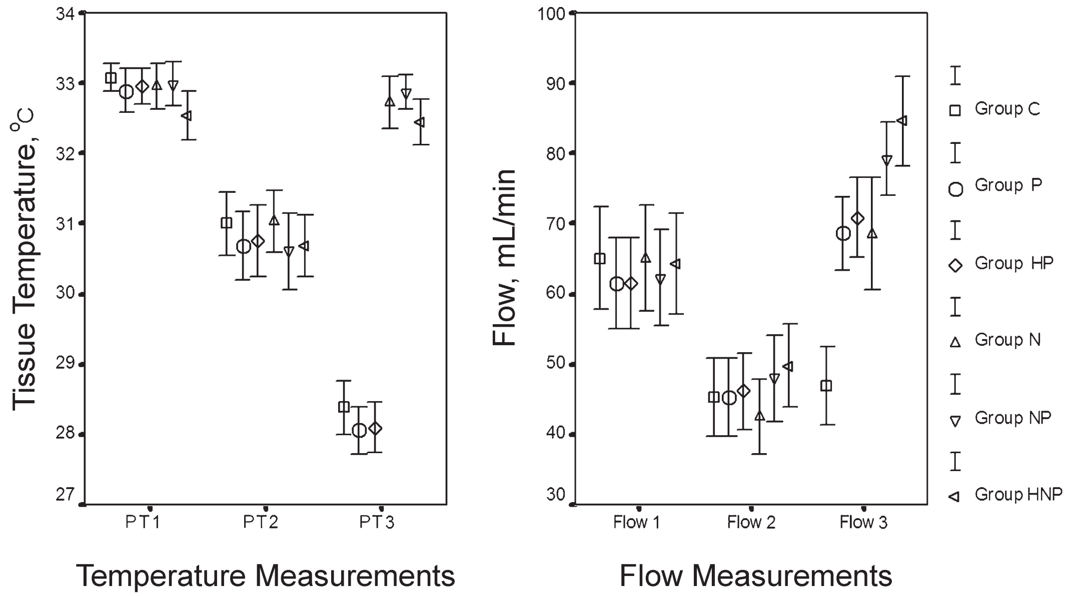
After minimal harvesting, measured preharvesting flows showed no significant difference between the 6 groups. Similar to the change in pedicle temperatures, second measurements of postharvesting flows decreased significantly ($P < .001$) in all groups (Table 3). When the postharvesting flows were compared between groups, no significant difference was detected. When the postharvesting and posttreatment flows were compared within groups, there were significant increases ($P < .001$), except for the control group (Table 3). In the control group, final flow was statistically lower than the preharvesting flow ($P < .001$), whereas in the pure normothermic conditions group, the difference between preharvesting flow and posttreatment flow was not statistically significant. In groups P, HP, NP, and NHP, posttreatment flows were significantly higher than preharvesting flows ($P < .01$ in group P and $P < .001$ in the other groups).

Pedicle storage in normothermic conditions following heated papaverine application (group NHP) increased the flow more than the preservation of the pedicle in normothermic conditions only ($P < .01$). There was no significant difference on the flow improvement between normothermic preservation following room temperature papaverine application and normothermic pedicle preservation only ($P > .05$), but the mean difference in 95% CI was 10.700 mL in favor of group NP. Flow increase was more prominent in group NHP in comparison to the papaverine group ($P < .01$) and the heated papaverine group ($P < .05$).

Between groups P and HP, posttreatment flows were not different statistically ($P > .05$, mean difference = –2.300). When group P was compared to group N, posttreatment flows were similar ($P > .05$, mean difference = 0.05 in 95% CI). Posttreatment flow results between group NP and group NHP were similar as well ($P > .05$, mean difference = –5.400 in 95% CI).

DISCUSSION

Particularly after being harvested, ITA spasm reveals itself as a decrease in ITA flow, which is a familiar circumstance for cardiac surgeons. Different vasodilators have been used to either prevent or treat ITA spasm, but the best agent and the best treatment method is still controversial. Besides surgical



Internal thoracic artery (ITA) pedicle tissue temperature and flow data are shown with error bars. PT indicates pedicle tissue temperature. PT1 is measured during the flow 1 measurement after minimal distal harvesting of the ITA. PT2 is measured during the flow 2 measurement that is after the total harvesting of the ITA. PT3 is measured during the flow 3 measurement at the end of a waiting period after treatment of the ITA pedicle.

trauma, moderate heat loss is an important factor for vasospasm. There are many studies about moderate hypothermia as part of open heart operations or cardiopulmonary bypass. However, the role of hypothermia in ITA spasm has not been adequately investigated so far. In our former studies [Tarhan 2006a; Tarhan 2006b], we have demonstrated the correlation between pedicle tissue temperature loss and flow reduction. In this study, we sought to demonstrate the efficacy of preserving an ITA graft in normothermic conditions after being harvested.

During the study, we made an effort to standardize the process beginning with the patients' arrival to the operating room. The patients who had excessive delays during anesthesia preparation were excluded from the study. Duration of each phase was not statistically different between the groups, and it can be stated that the subjects were exposed to

Table 2. Esophageal and Internal Thoracic Artery (ITA) Pedicle Tissue Temperatures*

	Group C	Group P	Group HP	Group N	Group NP	Group NHP
Treatment	No Treatment	Papaverine at Room Temperature	Heated Papaverine (37°C)	Normothermic Pedicle Rewarming Procedure	Normothermic Pedicle Rewarming Procedure after Papaverine at Room Temperature	Normothermic Pedicle Rewarming Procedure after Heated Papaverine
ET1	35.63 ± 0.17	35.67 ± 0.23	35.67 ± 0.28	35.66 ± 0.21	35.61 ± 0.17	35.66 ± 0.2
ET2	35.47 ± 0.12	35.53 ± 0.21	35.43 ± 0.2	35.57 ± 0.22	35.45 ± 0.16	35.54 ± 0.18
ET3	35.3 ± 0.15	35.37 ± 0.17	35.31 ± 0.2	35.44 ± 0.3	35.28 ± 0.19	35.35 ± 0.2
PT1	33.08 ± 0.41	32.9 ± 0.67	32.96 ± 0.55	32.95 ± 0.7	32.99 ± 0.67	32.55 ± 0.73
PT2	31.01 ± 0.96†	30.69 ± 1.04‡	30.76 ± 1.1†	31.04 ± 0.92†	30.6 ± 1.2†	30.68 ± 0.95†
PT3	28.38 ± 0.8†§	28.05 ± 0.7†‖	28.09 ± 0.76†§	32.73 ± 0.82§¶	32.88 ± 0.53§¶	32.45 ± 0.68§¶

*Data are presented as mean ± standard deviation. ET indicates esophageal temperature; PT, ITA pedicle temperature.
†$P < .001$ versus first PT in all groups except group P.
‡$P < .01$ versus first PT in group P.
§$P < .001$ versus second PT in all groups except group P.
‖$P < .01$ versus second PT in group P.
¶$P < .001$ versus third PT of groups C, P, and HP.

Table 3. Flow Data According to the Treatment Configurations*

	Group C	Group P	Group HP	Group N	Group NP	Group NHP
Treatment	No Treatment	Papaverine at Room Temperature	Heated Papaverine (37°C)	Normothermic Pedicle Rewarming Procedure	Normothermic Pedicle Rewarming Procedure after Papaverine at Room Temperature	Normothermic Pedicle Rewarming Procedure after Heated Papaverine
Preharvesting Flow	65.1 ± 15.5	61.55 ± 13.98	61.5 ± 14.04	65.05 ± 16.17	62.3 ± 14.73	64.25 ± 15.4
Postharvesting Flow	45.35 ± 11.79†	45.3 ± 12†	46.2 ± 11.65†	42.55 ± 11.5†	48 ± 13†	49.8 ± 12.62†
Posttreatment Flow	46.95 ± 11.79§¶	68.6 ± 11.29‡‖	70.9 ± 12.33‡§	68.55 ± 17.23‡	79.25 ± 11.08‡§	84.65 ± 13.58‡§**

* Data are presented as mean ± standard deviation. Treatment configurations are preharvesting flow after minimal distal harvesting, postharvesting flow after total harvesting, and posttreatment flow after treatment

†$P < .001$ versus preharvesting flow within all groups.

‡$P < .001$ versus postharvesting flow within all groups except group C.

§$P < .00$ versus preharvesting flow within groups C, HP, NP, and NHP.

‖$P < .01$ versus preharvesting flow within group P.

¶$P < .01$ versus posttreatment flow of groups P, HP, and N; $P < .001$ versus posttreatment flow of groups NP and NHP.

**$P < .05$ versus posttreatment flow of groups P and N.

operating room temperatures for similar periods (Table 1). Patients' characteristics were similar, and groups were homogenous. During procedures, hemodynamic changes were not significant. Patients who experienced diverse hemodynamic changes were excluded from the study.

As patients were exposed to the operating room temperature as soon as they entered, all subjects' core temperatures were lower than normal body temperature at initial measurements. In moderate environments, peripheral compartment temperature is usually 2°C to 4°C less than core temperature. This difference increases in extreme thermal and physiological conditions [Sessler 2000]. In our study, the esophageal temperatures, which reflect the core, were above 35°C. ITA pedicle temperatures decreased significantly to around 28°C in the room temperature groups. This generally neglected temperature loss due to exposure to the relatively lower temperature in the operating room was more remarkable in the periphery than the core. As a result, the subsequent ITA pedicle temperatures decreased significantly more than was expected in all patients. The tissue temperature gradient was higher than the esophageal temperature gradient. The gap between esophageal and tissue temperature gradients can indicate that the inner surface of the thorax and ITA pedicle act like a periphery after the chest is opened. The reactive vasoconstriction to store metabolic heat in the core may be responsible for the increase of the temperature gradient between the core and periphery. Correlated decrease of second ITA temperature with postharvesting flow may indicate that spontaneous heat loss is one of the vasospasm factors.

There are a variety of experimental studies on factors augmenting vasospasm by moderate cooling [Harker 1988; Harker 1991a; Harker 1991b]. Although there is a differential modulation of responses to exogenous norepinephrine in superficial and deep circulation with moderate cooling, cooling-induced augmentation of contractile responses to sympathetic nerve stimulation has been observed [Flavahan 1985; Yamamoto 1989]. Norepinephrine release is both nitric oxide dependent and nitric oxide independent [Yamamoto 1997].

In free-flow based studies, 2 flow measurements have been performed methodologically [Cooper 1992; He 1994; Sasson 1995]. In free-flow based studies, evaluations would be more accurate if the baseline ITA flows were known. However, the previous studies have a tendency of disregarding this baseline flow of ITA before harvest. In the former study [Tarhan 2006b], we also did not measure preharvesting flow. This study's innovation is measuring the preharvesting flow, which was performed at the initiation of harvesting. Adding vascular Doppler investigation to such studies might produce more accurate baseline flow results. Our preharvesting flow measurement method may not be ideal, but it reflects ITA native flow with a small error, which might result from the minimal harvesting trauma and the operating room temperature exposure.

Papaverine is a potent vasodilator drug, mostly used for the ITA spasms. It is used topically in different ways. Perivascular injection, spraying, and intraluminal application are recommended in the literature. However, intraluminal application of this drug was found to be harmful to the vascular endothelium because of its acidic character [Van Son 1992; Dipp 2001]. We used a combination of perivascular injection and spraying in this study. Generally, the preferred application of papaverine is at operating room temperature. The influence of heated papaverine at 37°C has also been investigated [Bilgen 1996]. Authors stated that the enzymatic activity that is induced at 37°C results in more vasorelaxation.

In our previous study, we did not investigate the effect of heated papaverine and that was a limitation of that study [Tarhan 2006b]. We could not comment on whether heated papaverine was superior to normothermic conditions or not. In group HP, posttreatment tissue temperatures did not improve statistically ($P > .05$). Posttreatment flow superiority of group NHP to group HP ($P < .05$) and the similarity of groups HP and N ($P > .05$, mean difference = 2.350 in 95% CI) may suggest that warming the tissue is a better choice than heating the papaverine itself.

The skeletonized ITA free flows indicate better flows when compared with those harvested as a pedicle [Athanasiou 2004]. The mechanism by which skeletonization might improve flow is uncertain. It may act by increasing graft diameter and decreasing resistance [Takami 2002]. Another factor is that when the ITA is naked, topical vasodilator papaverine may reach a wider surface area [Athanasiou 2004]. Deja states that skeletonization results in sympathectomy of ITA [Deja 2005]. He concludes that it has no effect on endothelium-dependent relaxation but increases reactivity of ITA to norepinephrine. It has been demonstrated that perivascular adipose tissue in human ITA releases a relaxation factor that acts through the activation of calcium-dependent potassium channels [Gao 2005]. New studies investigating the effect of cooling on pedicled and skeletonized ITA would be helpful to understand the pathophysiology.

ITA vasospasm is a phenomenon in consequence of moderate hypothermia and results in flow reduction after harvesting. To provide adequate flow in the ITA pedicle, several methods such as papaverine addition or tissue warming manipulations can be used. The key is warming the pedicle. As normothermic conditions are provided for the pedicle, heating the papaverine is unnecessary. The ideal solution is to remedy the basic cause of the problem. We suggest that matching the artery's initial flow can be targeted for treatment efficacy, instead of a final flow higher than the initial flow.

In conclusion, topical application of heated papaverine itself does not warm the pedicle, but papaverine efficiency increases when the pedicle is stored in normothermic conditions. Since the preharvesting flows are matched, preserving the ITA pedicle in normothermic conditions can be the preferred treatment of spasm. We suggest that preservation of the ITA in normothermic conditions without papaverine application may be adequate clinically.

REFERENCES

Athanasiou T, Crossman MC, Asimakopoulos G, et al. 2004. Should the internal thoracic artery be skeletonized? Ann Thorac Surg 77:2238-46.

Bilgen F, Yapici MF, Serbetçioglu A, et al. 1996. Effect of normothermic papaverine to relieve intraoperative spasm of the internal thoracic artery. Ann Thorac Surg 62:769-71.

Cooper GJ, Wilkinson AL, Angelini GD. 1992. Overcoming perioperative spasm of the internal mammary artery. Which is the best vasodilator? J Thorac Cardiovasc Surg 104:465-8.

Deja MA, Golba KS, Malinowski M, et al. 2005. Skeletonization of internal thoracic artery affects its innervation and reactivity. Eur J Cardiothorac Surg 28:551-7.

Dipp MA, Nye PCG, Taggart DP. 2001. Phenoxybenzamine is more effective and less harmful than papaverine in the prevention of radial artery vasospasm. Eur J Cardiothorac Surg 19:482-6.

Flavahan NA, Lindblad LE, Verbeuren TJ, Shepherd JT, Vanhoutte PM. 1985. Cooling and alpha$_1$- and alpha$_2$-adrenergic responses in cutaneous veins: fole of receptor reserve. Am J Physiol 249:H950-5.

Formica F, Ferro O, Brustia M, et al. 2006. Effects of papaverine and glycerilnitrate-verapamil solution as topical and intraluminal vasodilators for internal thoracic artery. Ann Thorac Surg 81:120-4.

Gao YJ, Zeng ZH, Teoh K, et al. 2005. Perivascular adipose tissue modulates vascular function in the human internal thoracic artery. J Thorac Cardiovasc Surg 130:1130-6.

Girard DS, Sutton JP 3rd, Williams TH, et al. 2004. Papaverine delivery to the internal mammary artery pedicle effectively treats spasm. Ann Thorac Surg 78:1295-8.

Harker CT, Vanhoutte PM. 1988. Cooling the central ear artery of the rabbit: myogenic and adrenergic responses. J Pharmacol Exp Ther 245:89-93.

Harker CT, Ousley PJ, Harris EJ, et al. 1990. The effects of cooling on human saphenous vein reactivity to adrenergic agonists. J Vasc Surg 12:45-9.

Harker CT, Ousley PJ, Bowman CJ, Porter JM. 1991. Cooling augments alpha$_2$-adrenoceptor-mediated contractions in rat tail artery. Am J Physiol 260:H1166-71.

Harker CT, Taylor LM Jr, Porter JM. 1991. Vascular contractions to serotonin are augmented by cooling. J Cardiovasc Pharmacol 18:791-6.

He GW, Buxton BF, Rosenfeldt FL, Angus JA, Tatoulis J. 1994. Pharmacologic dilatation of the internal mammary artery during coronary bypass grafting. J Thorac Cardiovasc Surg 107:1440-7.

Jones EL, Lattouf OM, Weintraub WS. 1989. Catastrophic consequences of internal mammary hypoperfusion. J Thorac Cardiovasc Surg 98:902-7.

Rosenfeldt FL, He GW, Buxton BF, Angus JA. 1999. Pharmacology of coronary artery bypass grafts. Ann Thorac Surg 67:878-88.

Sasson L, Cohen AJ, Hauptman E, Schachner. 1995. Effect of topical vasodilators on internal mammary arteries. Ann Thorac Surg 59:494-6.

Sessler DI. 2000. Perioperative heat balance. Anesthesiology 92:578-96.

Takami Y, Ina H. 2002. Effects of skeletonization on intraoperative flow and anastomosis diameter of internal thoracic arteries in coronary artery bypass grafting. Ann Thorac Surg 73:1441-5.

Tarhan IA, Kehlibar T, Yapici F, et al. 2006. Efficacy of physiologic temperature on the spasm of harvested radial artery. Heart Surg Forum 9:E765-9.

Tarhan A, Kehlibar T, Yapici F. 2006. Role of physiological state 'normothermia' in internal thoracic artery spasm after harvesting. Eur J Cardiothorac Surg 30:749-52.

Van Son JAM, Tavilla G, Noyez L. 1992. Detrimental squeal on the wall of the internal mammary artery caused by hydrostatic dilation with diluted papaverine solution. J Thorac Cardiovasc Surg 104:972-6.

Yamamoto R, Cline WH Jr, Takasaki K. 1989. Effect of moderate cooling endogenous norepinephrine release from the mesenteric vasculature of rats. J Auton Pharmacol 9:347-55.

Yamamoto R, Takasaki K, Nickols GA. 1992. Purinergic vasoconstrictor component revealed by moderate cooling in the isolated mesenteric vasculature of Sprague-Dawley rats. J Pharmacol Exp Ther 262:1133-8.

Yamamoto R, Wada A, Asada Y, et al. 1997. Nitric oxide-dependent and independent norepinephrine release in rat mesenteric arteries. Am J Physiol 272:H207-10.

Yavuz S, Celkan A, Göncü T, Türk T, Ozdemir A. 2001. Effect of papaverine applications on blood flow of the internal mammary artery. Ann Thorac Cardiovasc Surg 7:84-8.