Effects of normothermic organ bath and verapamil—nitroglycerin solution alone or in combination on the blood flow of radial artery

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Abstract

Objective: Radial artery pedicle tissue cooling during harvesting is one of the major causes of vasospasm. We aimed to compare the effects of the pedicle rewarming method, normothermic organ bath, and one of the most preferred topical antispasmodic agents, verapamil—nitroglycerin solution alone or in combination on the blood flow of radial artery. Methods: Consecutively randomized patients \( (n = 80) \) undergoing coronary bypass were organized as four equal-sized groups. Effects of normothermic organ bath and topically performed verapamil—nitroglycerin solution alone or in combination on the blood flow of radial artery were investigated. In the control group no antispasmodic treatment was performed. Free flows were measured at three stages: as initial flow after minimal distal harvesting, post-harvesting flow after total harvesting, and post-treatment flow following a waiting period after the application of the antispasmodic protocol. At each stage, pedicle and esophageal temperatures were also recorded. Results: Radial artery pedicle temperatures decreased significantly during harvesting in all groups \((p < 0.001)\). Normothermic organ bath, topical verapamil—nitroglycerin solution treatment, and their combination increased flow significantly \((p < 0.001)\), from \(40.3 \pm 10.48\) ml/min to \(64.3 \pm 18.8\) ml/min, from \(38.9 \pm 13.91\) ml/min to \(62.75 \pm 15.23\) ml/min, from \(41.4 \pm 11.19\) ml/min to \(75.4 \pm 15.32\) ml/min, respectively). The differences between the initial and post-treatment flows were not significant in the combined procedure group \((p > 0.05)\), whereas the initial levels were not reached in the post-treatment flows \((p < 0.05)\) in the normothermic organ bath and verapamil—nitroglycerin groups. Conclusions: Hypothermia plays an important role in radial artery vasospasm. Normothermic organ bath and verapamil—nitroglycerin solution alone or in combination relieve spasm of radial artery. © 2007 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.

Keywords: Radial artery; Vasospasm; Normothermia; Hypothermia; Verapamil; Nitroglycerine

1. Introduction

With high patency rates, internal thoracic artery is accepted as the gold standard for graft choice in coronary bypass surgery [1]. In the last decade, with good mid- and long-term results, radial artery has been increasingly preferred as the second graft choice for coronary surgery [2,3].

Since radial artery was first used as a coronary artery bypass graft by Carpentier et al. [4], perioperative spasm of the graft has been a major concern. Spasm that was thought to be due to harvesting techniques was the reason for the abandonment of Carpentier’s initial advocacy for using RA for coronary artery bypass grafting [5]. Since Acar et al.’s reintroducing RA graft in 1992 [5], besides a meticulous harvesting technique, a systemic or topical vasodilating treatment has been recommended. Various in vitro studies suggest utilization of different vasodilating agents for prevention of vasospasm [6–8]. Heat loss in the operating room and peripheral cooling by the redistribution of heat can induce vasospasm. It is demonstrated that cooling occurs during the harvesting procedure and rewarming of the harvested left internal thoracic artery and radial artery pedicles can be an effective spasmolytic method [9,10].

We aimed to evaluate the efficiency of two different spasmolytic methods: topical vasodilating solution application and pedicle rewarming method, alone or in combination. As the combination of verapamil and nitroglycerin solution (VG solution) has been suggested to be an effective vasodilator providing a rapid onset, a complete relaxation, and a long-lasting vasorelaxation effect [6], we preferred this solution as the topical vasodilator. To compare the effects of VG solution and pedicle rewarming, alone or in combination on the free flow of radial artery, this randomized, prospective study is designed.
2. Patients and methods

After having informed consent from patients and the ethical committee approval, 80 patients, whose radial arteries were used as a conduit for elective first-time myocardial revascularization, were included in the study. Each patient was randomly allocated in one of the four equal-sized groups (Table 1). The effects of normothermic organ bath procedure, topical VG solution application, and their combined application were investigated. In the control group no treatment was performed.

Patients who had one of the following criteria — age over 70 years, peripheral arterial disease, chronic renal disease, low cardiac ejection fraction, perioperative vasoactive agent utilization, and excessive delays during anesthesia preparation — were not included in the study. Pharmaceuticals, which have vasodilator activity, were stopped on the last day before surgery.

2.1. Preoperative management

All patients underwent a modified Allen’s test preoperatively. Oxygen saturation was measured by connecting the patients’ thumb or index finger to the oximeter gauge. The radial and ulnar arteries were compressed until the saturation value decreased to zero. The ulnar artery was then released and the period that the oxygen saturation reached the prior value was noted. Beyond 10 s, the test was considered unacceptable. The test was performed on both hands of the patients.

The arrival time of the patient to the anesthesia room was also recorded. The time period between the patients’ entrance to the operating room and the first measurements; t1, time period between the patients’ entrance to the operating room and the first measurements; t2, time period between the first and second measurements; t3, time period between the second and third measurements.

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control group (n = 20)</th>
<th>NOB group (n = 20)</th>
<th>VG group (n = 20)</th>
<th>VG + NOB group (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>15/5</td>
<td>14/6</td>
<td>13/7</td>
<td>14/6</td>
</tr>
<tr>
<td>Age (year)</td>
<td>60.25 ± 5.8</td>
<td>58.4 ± 6</td>
<td>60.5 ± 5.9</td>
<td>59.65 ± 7.8</td>
</tr>
<tr>
<td>Range</td>
<td>48—69</td>
<td>50—67</td>
<td>49—69</td>
<td>43—69</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.85 ± 0.11</td>
<td>1.89 ± 0.11</td>
<td>1.93 ± 0.11</td>
<td>1.92 ± 0.1</td>
</tr>
<tr>
<td>Range</td>
<td>1.68—2.04</td>
<td>1.72—2.1</td>
<td>1.7—2.08</td>
<td>1.65—2.06</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>75.7 ± 8.6</td>
<td>74.8 ± 9.2</td>
<td>75.6 ± 6.7</td>
<td>75.8 ± 9.3</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>75.8 ± 8.9</td>
<td>75.7 ± 8.2</td>
<td>76.3 ± 6.3</td>
<td>76.6 ± 8.6</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>76.9 ± 9.2</td>
<td>76.1 ± 7.8</td>
<td>75.6 ± 6.3</td>
<td>76 ± 7.9</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>77.5 ± 4</td>
<td>78.5 ± 4.5</td>
<td>77.85 ± 3.6</td>
<td>74.4 ± 4.6</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>78.05 ± 5.2</td>
<td>78.4 ± 3.7</td>
<td>77.25 ± 2.8</td>
<td>77.1 ± 4.3</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>77.65 ± 3.9</td>
<td>79.1 ± 3.4</td>
<td>76.9 ± 2.8</td>
<td>77.05 ± 4.4</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>3.95 ± 2</td>
<td>4 ± 1.9</td>
<td>3.6 ± 1.9</td>
<td>3.3 ± 1.9</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>4 ± 1.3</td>
<td>3.7 ± 1.7</td>
<td>3.5 ± 1.6</td>
<td>3.2 ± 1.7</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>4.3 ± 1.6</td>
<td>4.1 ± 1.7</td>
<td>3.7 ± 1.4</td>
<td>3.3 ± 1.8</td>
</tr>
<tr>
<td>t1 (min)</td>
<td>32.6 ± 4.6</td>
<td>33.6 ± 8.5</td>
<td>32.8 ± 7.2</td>
<td>37 ± 7.2</td>
</tr>
<tr>
<td>t2 (min)</td>
<td>14.7 ± 2</td>
<td>14.5 ± 2.3</td>
<td>14.8 ± 1.2</td>
<td>15.2 ± 1.5</td>
</tr>
</tbody>
</table>
| t3 (min)       | 13.9 ± 1.5             | 13.5 ± 1.7        | 12.8 ± 3         | 14.5 ± 1.2             

Data are presented as mean ± standard deviation except gender ratios. BSA, body surface area; MAP, mean arterial pressure; CVP, central venous pressure; t1, time period between the patients’ entrance to the operating room and the first measurements; t2, time period between the first and second measurements; t3, time period between the second and third measurements.
2 min. We called this rewarming procedure as ‘normothermic organ bath’ (NOB).

In the VG group, 10 ml VG solution (consisted of verapamil hydrochloride 5 mg, nitroglycerin 2.5 mg, heparin 500 units, 8.4% NaHCO₃ 0.2 ml, and Ringer’s solution 300 ml) at room temperature (20 °C) was topically performed and the pedicle was placed into gauze soaked with normal saline solution at room temperature.

In the combined procedure group after the application of 10 ml VG solution at 36 °C, normothermic organ bath method was performed.

Following the relevant treatment, post-treatment flows were measured after approximately a 15-min waiting period. The volume of blood expelled from the end of the bleeding artery in a 30 s period was the evaluation method for the free flow measuring. The flow per minute was calculated by multiplying the value twice (ml/min). After each measurement, the bleeding end of the artery was occluded with a bulldog clamp.

Within all groups, overall three subsequent flows were noted down as: initial flow, after minimal distal harvesting; post-harvesting flow, after total harvesting of the pedicle; and post-treatment flow, after a waiting period following the antispasmodic protocol. Whenever free flows were measured, time of the measurement, esophageal temperature, pedicle tissue temperature, mean arterial pressure, heart rate, and central venous pressure values were simultaneously noted down.

Pedicle temperature levels were measured from the areolar tissue around the radial artery using a myocardial temperature probe (De Royal, REF 81-030418). In addition, the probe was left inside the gauze pack during the process in order to monitor the pedicle local temperature consistently. A general-purpose temperature probe (De Royal, REF 81-020409) was used to measure the esophageal temperature. Until the utilization of radial artery for anastomosis, radial artery pedicle was left in situ, attached to the brachial artery, stored in the gauze pack, and normothermic bath was performed. In the control group after measuring the final flows we applied VG solution and stored pedicle in NOB.

2.3. Statistical analysis

All statistical analyses were performed by using the program GraphPad InStat® version 3.06. All values were expressed as mean ± standard deviation. In order to compare the flows, esophageal temperatures, pedicle tissue temperatures, mean arterial pressures, heart rate values, and central venous pressure measurements, repeated measures analysis of variance was used in each group.

The comparison of measurements between groups was made by one-way analysis of variance and Tukey’s multiple-comparison tests. Gaussian distributions were tested by using Kolmogorov and Smirnov assumption test, Kruskal—Wallis test for comparisons between groups, Friedman test for comparisons within groups, and Dunn’s multiple comparison test as post-test were performed whenever the normality test failed with p < 0.05. A p-value of less than 0.05 was considered significant.

3. Results

We had no permanent major local complications. In the postoperative period, no patient had ischemic coronary event.

Clinical characteristics and hemodynamic data of the patients are presented in Table 1. When the hemodynamic variables were compared within and between the groups, there was no significant difference. Perioperative hemodynamic parameters — heart rate, mean arterial pressure, and central venous pressures — were stable during the procedure. The three periods, between the arrival of the patient to the anesthesia room and the initial measurements, between the initial and post-harvesting measurements, and between the post-harvesting and post-treatment measurements were also not statistically different between the four groups.

Esophageal and pedicle temperature measurements are presented in Table 2. Esophageal temperature measurements in each phase were not significantly different among the groups. Although esophageal temperatures decreased slightly in the post-harvesting measurements, final measurements remained over 35 °C (Fig. 1). In the first and second phases, the pedicle tissue temperatures were similar between groups. Pedicle temperatures decreased significantly during harvesting in all groups (p < 0.001). The pedicle temperature decrease continued in the post-treatment measurements in the control group and VG group (from 30.78 ± 0.6 to 28.88 ± 0.5 and from 30.45 ± 0.55 to 28.71 ± 0.5, respectively, p < 0.001), whereas in the NOB group and combination group final tissue temperature levels increased significantly (p < 0.001) (Fig. 1).

The initial and post-harvesting flows were not statistically different among groups. Free flows decreased significantly (p < 0.001) after harvesting in all groups. Normothermic organ bath, topical verapamil—nitroglycerin solution treatment, and their combination increased flow (ml/min) significantly (p < 0.001, from 40.3 ± 10.48 to 64.3 ± 18.8 in NOB group, from 38.9 ± 13.91 to 62.75 ± 15.23 in VG group, from 41.4 ± 11.19 to 75.4 ± 15.32 in combined group). In the control group, final flow was significantly decreased when compared to the initial flow (p < 0.001). The final flow of the control group was significantly different from the post-treatment flows of three treatment groups (p < 0.001). There was not a significant difference between the post-treatment flows of the treatment groups.

### Table 2

<table>
<thead>
<tr>
<th>Temperature values</th>
<th>Control group</th>
<th>NOB group</th>
<th>VG group</th>
<th>VG + NOB group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET₁ (°C)</td>
<td>35.36 ± 0.3</td>
<td>35.4 ± 0.2</td>
<td>35.42 ± 0.3</td>
<td>35.39 ± 0.2</td>
</tr>
<tr>
<td>ET₂ (°C)</td>
<td>35.3 ± 0.3</td>
<td>35.22 ± 0.2</td>
<td>35.27 ± 0.2</td>
<td>35.23 ± 0.2</td>
</tr>
<tr>
<td>ET₃ (°C)</td>
<td>35.16 ± 0.2</td>
<td>35.2 ± 0.2</td>
<td>35.15 ± 0.2</td>
<td>35.15 ± 0.2</td>
</tr>
<tr>
<td>TT₁ (°C)</td>
<td>32.67 ± 0.5ᵇ</td>
<td>32.61 ± 0.5ᵃ</td>
<td>32.57 ± 0.46ᵇ</td>
<td>32.66 ± 0.46ᵃ</td>
</tr>
<tr>
<td>TT₂ (°C)</td>
<td>30.78 ± 0.6ᵃ</td>
<td>30.6 ± 0.6ᵈ</td>
<td>30.45 ± 0.55ᵈ</td>
<td>30.57 ± 0.6ᵈ</td>
</tr>
<tr>
<td>TT₃ (°C)</td>
<td>28.88 ± 0.5ᵃ</td>
<td>32.55 ± 0.4</td>
<td>28.71 ± 0.5ᵃ</td>
<td>32.43 ± 0.4</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation. ET, esophageal temperature; TT, radial artery pedicle tissue temperature.

ᵃ p < 0.001 vs second TT within all groups.
ᵇ p < 0.001 vs third TT within VG group.
ᶜ p < 0.001 vs third TT within VG + NOB group.
ᵈ p < 0.001 vs third TT within all groups.
ᵉ p < 0.001 vs third TT of groups NOB, and VG + NOB.
95% confidence interval (CI) was computed for post-treatment flow difference NOB versus VG, the following figures were found: mean difference = 1.550 ml/min, lower 95% CI = -11.149, and upper 95% CI = 14.249. These changes are not clinically relevant. However, for NOB versus combined treatment (mean difference = 11.100 ml/min, lower 95% CI = 23.799, and upper 95% CI = 1.599) and VG versus combined treatment (mean difference = -12.650 ml/min, lower 95% CI = -25.349, and upper 95% CI = 0.04884), the changes can be postulated as clinically relevant. The post-treatment flows reached initial levels in the combined procedure group (p > 0.05), whereas the difference between the initial and the post-treatment flows were significantly different (p < 0.05) in the NOB and VG groups (Table 3).

4. Discussion

Vasospasm occurs in all kinds of vessels but especially in type III arteries, e.g. RA that contains more smooth muscle cells in their walls. To overcome spasm, the combination of topical and systemic vasodilator treatment is a generally accepted treatment. But there is still a debate on the ideal vasodilator agent [11]. Most used vasodilators are Ca antagonists [5,12], papaverine [13], phosphodiesterase inhibitor milrinone [14], phenoxybenzamine [15] and verapamil—nitroglycerine [6], verapamil—papaverine [16] solution.

Since the initial report by Taggart et al. [15] phenoxybenzamine has gained popularity to treat radial artery spasm. Then Conant et al. found out that a phenoxybenzamine-treated radial artery failed to respond to noradrenalin. Although phenoxybenzamine is effective in eliminating the vasoconstriction mediated by noradrenalin the contribution of other circulating vasoconstrictors could be as important [17].

The in vivo topical vasodilator comparing study of Nisanoglu et al. states that nitroglycerin solution effectively prevents perioperative RA spasm [18]. VG solution is documented to provide a rapid onset, a complete relaxation, and a long-lasting vasorelaxation effect [6].

Surgical trauma and diathermy are the major factors of vasospasm during harvesting of the RA. In addition to the major factor trauma, recent studies indicate that hypothermia plays an active role in radial artery spasm. It is documented that radial artery pedicle temperature decreases during harvesting. In Tarhan et al.’s study [9], concurrent with the decreasing temperatures, the radial artery free flows also decreased significantly. This study suggests that rewarming of the pedicle after harvesting is an effective spasmolytic method as rewarming successfully increased radial artery flow. The recent in vitro study of Oo et al. [19] provided an important insight. They have investigated the effects of rapid and gradual cooling on radial artery contraction. According to the authors, rapid cooling is a 1–2 min period, because they inserted in vitro the radial artery segment into 22°C from 37°C, but in the gradual

Table 3

<table>
<thead>
<tr>
<th>Flow values</th>
<th>Control group (ml/min)</th>
<th>NOB group (ml/min)</th>
<th>VG group (ml/min)</th>
<th>VG + NOB group (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial flow</td>
<td>74.3 ± 25.92</td>
<td>70.5 ± 20.64</td>
<td>69.95 ± 23.6</td>
<td>73.1 ± 22.6</td>
</tr>
<tr>
<td>Post-harvesting flow</td>
<td>43.1 ± 12.15</td>
<td>40.3 ± 10.48</td>
<td>38.9 ± 13.91</td>
<td>41.4 ± 11.19</td>
</tr>
<tr>
<td>Post-treatment flow</td>
<td>39.7 ± 10.53</td>
<td>64.3 ± 18.8</td>
<td>62.75 ± 15.23</td>
<td>75.4 ± 15.32</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation.

* p < 0.001 vs second flow within all groups.

# p < 0.001 vs third flow within control group.

< p < 0.05 vs third flow within groups NOB and VG.

d p < 0.001 vs third flow within groups NOB, VG, and VG + NOB.

* p < 0.001 vs third flows of groups NOB, VG, and VG + NOB.
procedure they decreased the media temperature in 30 min slowly. They showed that rapid cooling induces contraction, since gradual cooling leads to vasodilation. Rapid cooling induced significant contraction, mediated by a rise in the intracellular calcium. Gradual cooling acted as a vasodilator by reducing the basal tension and the response to potassium chloride and noradrenaline. Their in vitro experiment resembles our in vivo situation. We take the patients into the cold (20°C) operating room and expose them to cold rapidly. They concluded that contraction induced by the rapid temperature changes could be blocked by glyceryl trinitrate.

There are a variety of experimental studies on factors augmenting the vasospasm by cooling [20–22]. Although there is a differential modulation of responses to exogenous norepinephrine in superficial and deep circulation with moderate cooling, the cooling-induced augmentation of contractile responses to sympathetic nerve stimulation were observed [23,24].

In moderate environments, peripheral compartment temperature is usually 2–4°C less than the core temperature. This gradient increases in extreme thermal and physiological conditions [25]. In the study, esophageal and local tissue temperature levels were surprisingly lower than expected in the initial measurements. This extreme spontaneous decrease in the temperatures may be due to the preoperative waiting period including initial anesthesia procedure.

Vasoconstriction, which stores metabolic heat in the core, increases the temperature gradient between core and periphery. In our study the esophageal temperatures indicating the core were saved at above 35°C. However, RA pedicle tissue temperatures decreased significantly to around 28.88 ± 0.5°C and 28.71 ± 0.5°C, respectively, in group C and group VG. This heat-preserving reaction induces vasoconstriction on radial artery as a member of the periphery.

During the operation when the room temperature was lowered to 20°C, this cooling at the periphery continued since exposure to hypothermia is inevitable. Esophageal temperature values indicating the core temperatures reduced slightly but did not fall below 35°C, possibly due to the heating blanket system and core keeping mechanism that enforces peripheral vasculature for constriction and spasm. Normothermic organ bath method by rewarming the pedicle tissue decreases the gradient between core and periphery and this can result in the recovery of vasoconstriction.

Our aim with NOB for rewarming was to reach normothermia. The temperature of the solution applied was 36°C and that is why we named the method 'normothermic organ bath'. Nevertheless, application of normothermic saline could not make the pedicle temperatures reach normothermia. According to us, the ideal technique is to keep the pedicle in a solution at 36°C constantly. A self-rewarming device, which is temperature-controlled with thermostat, would be ideal in order to keep the pedicle at constant temperature. We believe our simple method 'NOB' substitutes this imaginary ideal complicated device. After 13–14 min with NOB the temperatures of the pedicles did not reach normothermia and esophageal temperatures continued to decrease despite total body warming with heating blanket. NOB system has been successful to rewarm pedicle because the initial pedicle temperature values were regained. Initial pedicle temperatures were not normothermic even before surgery began.

We sprayed normothermic saline solution every 2 min constantly, that is why we did not experience major temperature fluctuations during in situ pedicle storage method (NOB) in previous studies with similar method [10,11,26].

When the radial artery harvesting methods were evaluated with transmission electron microscopy and tissue lipid peroxidation, the least damage was found in the method in which harvested radial arteries were left in situ with both ends open [27]. The authors concluded that arterial grafts that would be used for coronary artery surgery should not be left ischemic during harvesting to prevent endothelial damage. Ischemia of the conduits for coronary artery grafting can be prevented by leaving them in their anatomic position until the distal coronary artery anastomosis [27].

Taking the factors discussed so far into consideration, harvesting with minimal trauma to the vessel and close control of the temperature changes as Perrault and Mommerot [28] recommended are essential to the prevention of the radial graft spasm. We believe leaving the graft in situ after harvesting until the distal coronary anastomosis is best for preventing endothelial damage and performing topical VG solution seems to be the most effective agent, and with the combination of the pedicle rewarming method, the normothermic organ bath is a beneficial alternative protocol.

We prefer radial artery as the second choice graft in coronary bypass surgery. Radial artery is a valuable graft if treated appropriately. This study’s results and some previous experiences [10,11] demonstrate that normothermic treatment is the key for better antispasmodic results in arterial grafts [28]. We believe that pedicle rewarming is a good adjuvant treatment to pharmacological preferences. We prefer verapamil—nitroglycerine solution combined with NOB in order to treat radial artery against eventual post-harvesting spasm. We need to see mid-term and long-term comparative results of these methods.

In conclusion, the hypothermic process begins with the patient’s entrance to the operating room. Peripheral hypothermia was observed to be more profound than the core. Post-harvesting radial artery free flow decreases are parallel to the peripheral temperature drop. Normothermic organ bath and verapamil—nitroglycerine solution alone or in combination increases free flow of radial artery.

We believe that appropriate pedicle rewarming is successful in increasing free flows of harvested in situ radial arteries, but verapamil—nitroglycerine solution has better clinical results on radial artery flow, under higher pedicle temperature conditions. Therefore, we suggest the combination of normothermic rewarming and topical application of verapamil—nitroglycerine.

References


