

# Effect of Papaverine Applications on Blood Flow of the Internal Mammary Artery

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**The aim of this prospective study was to compare the effect of different papaverine applications on the free blood flow in the internal mammary artery (IMA) prepared for coronary artery bypass grafting (CABG). The patients were divided into three groups: group I (n=50; intraluminal papaverine application), group II (n=50; topical papaverine application), and group III (n=50; periarterial papaverine application). The free flow from the distal cut end of the IMA was measured under controlled hemodynamic conditions (Flow 1). Just before the establishment of cardiopulmonary bypass, the flows of the IMA were measured again (Flow 2). The mean blood flow in the IMA was  $60.7 \pm 6.0$  ml/min before papaverine application. After papaverine application, the mean blood flow in group I was  $129.3 \pm 10.0$  ml/min, in group II, it was  $87.7 \pm 3.8$  ml/min, and in group III, it was  $130.6 \pm 9.2$  ml/min ( $p < 0.0001$ ). Proportional increases in blood flow observed in group I (106.3%) and group III (116.2%) were higher than in group II (44.2%) ( $p < 0.0001$ ).**

**Consequently, to relieve perioperative spasm of the IMA, application of papaverine injected into the periarterial tissues of its pedicle was considered to be a safe and effective alternative to topical or intraluminal application. (Ann Thorac Cardiovasc Surg 2001; 7: 84-8)**

**Key words:** internal mammary artery, papaverine applications, topical vasodilators, periarterial application

## Introduction

The internal mammary artery (IMA) graft has been shown to yield superior clinical results at 20 years,<sup>1)</sup> and it is today considered the conduit of choice for coronary artery bypass grafting (CABG). However, perioperative vascular spasm with insufficient blood flow rate has been reported to cause perioperative morbidity.<sup>2-4)</sup> Vasospasm can occur during harvesting of the IMA and its pedicle. Therefore, to overcome this problem most cardiac centers routinely advocate the use of papaverine during the

IMA preparation.<sup>5)</sup>

The aim of the present study was to report our experience with regard to the effect of different papaverine applications on the free blood flow in the IMA prepared for CABG.

## Materials and Methods

### Patients

This study consisted of one hundred and fifty patients who underwent harvesting of the IMA prepared for elective CABG between August 1998 and December 1999. All patients signed a consent form approved by the local institutional human research committee. The patients ranged in age from 36 to 79 years (mean, 57.8 years). There were 103 men and 47 women, and body surface area was  $1.83 \pm 0.17$  m<sup>2</sup> (range, 1.54 to 2.3 m<sup>2</sup>). Angina classification according to the Canadian Cardiovascular

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Society was as follows: 2 patients in class I, 8 in class II, 121 in class III, and 19 in class IV. Forty-seven patients had a previous history of myocardial infarction; 28 had an anteroseptal myocardial infarction. One hundred and one patients (94%) had multivessel disease. Seven patients (4.6%) had left main coronary artery lesion. The mean preoperative ejection fraction was  $52.7 \pm 11.3\%$  (range, 32% to 70%); mean left ventricular end-diastolic pressure was  $12.8 \pm 5.9$  mmHg (range, 6 to 35 mmHg). Two patients (1.3%) had previous CABG. In three patients (2%) mitral valve replacement (2 patients) and mitral valve reconstruction (1 patient) in addition to CABG were performed.

The left IMA (LIMA) to the left anterior descending artery (LAD) anastomosis was performed in 146 patients (97.3%). In 1 patient the LIMA was anastomosed to the first large diagonal branch of the LAD because of the poor quality of the LAD itself. The *in-situ* LIMA was not used in 2 patients due to intimal dissection but was used as a free graft. The mean number of grafts per patient was  $3.6 \pm 0.7$  (range; 1 to 5). Two patients had left ventricular aneurysmectomy.

### Surgical technique

All patients underwent standard general anesthesia with fentanyl and pancuronium. A Swan-Ganz catheter was inserted through the right internal jugular vein. The surgical technique consisted of standard cardiopulmonary bypass with moderate systemic hypothermia and topical cooling. Myocardial protection was achieved initially with antegrade crystalloid cardioplegia after application of the crossclamp and subsequently antegrade cold blood cardioplegia being administered into the aortic root after each distal anastomosis. All anastomoses were performed during a single clamp period. Just before the crossclamp was removed all patients received warm induction.

The IMA was mobilized with a wide musculofascial pedicle from the subclavian vein to just beyond the bifurcation into the superficial epigastric and musculophrenic branches using surgical clips and low-voltage electrocautery. Following systemic heparinization (3 mg/kg; sodium heparin), the IMA was divided distally.

### Flow measurements

Five minutes after systemic heparinization, the free flow from the distal cut end of the IMA was determined by allowing the IMA to bleed into an open beaker for 1 minute and measuring the volume per minute under controlled hemodynamic conditions (Flow 1). The IMA then

was occluded gently with a bulldog clamp. In this study, a total of 60 mg of papaverine hydrochloride in 40 ml of saline solution (pH 5.1) was administered to each patient.

The patients were divided into three groups: group I (n=50) had intraluminal papaverine applied retrogradely to the IMA, group II (n=50) had topical papaverine, and group III (n=50) had papaverine mixed saline solution injected into the periarterial tissues of the IMA pedicle. In group I, retrograde injection into the unclamped IMA through a fine cannula was performed gradually over a 30-second interval, with care taken to avoid hydrostatic dilatation. In group II, diluted papaverine was sprayed onto the IMA pedicle throughout its whole length with small syringe. The IMA pedicle was wrapped in a papaverine-soaked sponge. In group III, the papaverine was injected into the pedicle in the periarterial tissue along the entire length of the IMA pedicle with a fine cannula. Just before the establishment of cardiopulmonary bypass, the flows of the IMA were measured again (Flow 2).

### Statistical analysis

Statistical analyses were performed using the SPSS software package (SPSS for Windows, version 6.1; SPSS Inc, Chicago, IL, USA). Data are presented as the mean  $\pm$  the standard deviation of the mean or percent when necessary. Results were compared using Student's *t* test or one-way analysis of variance with subsequent paired comparisons according to Duncan's multiple range test. A *p* value of less than 0.05 was considered to be statistically significant.

### Results

The demographic and hemodynamic data are shown in Table 1. There were no significant changes found between the groups with respect to variables ( $p > 0.05$ ). Heart rates, mean arterial pressure and central venous pressure at the time of flow measurement were not significantly different between the groups.

There was no in-hospital mortality. In Group II, abnormal ST change in anterior derivations on electrocardiogram was observed in 2 patients (1.3%) and possibly caused by IMA spasm. Mean stay in the intensive care unit was 3.1 days (range, 2 to 7 days). Low cardiac output syndrome was noted in 3 patients (2%) and needed intraaortic balloon pumping (IABP). The IABP was explanted within 24 to 48 hours. These patients completely recovered. No patient needed reexploration for bleeding.

**Table 1. Clinical Characteristics and Hemodynamic Data of the Patients<sup>a</sup>**

Variable	Group I (n=50)	Group II (n=50)	Group III (n=50)
Male	32	28	33
Age (y)	58.6 ± 11.3	57.1 ± 8.7	58.2 ± 7.1
Range	(36-79)	(38-73)	(40-73)
BSA (m <sup>2</sup> )	1.84 ± 0.14	1.84 ± 0.16	1.82 ± 0.17
Range	(1.62-2.13)	(1.61-2.3)	(1.54-2.24)
HR 1 (beats/min)	77.8 ± 9.6	74.0 ± 8.6	75.2 ± 7.8
HR 2 (beats/min)	76.8 ± 8.2	75.2 ± 8.5	74.2 ± 8.1
MAP 1 (mmHg)	71.9 ± 8.5	73.2 ± 10.1	72.5 ± 8.0
MAP 2 (mmHg)	71.9 ± 8.5	74.1 ± 9.6	71.8 ± 7.4
LIMA length (cm)	72.2 ± 8.4	11.8 ± 0.8	12.1 ± 1.2
Time (min)	11.6 ± 0.9	16.5 ± 1.7	16.1 ± 1.7

Data are presented as mean ± standard deviation of the mean. <sup>a</sup>There were no statistically significant differences between the groups.

BSA: body surface area, HR: heart rate, LIMA: the left internal mammary artery, MAP: mean arterial pressure, Time: interval between flow 1 and flow 2.

There was postoperative atrial fibrillation in 5 patients (3.3%) and superficial wound infection in 3 patients (2%).

There were no injuries to the IMA during mobilization. There were 3 patients (2%) with intimal dissection due to intraluminal injection of papaverine. These dissections were at the distal end in 2 patients, and the grafts could be salvaged. The IMA was not used in 1 patient in Group I due to extended intimal dissection and 2 patients in Group II due to insufficient blood flow (less than 40 ml/min)

Mean length of the IMA was 11.8±1.3 cm. Mean waiting period from papaverine injection to blood flow measurement (Flow 2) was 16.8±1.5 min in Group I, 16.5±1.7 min in Group II, and 16.1±1.7 min in Group III ( $p>0.05$ ). Mean blood flow in the IMA was 60.7±6.0 ml/min before papaverine application. After application, it increased to 117.2±21.8 ml/min ( $p<0.0001$ ). There was no significant difference among the first flow rates (Flow 1) of the three groups (Table 2).

After papaverine application, the mean blood flow in Group I was 129.3±10 ml/min, in Group II, it was 87.7±3.8 ml/min and in Group III, it was 130.6±9.2 ml/min ( $p<0.0001$ ). The proportional increases observed in Group I (106.3%) and Group III (116.2%) were significantly higher than in Group II (44.2%) ( $p<0.0001$ ).

## Discussion

Long-term patency rate, survival, and prevalence of myocardial infarction are improved with the use of the IMA for CABG operations.<sup>1)</sup> The IMA, however, is suscep-

**Table 2. Flow rates obtained before and after papaverine application**

Measurement	Group I	Group II	Group III
Flow 1 (ml/min)	62.7 ± 6.1	59.7 ± 6.2	60.4 ± 5.7
Flow 2 (ml/min)*	129.3 ± 10 <sup>a,b</sup>	87.7 ± 3.8 <sup>a</sup>	130.6 ± 9.2 <sup>a,b</sup>

Data are presented as mean ± standard deviation of the mean. <sup>a</sup> $p<0.0001$  versus first flow, <sup>b</sup> $p<0.0001$  versus second flow in group II, \* $p$  value of group I versus group III=0.858 (not significant).

tible to vasospasm during and after mobilization, which is a common arterial response to low blood flow and operative handling.<sup>2-4,6,7)</sup> Spasm of the IMA during CABG may cause inadequate graft flow and makes accurate placement of sutures difficult. Therefore, to overcome this problem most cardiac centers routinely advocate the use of papaverine during the IMA harvesting.<sup>5)</sup> Pharmacological dilatation of the IMA with papaverine application allows better qualitative assessment of the IMA before use and facilitates the anastomosis. Papaverine may be applied either intraluminally<sup>8,9)</sup> or extraluminally<sup>10)</sup> depending on the surgeon's preference. It has been described that the blood flow in the IMA significantly improved after papaverine application.<sup>11,12)</sup> The most effective method of papaverine application is still controversial.<sup>8,10,13)</sup>

To measure free blood flow is important for assessing the adequacy of the IMA as a graft. Various methods have been used to evaluate IMA flow capacity intraoperatively. Timed volumetric collections of the cut end of the IMA

is the simplest method, and lower limits of flow have been established. In the previous reports the free flow of the IMA grafts was measured and compared just before cardiopulmonary bypass.<sup>4,14</sup> In this study we also used the same method.

Measurement of the IMA flow into an open beaker depends on the resistance imposed by the artery, systemic pressure, and also the diameter of the vessel. It is known that the diameter of the IMA diminishes in distal direction. A previous study by He<sup>15</sup> demonstrated that at the distal end of the IMA, pharmacologic contractility increases. In addition, it appears that the bifurcation of the IMA often shows a strong tendency to spasm during operation. Therefore, the IMA length plays an important role in the volume of blood flow.<sup>8,10</sup> In our study, there was no significant difference among the groups with respect to the IMA length.

Cooper et al.<sup>7</sup> compared the effects on the IMA free flow of normal saline, papaverine, nifedipine, glyceryl trinitrate, and sodium nitroprusside. They found that the most effective vasodilator was sodium nitroprusside. In our study flows obtained by topical papaverine application (87.7 ml/min) were less than the flows resulting from topical application of sodium nitroprusside (108 ml/min) reported by Cooper et al.<sup>7</sup> In contrast, Sasson and associates<sup>14</sup> suggested that topical vasodilators have no significant effect on the vasodilation.

He et al.<sup>9</sup> developed a buffered vasodilator solution containing glyceryl trinitrate and verapamil at pH 7.4 and tested the human IMA segments in the human bath.

They concluded that intraluminal injection of the vasodilator solution is effective in dilating the IMA graft and that because of its rapid onset, long action, and neutral pH, glyceryl trinitrate-verapamil solution may be preferable to papaverine. However, Jett et al.<sup>6</sup> demonstrated that among various vasodilators, papaverine produced the greatest maximal inhibition of both potassium- and norepinephrine-induced contraction of the human IMA.

Even though van Son et al.<sup>16</sup> showed that increased shear stress may have detrimental effects on the histologic characteristics of the intima and the internal elastic lamina of the IMA. Hillier and associates<sup>8</sup> refuted the suggestion that intraluminal papaverine may damage endothelial cells of the IMA.

Intraluminal papaverine solution injected once or twice in addition to external papaverine exposure therefore provides a better blood flow rate and distal dilatation than submersion in papaverine solution, but a considerable

risk of mechanical wall injury.<sup>17</sup> In our series, although any hydrostatic dilation of the IMA was carefully avoided, mechanical IMA wall injury (intimal dissection) occurred in 3 patients with applied intraluminal papaverine.

In our study, in group I with intraluminal injection of diluted papaverine, the flow in the pedicled graft increased extremely significantly (62.7 ml/min versus 129.3 ml/min). Although we have performed the intraluminal papaverine injection to increase the free flow of the IMA pedicle grafts with few problems, we have been concerned about a possible mechanical injury and adverse effects of acidic papaverine solution on the friable IMA intima. In this group the IMA was not used in 1 patient as to be due to extended intimal dissection.

This study showed an average flow of 87.7 ml/min in the IMA pedicled graft prepared only with topical application of papaverine via forceful spraying and wrapping with a soaked sponge (Group II). This flow rate is acceptable for the LAD anastomosis.<sup>4,12</sup> In this group the IMA was not used in 2 patients due to insufficient blood flow of less than 40 ml/min.

Recently, we have used the periarterial injection of the papaverine into the IMA pedicle. In group III with periarterial injection into the vascular pedicle, as performed by Hausmann et al.,<sup>18</sup> similarly significant flow increases (60.4 ml/min versus 130.6 ml/min) were obtained. According to results of our study, there were no complications by this method of papaverine application. In our study, IMA free flow was significantly higher in the groups having intraluminal and periarterial application of papaverine than in the group having topical application (129.3±10 ml/min and 130.6±9.2 ml/min, respectively, versus 87.7±3.8 ml/min)

In this study we compared the effect of different papaverine applications on the free blood flow of the IMA dissected in a fully pedicled fashion. However the way of harvesting the IMA is a matter of concern. In order to obtain the full length available of the IMA, skeletonization or the semi-skeletonization technique have been widely applied. These techniques have been reported to provide maximum free blood flow of the IMA. Choi and Lee<sup>19</sup> have reported skeletonization of the IMA was as efficient a strategy to increase the flow as intraluminal papaverine injection for the IMA pedicled graft. The skeletonization technique, however, is not more difficult in comparison with the conventional pedicled technique, even in training.

Consequently, to relieve perioperative spasm of the IMA, application of papaverine injected into the periar-

terial tissues of its pedicle was considered to be a safe and effective alternative to topical or intraluminal application.

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