DOES INTRALUMINAL PAPVERINE INJECTION IMPROVE INTERNAL MAMMARY ARTERY FREE FLOW DURING CORONARY ARTERY BYPASS GRAFTING?

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second flow measurements (40.2 ± 9.2 versus 56.4 ± 11.3 ml/min, p > 0.05). Group B and C showed a significant increase from first flow to second flow measurements (group B, 38.4 ± 7.2 versus 84.9 ± 14.7 ml/min, p = 0.003 and group C, 42.8 ± 6.3 versus 126.9 ± 19.7 ml/min, p = 0.0001). Also, the increase in the mean flow measurements induced by intraluminal plus topical papaverine application, group C (84.1 ml/min) was significantly greater than that induced by the sole topical papaverine application, group B (46.5 ml/min) (p = 0.012).

Conclusion: Topical application of papaverine to the harvested left internal mammary artery, during CABG operations, improves its blood flow at the time of anastomosis to the left anterior descending artery. Additional intraluminal papaverine injection, through an olive-tip metal cannula, significantly improves LIMA free flow without risk of intimal injury.

Introduction

The internal mammary artery (IMA) is the conduit of choice for myocardial revascularization because of its proven long-term patency rate, however vasospasm during isolation of the vessel with insufficient early graft flow has been reported (Sarabu et al, 1987). This spasm is most probably triggered by mechanical manipulation of the artery and physical factors such as diathermy (Frierson et al, 1993) and (He et al, 1989). IMA spasm can cause inadequate flow, which may be detrimental during periods of increased nutritional demand such as weaning from cardiopulmonary bypass (von Segesser et al, 1987) or during hypovolemia after operation (von Segesser et al, 1989). Also, IMAs with poor perioperative flow rates are more likely to occlude (Huddleston et al, 1986). In order to overcome this relatively common problem, various topical or intraluminal vasodilators, as well as mechanical dilatation of the artery, have been used to prevent or reverse vasospasm (Mills and Bringaze 1989 & Cooper et al, 1992). After a dilating agent, as papaverine, is injected into the IMA and it is clamped, the intraluminal volume of the vessel increases. Blood entering from the subclavian artery thus dilutes or pushes distally the dilating agent
(Hiller et al., 1992). Maximal pharmacologic dilation of the IMA allows the surgeon to evaluate the flow-carrying capacity of the IMA and provides a relaxed, dilated distal vessel that facilitates a precise anastomosis. Vasodilatation of the IMA pedicle may also unmask small bleeding points at the time of surgery and thus improve haemostasis (Rosenfeldt et al. 1999). This study was designed to determine the effectiveness of the intraluminal injection of papaverine in inhibiting vasospasm and increasing free flow of the IMA prior to LIMA-LAD anastomosis.

**Patients and Methods**

This study comprised 60 consecutive patients, 42 men and 18 women of median age of 47.5 years (range 38 to 59), who underwent harvesting of the LIMA in preparation for elective first time coronary artery bypass grafting between June 2001 and May 2002 (Table 1). Routine sternotomy was done followed by harvest of the LIMA, as a pedicle, from the subclavian vein superiorly to beyond its bifurcation inferiorly. The dissection was made in large part with electrocautery, and the side branches were occluded with Liga clips. From the first intercostal space upward, the artery was freed without the use of cautery to avoid injury to the phrenic nerve. The patients were randomized into three equal sized groups, of 20 patients each, to compare the effect of papaverine on LIMA free flow measurements. In group A (control group) no papaverine treatment was applied. In group B papaverine was applied topically (1 mg/ml normal saline) whereas in group C papaverine was applied topically and injected intraluminally (1 mg/ml heparinized blood) through an olive-tip metal cannula (Delvo, 0.8x40, Arnold Bott AG, Glattbrugg, Switzerland) with an inner diameter of 0.8mm and length of 40mm (Figure 1). The LIMA was used routinely as the bypass graft to the left anterior descending coronary artery (LAD). All patients were hemodynamically stable with no evidence of ischaemia before cardiopulmonary bypass.

After its mobilization as a pedicle and when the activated clotting time (ACT) exceeded 400 seconds, the LIMA was divided distally before its bifurcation and
allowed to bleed freely. The blood volume was collected for 30 seconds in a graduated container. A fine bulldog clamp was then applied to the distal end of LIMAs. The LIMA post-division free flow per minute (flow 1) was then calculated. Group A LIMs were sprayed with and rapid in saline-soaked gauze. In group B, papaverine (1 mg/mL of normal saline solution) was sprayed on the vessel throughout its whole length with a small syringe and size 25 needle, then the LIMA pedicles were wrapped in a papaverine-soaked gauze of the same solution. In group C, the bulldog clamp was removed and an olive-tip metal cannula was inserted into the distal end of the vessel through which ten milliliters of heparinized blood containing papaverine (1 mg/mL) was injected without pressure. Then the fine bulldog clamp was re-applied to the distal end of the vessel while the olive-tip cannula being withdrawn. In all groups, the LIMA grafts were left under the left sternal blade awaiting anastomosis to LAD. The artery was allowed to dilate under the arterial pressure before and during the cardiopulmonary bypass, but hydrostatic (manual) or mechanical dilation was not performed.

After construction of distal vein graft anastomoses, the LIMA was trimmed as proximal as possible commensurate with each patient’s anatomy and estimated site of LAD anastomosis. Then, the LIMA pre-anastomosis free flows per minute was measured (flow 2). The mean arterial blood pressure (MAP) was simultaneously recorded for each flow measurement. The time between measurements was also recorded. The discarded LIMA segments were sent for histological examination.

Statistical analysis was conducted using SPSS (version 8) for windows statistical package. Data were analysed using t-test. P-values less than 0.05 were considered statistically significant.

Fig. 1: Delvo cannula 0.8x40 mm (left to right). Arnold Bott AG, Glattbrugg, Switzerland.
Results

Demographic and hemodynamic data of the three patient groups are shown in Table 1. No statistically significant differences were found between the three groups with respect to age, gender, body surface area (BSA) and number of grafts per patient. There was no significant difference in the time interval between the first and the second LIMA free flow measurements for each group or between the groups (p > 0.05). Also, the values of the mean arterial pressure (MAP) measured at the time of the first and second LIMA free flows were not significantly different either within or between the groups (p > 0.05).

The LIMA free flow measurements of all groups before and after treatment are shown in Table 2. There was no statistically significant differences between the three groups regarding the LIMA post division free flow (first flow) (p>0.05). The LIMA free flow measured immediately prior to LIMA-LAD anastomosis (flow 2) was higher compared to the post division free flow (flow 1) in all groups. Group A showed a small increase from first flow to second flow measurements (40.2±9.2 versus 56.4±11.3 ml/min, p > 0.05).

Group B and C showed a statistically significant increase from first flow to second flow measurements (group B: 38.4±7.2 versus 84.9±14.7 ml/min, p = 0.003 and group C: 42.8±6.3 versus 126.9±19.7 ml/min, p = 0.0001). Also, the increase in the mean values of the LIMA free flow induced by intraluminal plus topical Papaverine application, group C (84.1 ml/min) were significantly greater than that induced by the sole topical Papaverine application, group B (46.5 ml/min) (p = 0.012).

| Table 1. Patient's demographic and inoperative data |
|---------------------------------------------|-----------------|-----------------|
|                                    | Group A (20 patients) | Group B (20 patients) | Group C (20 patients) |
| Male/Female                          | 14/6             | 12/8             | 16/4             |
| Age                                  | 49.7±7.9         | 51.1±7.8         | 50.8±8.1         |
| BSA (m²)                             | 1.8±0.3          | 1.8±0.3          | 1.8±0.3          |
| No. of grafts                         | 3.7±0.8          | 3.2±0.2          | 3.3±0.4          |
| MAP (mm Hg)                          | 70.5±8.9         | 72.8±4.2         | 70.8±10.3        |
| MAP2 (mm Hg)                         | 68.5±3.2         | 66.8±2.2         | 67.8±3.2         |
| T1-T2 (min)                          | 61.6±8.3         | 59.1±8.8         | 62.4±11.9        |

Values are expressed as mean ± standard deviation, except as noted. MAP=mean arterial pressure, MAP2=mean arterial pressure during first and second flow measurements, T1-T2= time between first and second flow measurements.
Table 2. LIMA free flow measurements before and after papaverine treatment

<table>
<thead>
<tr>
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<th>Group A (20 patients)</th>
<th>Group B (20 patients)</th>
<th>Group C (20 patients)</th>
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<tbody>
<tr>
<td>First flow (F1)</td>
<td>40.2 ± 9.4</td>
<td>38.4 ± 0.7</td>
<td>42.8 ± 6.3</td>
</tr>
<tr>
<td>Second flow (F2)</td>
<td>38.4 ± 0.7</td>
<td>38.4 ± 0.7</td>
<td>42.8 ± 6.3</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation.

Discussion

The internal mammary artery (IMA) is the conduit of choice for coronary artery bypass surgery because of superior long-term patency rate compared with saphenous vein grafts. The survival of patients is improved when the left IMA (LIMA) is grafted to the LAD (Jeanmart et al. 2001). However, suboptimal flow due to spasm of this conduit in the early postbypass period may be detrimental, particularly in cases of hypertrophied myocardium, poor left ventricular function, and recent myocardial infarction (Mulay et al. 1997). In the current study, the LIMA free flow measured immediately after mobilization from the chest wall (flow 1) was 40.2±9.4, 38.4±0.7, and 42.8±6.3 mL/minute for group A, B, and C respectively without a statistically significant difference between the studied groups (P>0.05). Similar observations have been reported by others (Cooper et al., 1992) and (Canzer et al., 1994). The early reduced IMA free flow is most probably due to vasoconstriction triggered by mechanical manipulation of the artery and physical factors such as diathermy (Nil et al., 1999).

Many surgeons use vasodilators to either prevent or treat LIMA spasm, but the best agent is not known (Jett et al., 1992), (He et al., 1994) and (Sasson et al., 1995). Papaverine is the most frequently studied vasodilator agent that relaxes blood vessels through multiple mechanisms. As a phosphodiesterase inhibitor, papaverine may raise cyclic adenosine monophosphate (cAMP) level in vascular smooth muscle cells which promotes vascular smooth muscle relaxation. Papaverine-induced relaxation is also caused by other actions such as decreased calcium influx or inhibition of the release of calcium from intracellular stores (Rosenfeldt et al., 1999). Pa-
Papaverine delivery to the LIMA has ranged from topical exposure, to pedicle injection, and intraluminal administration with or without hydrostatic dilatation, however, the best delivery method has not been established (Cooper et al, 1992). Topical therapy has included covering the artery with a papaverine soaked sponge, spraying the vessel with papaverine, and immersion of the LIMA in a papaverine filled surgical glove (Cooper et al, 1992) and (Dregelid et al, 1995).

In the current study, we have recorded the pre-anastomotic LIMA free flow (flow 2) late in CABG operations to allow maximal exposure of the LIMA to papaverine in the experimental groups (B and C) as well as to detect LIMA spontaneous dilatation in the control group, if any. The flow 2 has increased by 121.0% and 219.6% after topical (group B) and both of topical and intraluminal papaverine therapy (group C) respectively (P< 0.05). Hausmann and colleagues, 1996 have found LIMA flow to be the best after intraluminal injection of papaverine with hydrostatic dilatation performed if needed. In other study comparing intraluminal administration of papaverine to LIMA pedicle injection and topical therapy with a drug soaked sponge revealed that LIMA flow after intraluminal administration was 3 times greater than pedicle injection and 4 times greater than topical delivery. (Mills and Bringaze, 1989). Dregelid and colleagues, 1995 concluded that the addition of papaverine intraluminally provided better flow and distal dilatation than mere submersion of the artery in papaverine solution. There are many benefits of intraluminal administration of papaverine besides an increase in the LIMA free flow. With a larger diameter vessel to work with, the surgeon is less likely to make a technical error. Furthermore, potential bleeders from side branches can be readily identified (Choi and Lee, 1996).

Some studies, including ours, recorded spontaneous dilatation and increased flow after a mean time interval between 38 and 75 minutes (Sassan et al, 1995) and (Vilandt et al, 1999). This time interval allows a good opportunity for natural relaxation to take place.
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(Vilandt et al. 1999). In the control group of the current study, the mean time interval between the two flow measurements was 60 minutes that allows satisfactory flow of 56.4±11.3 ml/min without any clinical evidence of hypoperfusion during the immediate postoperative period. On the other hand, spontaneous relaxation of the LIMA graft does not occur when mean time intervals between the first and second set of flow measurements ranging from 18 to 30 minutes (Cooper et al. 1992) and (Bilgen et al. 1996).

Papaverine dosage in the literature has varied widely up to a maximum of 50 mg (Hausmann et al. 1996) and concentrations have ranged from 0.3 mg/mL to 1.5 mg/mL, making it somewhat difficult to compare study results. However, Dregelid and associates in two separate studies, suggested that concentration of topical papaverine from 0.8 mg/mL to 1.5 mg/mL may have similar effects (Dregelid et al. 1993) and (Dregelid et al. 1995). We have used 20 mg of papaverine, at room temperature, to prevent LIMA spasm in a concentration of 1 mg/ml and all flow measurements were made after this dosage. However, normothermic papaverine has been revealed to be superior to room temperature solution when applied topically (He et al. 1989) and (Mulay et al. 1997).

Some studies have postulated, on histological examination of the discarded LIMA segments, that intraluminal papaverine administration, through a plastic cannula, exposes 15% -17% of the IMA grafts to intimal or medial disruption (Dregelid et al. 1995) and (van Son et al. 1992). However, these studies could not intraoperatively, identify which vessels were injured when blood flow was measured (Dregelid et al. 1993). Also, the effect of intraluminal delivery of papaverine on long-term IMA patency is not known (van Son et al. 1992). In the current study, histological examination of the discarded LIMA segments (group C) have revealed an intact intima and internal elastic lamina demonstrating that the use of an olive-tip metal cannula for intraluminal papaverine injection can avoid the potential hazard of intimal tear.

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In conclusion, careful harvesting and handling of the left internal mammary artery pedicle during CABG operations, is a key factor to achieve adequate flow prior to its anastomosis to the left anterior descending artery. Topical application of papaverine to the harvested LIMA pedicle improves its blood flow at the time of anastomosis to LAD. Additional intraluminal papaverine injection, through an olive-tip metal cannula, significantly improves LIMA free flow without risk of intimal injury.

References


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Van Son J., Tavilla G. and


