Paper IV
Flow measurement before and after papaverine injection in above-knee prosthetic femoropopliteal bypass

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Objective: To investigate the value of intraoperative blood flow measurements on early and long-term patency of above-knee prosthetic femoropopliteal bypass.

Methods: Flow was measured with a transit time flowmeter before (basal flow) and after an intragraft injection of papaverine (papaverine flow) in 87 operations (86 patients) between January 1990 and December 2001. Sixty-one grafts were of polyester, and 26 were of polytetrafluoroethylene. The operations were done under epidural anesthesia. The preoperative angiographic run-off score and clinical risk factors were recorded. Patency rates were analyzed with the product limit method and compared with the log-rank test. Variables found to be near significantly related to patency rates (P < .1) were included in a multivariate analysis performed with the Cox proportional hazard model.

Results: Basal flow measurements were not related to patency. The 2- and 5-year patency rates for grafts with a papaverine flow ≤500 mL/min were 48% and 18% compared with 66% and 52% for grafts with a papaverine flow ≥500 mL/min. These differences were statistically significant (P = .012, hazard ratio, 2.6). Two- and 5-year patency rates for smokers vs nonsmokers were 44% and 18% vs 69% and 54%. The patency rates for patients with poor vs good run-off were 42% and 27% vs 66% and 31%. Smoking (P = .008, hazard ratio, 2.75) and poor run-off score (P = .009, hazard ratio, 2.38) were found to be independent risk factors for reduced patency rates. Poor run-off score did not correlate with low values of measured basal or papaverine flow.

Conclusions: Papaverine flow of ≤500 mL/min is associated with reduced mid- and long-term patency rates. Additional antithrombotic medication and frequent follow-up for these grafts should be considered. The inferior patency rates of smokers and patients with poor run-off indicate that prosthetic bypass is less suitable for these groups of patients. (J Vasc Surg 2006;43:729-34.)
gram as good (≥1 patent artery) or poor (≤1 patent artery). Run-off score was recorded in 82 patients, of which 39 were classified as poor. In three patients, the angiograms were missing at the time of the study, and two operations were performed without a preoperative angiography.

All operations were done under epidural anesthesia. The surgical technique was uniform, with end-to-side anastomosis between the graft and the native artery in both the proximal and the distal anastomosis. Heparin (5000 IU) was administered intravenously before the common femoral artery was clamped. Postoperatively, all patients were given aspirin (160 mg daily) on a permanent basis, if tolerated. No other antithrombotic agent was given.

A transit time Doppler flowmeter (CardioMed 1000, Medi-Stim AS, Oslo, Norway) was used for blood-flow measurements. The probes were precalibrated by the manufacturer, and the measurement error was ±10%. Flow was measured with the probe placed around the popliteal artery below the distal anastomosis. Where lack of exposure prohibited flow measurement of the popliteal artery, flow was measured in the common femoral artery while the profunda femoral artery was clamped. Flow was measured before and after a 40-mg intragraft injection of papaverine. The basal flow was defined as the flow measured before the papaverine injection, and the maximum flow after the papaverine injection was defined as the papaverine flow.

Follow-up was done after 1, 3, 6, and 12 months, and annually thereafter with duplex ultrasound examination and ankle-brachial pressure measurements. The mean and median graft follow-up was 28 and 21 months (range, 0 to 116 months). According to the department’s protocol, graft-related significant stenoses (≥50% diameter reduction) were treated, usually with endovascular techniques. Graft occlusion was confirmed with either duplex scanning or angiography. The end point of the study was the primary occlusion date.

Fisher’s exact test was used for comparison of categoric data. Primary assisted patency rates were calculated with the product-limit method and illustrated as Kaplan-Meier curves. Univariate comparisons of patency were done with the log-rank test. Variables found to be near significantly correlated with patency (P < .1) were subjected to multivariate analysis performed with the Cox proportional hazard model. The software program SPSS 13.0 (SPSS Inc. Chicago, Ill) for Windows (Microsoft, Redmond, Wash) was used for statistical computations. Differences were considered statistically significant at the 5% level (P < .05).

**RESULTS**

The overall primary assisted patency rates were 93% at 30 days, 80% at 6 months, and 76% at 12 months. The 2- and 5-year patency rates were 52% and 31% (Fig 1). Primary occlusion was recorded for 46 grafts during follow-up (53%). One patient was treated with percutaneous transluminal angioplasty for a graft-related stenotic lesion. The 30-day mortality was zero. Graft type (PTFE or Polyester) and graft diameter (6 or 8 mm) did not influence patency.

The mean and median basal flow was 266 and 211 mL/min (range, 52 to 1300). The distribution is illustrated in Fig 2. Injection of papaverine increased the value to a mean of 400 mL/min and a median of 489 mL/min (range, 120 to 2400 mL/min). The distribution of papaverine flow measurements is illustrated in Fig 3.

Basal flow had no association with reduced patency rates. Papaverine flow levels of 300, 400, 500, and 600 mL/min were analyzed for impact on patency rates. A papaverine flow of ≥500 mL/min was significantly associated with reduced primary assisted patency as calculated by both univariate (P = .030) and multivariate analyses (P = .012, hazard ratio, 2.6). A papaverine flow of ≥500 mL/min was recorded in 59 patients (68%). The primary assisted patency rates for grafts with papaverine flow ≥500 mL/min were 89% at 30 days, 69% at 6 months, 58% at 12 months, 48% at 2 years, and 18% at 5 years; for grafts with papaverine flow of ≥500 mL/min, the respective patency rates were 97%, 86%, 83%, 66%, and 52%. The impact of papaverine flow on graft patency is presented in Table II and Fig 4.

Flow increase, expressed as papaverine flow/basal flow and as papaverine flow minus basal flow was then analyzed.
for possible impact on patency. Although different levels of flow increase were analyzed, no association between flow increase and patency could be found. This was the case for papaverine flow/basal flow as well as for papaverine flow minus basal flow.

Smoking caused significantly reduced primary assisted patency in both univariate (\(P = .03\)) and multivariate analyses (\(P = .008\), hazard ratio, 2.75). The patency rates and statistic details are given in Tables II and III. There was a similar distribution of poor run-off scores for smokers and nonsmokers and for patients with high or low flow (both basal and papaverine flow), as analyzed with Fisher’s exact test.

Poor run-off score was not significantly associated with reduced patency in univariate analysis (\(P = .090\)), but multivariate analysis revealed poor run-off as an independent risk factor for reduced graft patency (\(P = .009\), hazard ratio, 2.38). Low papaverine flow was not more frequent among those with a poor run-off score compared with those with a good run-off score.

Six grafts occluded during the first postoperative month (6.9%), and 17 grafts (20%) occluded at 3 months of surgery. There were no differences in the distribution of risk factors or flow measurements between the early occluders and those that stayed open at 3 months by Fisher’s exact test.

The 2- and 5-year patency rates for grafts implanted for intermittent claudication and with a high papaverine flow were 68% and 60% vs 60% and 18% for grafts implanted for intermittent claudication and low papaverine flow. This difference was statistically significant (\(P = .043\), log-rank test). The same was tested for intermittent claudication and run-off, for the combination of intermittent claudication plus high flow plus good run-off, and for the combination of intermittent claudication plus high flow plus good run-off, but no association was revealed.

DISCUSSION

We aimed to investigate the predictive value of intraoperative transit-time flow measurements on primary assisted patency in above-knee prosthetic femoropopliteal bypass. Transit-time flow measurement has been demonstrated to be a reliable method with reproducible results.\(^7\)\(^-\)\(^9\) Blood flow in prostheses can only be measured indirectly with this method, however, by measuring inflow or outflow in the adjacent arteries. This is due to the attenuation of Doppler signals in the prosthesis wall.

Outflow can be measured by placing the probe distally to the reconstruction, which was done in most cases in the present study. Inflow can be measured likewise by placing the probe proximally to the reconstruction. In this study, this was done in cases with technical difficulties by placing the probe around the popliteal artery. In these patients, the profunda femoral artery was clamped while flow was measured in the common femoral artery. If a proximal part of the superficial femoral artery was open, a higher flow volume than the actual graft flow may have been recorded. Likewise, flow measurements in the popliteal artery may not have reflected the actual flow volume in the femoropopliteal graft. Because the anastomoses in the present series were created end-to-side, some degree of retrograde flow from the popliteal artery may have occurred in some patients. If this was the case, the recorded flow was lower than the actual graft flow.

Intraoperative Duplex ultrasound scans can also be used to indirectly measure graft volume flow. One of the main advantages with this method is visualization of the reconstruction, which may detect technical errors. Other advantages are that systolic and diastolic velocities may be measured. Low end-diastolic velocities have been reported to be associated with early graft failure in infragenicular vein bypass.\(^10\) The main disadvantages of Duplex ultrasound imaging are its complexity and user-dependent results.
Intraoperative angiography visualizes the arterial reconstruction and run-off but gives little information of flow. Flow measurement has been reported to be a better predictor of outcome than angiography.5 Angiography may detect operative technical errors, however. Lundell and Bergqvist1 reported that increased peripheral resistance was more predictive for early graft occlusion then flow measurements. In the present study, peripheral resistance was not estimated; however, the increase in papaverine flow was caused by a reduced peripheral resistance.11 In patients with extensive peripheral atherosclerosis, a lesser increase in papaverine flow may be expected compared with patients with good run-off. However, we did not find such an association between run-off score and measured flow. A possible reason for this may be the presence of extensive collateral vessels in patients with poor main run-off vessels. Furthermore, crural arteries classified as patent on angiography may be occluded distally with poor collateral flow to the foot, leading to high peripheral resistance.

Epidural anesthesia has been reported to reduce peripheral resistance owing to a reduction of the sympathetic vasomotor tone.12 The level of epidural anesthesia has been shown to influence the increase in flow: a low level of anesthesia leading to a larger flow increase than a high level.13 The levels of epidural anesthesia given were not recorded in the present study, and we were therefore not able to evaluate these findings. Peripheral resistance may also be altered by drugs administered intravenously during surgery, such as dopamine or ephedrine.

A low increase in flow after the papaverine injection indicates a high peripheral resistance.11 In this study, flow increase showed no impact on patency, as it seems the relative increase in flow after papaverine injection has less influence on the fate of the graft compared with the absolute papaverine flow value.

The heparin dosage during clamping was 5000 IU for each patient. This is in agreement with established practice in Scandinavia. A subtherapeutic dosage may have been given in some cases, however, especially in obese patients.

Table II. Primary assisted patency for 87 above-knee prosthetic femoropopliteal bypass operations

<table>
<thead>
<tr>
<th>Variables</th>
<th>30 days (%)</th>
<th>6 months (%)</th>
<th>12 months (%)</th>
<th>2 years (%)</th>
<th>5 years (%)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papaverine flow &lt;500 mL/min</td>
<td>89</td>
<td>69</td>
<td>58</td>
<td>48</td>
<td>18</td>
<td>.03</td>
</tr>
<tr>
<td>≥500 mL/min</td>
<td>94</td>
<td>86</td>
<td>83</td>
<td>66</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>94</td>
<td>70</td>
<td>57</td>
<td>44</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>97</td>
<td>85</td>
<td>73</td>
<td>69</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Run-off score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 crural artery</td>
<td>94</td>
<td>66</td>
<td>57</td>
<td>42</td>
<td>27</td>
<td>.03</td>
</tr>
<tr>
<td>&gt;1 crural artery</td>
<td>97</td>
<td>86</td>
<td>83</td>
<td>66</td>
<td>31</td>
<td>.09</td>
</tr>
<tr>
<td>Degree of ischemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical</td>
<td>94</td>
<td>69</td>
<td>59</td>
<td>45</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Claudication</td>
<td>97</td>
<td>81</td>
<td>78</td>
<td>61</td>
<td>36</td>
<td>.52</td>
</tr>
</tbody>
</table>

The variables listed were analyzed with the product-limit method and compared with the log-rank test.

*Log-rank.

Table III. Multivariate analysis (Cox proportional hazard model) of risk factors in 87 above-knee prosthetic femoropopliteal bypass operations*

<table>
<thead>
<tr>
<th>Variables</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papaverine flow &lt;500 mL/min</td>
<td>0.959</td>
<td>0.382</td>
<td>0.012</td>
<td>2.609</td>
<td>1.233-5.521</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.014</td>
<td>0.383</td>
<td>0.008</td>
<td>2.757</td>
<td>1.301-5.843</td>
</tr>
<tr>
<td>Poor run-off score†</td>
<td>0.868</td>
<td>0.334</td>
<td>0.009</td>
<td>2.383</td>
<td>1.239-4.582</td>
</tr>
</tbody>
</table>

SE, Standard error; HR, hazard ratio; CI, confidence interval.

*These risk factors were demonstrated with univariate analysis to be nearly significantly associated with patency rates (P < .1).

†Defined as ≤1 patent crural artery as seen on the preoperative angiogram.

Fig 4. The primary patency rates of 59 grafts with a papaverine flow <500 mL/min and 28 grafts with a papaverine flow ≥500 mL/min. The numbers above and below the curves indicate the numbers at risk. The differences in patency rates are significant (P = .03, log-rank test). The median patency (time to reach 50% occlusion rate) for grafts with papaverine flow ≥500 mL/min is 48 months (SEM, 6.7; 95% confidence interval, 35 to 61). The median patency for grafts with papaverine flow <500 mL/min is 30 months (SEM, 4.3; 95% confidence interval, 21 to 38).

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The heparin dosage during clamping was 5000 IU for each patient. This is in agreement with established practice in Scandinavia. A subtherapeutic dosage may have been given in some cases, however, especially in obese patients.
Alternatively, a weight-based heparin protocol may be administered.

The overall patency rates in the present series are comparable to or somewhat lower than those reported before.14-18 There were no differences in the distribution of risk factors or flow values among the early occluders and those that stayed open >1 and 3 months after surgery. It was previously reported that early occlusion most often is caused by operative technical errors or inappropriate selection of patients for surgery.19 The former could not be shown in the present series because no intraoperative visualization with Duplex or angiography was done.

Smokers had significantly lower patency rates than non-smokers. This is in agreement with previous reports.20,21 A recently published meta-analysis demonstrated a threefold increase in graft failure for smokers compared with non-smokers.22 It has been assumed that most graft occlusions occur during the first postoperative year. This was the case for non-smokers in the present series. The grafts in smokers continued to occlude beyond the first year, and the difference in patency between smokers and non-smokers in our series increased with time (Table II). This difference may be due to an accelerated atherosclerosis in smokers. It also underlines that a long observation time is necessary to achieve a full overview. Because smoking is a modifiable risk factor, smokers who are candidates for bypass surgery should be informed of the magnitude of this risk factor before surgery.

Poor run-off score was significantly correlated with reduced patency rates, which is in accordance with previous reports.16,18 Renal failure has previously been reported to be associated with reduced patency rates.23,24 This was not the case in the present study, probably because of small numbers. Diabetes mellitus has also been reported to be associated with reduced patency rates,25 whereas others have reported no such association.26 In the present study, no association between diabetes mellitus and reduced patency was found; however, the number of patients was small and may not have been sufficient to achieve statistically significant differences. This may also be the reason for the similar results in patients with critical ischemia and intermittent claudication.

When flow values lower than expected are measured intraoperatively, the reconstruction should be visualized with either angiography or Duplex ultrasound scan to exclude operative technical errors. Because grafts with low papaverine flow have an increased tendency to occlude, frequent follow-up may be useful; however, it has not been proven that graft surveillance increases patency. In the present series, follow-up was annually beyond 1 year post-operatively. Many grafts with low papaverine flow occluded later than 1 year after surgery. If stenotic inflow or outflow lesions had been detected and treated in some patients, this might have improved patency rates.

Adjuvant antithrombotic medication is recommended. Clopidogrel should be given to all patients with aspirin intolerance regardless of flow values, because antiplatelet agents improve graft patency, especially in prosthetic grafts.27 Clopidogrel may add some effect to aspirin in patients with low papaverine flow, but this has not been proven in controlled trials. Warfarin has been reported to have an effect in preventing occlusion in infrainguinal vein grafts, but not in preventing prosthetic graft thrombosis.28

CONCLUSION

Intraoperative papaverine flow measurements predict mid- and long-term patency of above-knee prosthetic femoropopliteal bypass, whereas basal flow measurements yield no predictive information. In this study, flow measurement values could not be related to the preoperative angiographic run-off score. The inferior patency rates of smokers as well as patients with a poor run-off score indicate that alternative treatments may be more suitable for these groups of patients. In patients with low papaverine flow, additional antithrombotic medication and frequent follow-up should be considered.

AUTHOR CONTRIBUTIONS

Conception and design: GP, SA
Analysis and interpretation: GP, EL, SA
Data collection: GP, EL
Writing the article: GP, EL, SA
Critical revision of the article: GP, EL, SRA, ED, TJ, TN, SA
Final approval of the article: GP, EL, SRA, ED, TJ, TN, SA
Statistical analysis: GP, EL, ED, SA
Obtained funding: N/A
Overall responsibility: GP

REFERENCES


Submitted Jul 4, 2005; accepted Dec 16, 2005.