Factors Affecting Patency of Subintimal Infrainguinal Angioplasty in Patients with Critical Lower Limb Ischemia

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Background. Because subintimal angioplasty (SA) is a technique that can achieve recanalization of long arterial occlusions, it is considered an alternative to lower limb bypass operations. The aim of this prospective study was to identify the risk factors that affect patency of SA in patients suffering from critical limb ischemia (CLI).

Methods and results. 51 consecutive infrainguinal SA were done in 46 patients suffered from CLI. The patients were followed-up with regular duplex scans up to 12 months post-intervention. Sex, atherosclerosis risk factors, and some technical details of the procedure (number of patent run-off vessels after the procedure, length and re-entry point of angioplasty) were examined as potential risk factors of patency, using survival analysis statistical techniques.

The overall patency rate at 12 months post-intervention was 50%. According to Cox-regression analysis, the factors that affect patency were the number of run-off vessels and the length of occlusion. Patients with two or three run-off vessels had a hazard of occlusion of 0.30 (P = .027) compared to those who had one run-off vessel. The 12-months patency in patients with more than one run-off vessels was 81% vs. 25% in patients with one run-off vessel. Regarding the length of angioplasty, the hazard of reocclusion was 1.02 for every centimeter of occlusion (P = .049).

Conclusions. The number of patent run-off crural vessels after the angioplasty and the length of occlusion are significant risk factors for reocclusion of infrainguinal SA in patients with CLI. Trying to recanalize more than one run-off vessels could raise the SA patency.

Keywords: Critical limb ischemia; Subintimal angioplasty; Peripheral vascular disease; Patency rate.

Introduction

Lower limb subintimal angioplasty (SA) is now a well known technique which can achieve recanalization of long occluded arterial segments. It has been proposed as an alternative to lower limb bypass procedures, especially in patients with critical lower limb ischemia. Much of the criticism about this technique is based on its patency rate compared to bypass procedures. It is often stated that the approximate 50% primary patency rate at 12 months post-intervention is quite low compared to the almost 80 to 90% for bypass procedures. However, despite the relatively high reocclusion rate, subintimal angioplasty allows an exceptionally good limb salvage rate in patients with limb threatening ischaemia.

The factors that affect the patency after SA are not well defined. The aim of this prospective study was to identify the factors that affect the patency of infrangular SA in patients with critical lower limb ischemia.

Materials and Methods

A prospective study was designed to assess the patency of infrangular subintimal angioplasty in lower limbs suffering from critical limb ischemia (CLI) and to identify the factors that affect it. The study involved humans, thus an ethics committee approval was obtained.

On 46 patients (24 males) suffering from critical lower limb ischemia, 51 consecutive primary infrangular subintimal angioplasties were performed. This cohort of patients included the total number of patients treated for lower limb ischemia in our Vascular Unit for a six months period. It is the policy in this Unit to treat all patients suffering by critical limb ischemia with a percutaneous angioplasty first. The technique of this type of angioplasty has been

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1078–5884/000668 + 07 $32.00/0 © 2006 Elsevier Ltd. All rights reserved.
described by Bolia et al. Briefly, an intentional extraluminal dissection is performed along the occluded segment of the artery which is then followed by balloon dilatation and the creation of a new lumen. This technique achieves recanalization of long arterial occlusions which cannot be treated by other types of angioplasty as with transluminal angioplasty. Transluminal angioplasties, graft angioplasties and redo angioplasties were excluded from this study.

All patients suffered from critical lower limb ischemia as defined in TransAtlantic InterSociety Consensus Classification (Recommendations 73, 74). From clinical point of view, 14 out of the 51 patients (27%) suffered by rest pain, 32 (63%) by lower limb ulcers, and 5 (10%) of them had a digital necrosis. The morphology of occlusions in all patients were of type C (5 cases, 10%) and type D (46 cases, 90%) according to the TASC morphological stratification of femoropopliteal and infrapopliteal lesions (Recommendations 34, 93). Thus, subintimal angioplasty was the only treatment available to these patients with the exception of a femoro-popliteal or a femoro-distal bypass operation.

All sites in the lower arterial tree were amenable to angioplasty, as shown in Table 1. A flush occlusion of superficial femoral artery (SFA) was not a contraindication of subintimal angioplasty, as a subintimal plane on the SFA was always possible to be found even without a profound stump of SFA. Also, long occlusions of SFA, popliteal and even crural arteries (posterior and anterior tibial and peroneal) were usually attempted to be angioplastied. All patients received antiplatelet treatment (Aspirin 75 mg) after the procedure was completed. Patients were followed-up using lower-limb arterial duplex scans at 1, 3, 6, 9 and 12 months after the procedure.

The variables examined as possible factors affecting subintimal angioplasty patency rate were:

1. Sex
2. The risk factors of atherosclerosis (i.e. history of arterial hypertension, history of ischemic heart disease, history of diabetes mellitus and past history of smoking).
3. The number of patent crural vessels after the procedure (run-off vessels), in continuation with the femoropopliteal segment.
4. The length of occluded arterial segment recanalized.
5. The end-level of angioplasty. According to this description, the procedures were considered as femoropopliteal angioplasties, if the end-point was the popliteal artery and as distal angioplasties, if the end-point was one of the crural arteries (i.e. anterior and posterior tibial or peroneal artery).

### Statistical Methods

The primary patency rate on an intention-to-treat basis of angioplastied vessels was calculated by the survival analysis techniques (Life-table analysis and Kaplan-Meier curve). All examined factors were univariately related to the patency rate, and those that showed even a slight effect on patency (i.e. \( p < 0.30 \)) were included in a model of multivariable analysis in order to identify those that were significantly independent factors of patency. The multivariable analysis used was the proportional hazards model or Cox regression analysis. The factors that were found to affect patency significantly, according to the multivariable analysis, were univariately related to the patency so as to calculate the patency rates in the group of patients that carry this factor and in the group of patients that do not carry this factor. The statistical differences between the survival curves of the various groups examined were calculated using the Log-rank test. Mann-Whitney U test was used to check age difference between males and females. All reported \( p \)-values were two-tailed and considered significant if less than 0.05. All analyses were performed using Statsdirect Statistical Software (version 2.3.1).

### Results

Twenty seven male (53%) and 24 female (47%) patients were included in the trial. The age of the patients varied from 43 to 95 years (median 80, interquartile range 71 to 87). Female patients were slightly older than male patients (median 81 vs. 77, interquartile ranges 78 to 95 vs. 66 to 87), but this was not statistically significant (\( p = 0.12 \), Mann-Whitney U test). The prevalence of risk factors of atherosclerosis in our patient cohort varied from 39 to 54% as shown in Table 2.

### Table 1. Anatomical sites of occlusion

<table>
<thead>
<tr>
<th>Site of angioplasty</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFA</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>SFA-popliteal</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Popliteal</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>SFA-popliteal-crural</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Popliteal-crural</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Crural (ie AT, PT, peroneal)</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Femoropopliteal</td>
<td>27</td>
<td>53</td>
</tr>
<tr>
<td>Distal</td>
<td>24</td>
<td>47</td>
</tr>
</tbody>
</table>
Twenty-seven (53%) femoropopliteal and 24 (47%) distal angioplasties were performed (Table 1). One patent run-off vessel was present after the procedure in 25 (49%) cases and more than one (two or three) vessels in 26 (51%) (Table 3). The length of the occluded arterial segment varied from 5 to 80 cm (median 30, interquartile range 20 to 45). Technical success, i.e. recanalization of the occluded arterial segment with antegrade flow into the pedal arch at the end of the procedure, was achieved in 49 cases (96%). It must be noted that a direct perfusion to the pedal arch through a crural artery was necessary for the angioplasty to be completed. Perfusion of the pedal arch through collaterals was not accepted as a technical success of the procedure.

During the 12-month follow-up period, 5 patients (10%) needed a redo angioplasty, 3 (6%) needed a bypass operation and 4 patients (8%) required a major amputation (above or below the knee level). The survival analysis showed that the overall limb salvage rate at 12 months was 92% (Fig. 1). However, on an intention to treat basis, the primary patency rate at 12 months was only 50% (Fig. 2). Six of the 46 patients (13%) died during the 12-month period giving a survival rate of 82% at 12 months, according to the Life-table analysis.

Using Cox-regression analysis we examined the effect of all the predictor variables on the patency of angioplasty. The variables examined were: sex, history of arterial hypertension, ischemic heart disease, diabetes mellitus and smoking, the number of patent run-off vessels after the procedure, the length of the recanalized segment and the end point of the angioplasty. Firstly, all examined factors were univariately related to the patency rate, and those that showed even a slight effect on patency ($p < 0.30$) were included in the model of multivariable analysis (Table 4). By stepwise exclusion of the variables that had the least significant relationship to the outcome, it was concluded that the factors that affect independently the patency are the number of run-off vessels and the length of the recanalized artery (Table 5).

The number of run-off vessels is strongly related to the occlusion rate after subintimal infrainguinal angioplasty. The risk of occlusion according to the Cox-regression analysis of angioplastied legs with more than one run-off vessels is 0.30 (95% CI 0.11 to 0.87, $p = 0.027$) compared to legs with one run-off vessel. This means that patients with more than one patent run-off vessels (two or three) have a decreased risk of occlusion compared to the patients with one

### Table 2. Prevalence of factors predisposing to atheromatosis in our patient cohort

<table>
<thead>
<tr>
<th>Predisposing factors</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypertension</td>
<td>25</td>
<td>54</td>
</tr>
<tr>
<td>Ischemic cardiac disease</td>
<td>22</td>
<td>48</td>
</tr>
<tr>
<td>Smoking</td>
<td>22</td>
<td>48</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18</td>
<td>39</td>
</tr>
</tbody>
</table>

### Table 3. Patent run-off vessels after the angioplasty

<table>
<thead>
<tr>
<th>Run-off vessels</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>25</td>
<td>49</td>
</tr>
<tr>
<td>Two</td>
<td>13</td>
<td>25</td>
</tr>
<tr>
<td>Three</td>
<td>13</td>
<td>25</td>
</tr>
</tbody>
</table>

Fig. 1. Limb salvage rate: Kaplan-Meier survival curve and Life table analysis. Censored observations are marked by ticks on the survival curve. Times are in months.

Fig. 2. Primary patency rate: Kaplan-Meier survival curve and Life table analysis. Censored observations are marked by ticks on the survival curve. Times are in months.
run-off vessel. Thus, a patient with more than one run-off vessel has a risk of occlusion of about 0.3 times compared to the patient with one vessel run-off, or in reverse, a one run-off angioplasty has a 3.30 (95% CI 1.15 to 9.49) risk of occlusion compared to a patient with two or three run-off vessels. Using univariate survival analysis (Kaplan-Meier and LifeTable analysis) it can be seen that the 12-months patency rate in the patients that had more than one run-off vessels was 81% while in those with only one vessel run-off the patency was 25% at the same time interval (Fig. 3). The log-rank test comparing patency rates of the two groups showed that there is a significant difference between the two groups confirming the results of Cox-regression analysis. The p value was less than 0.001 with a hazard ratio 4.6 (95% CI 2.0 to 10.4).

The length of angioplasty is also related to the patency rate. According to the Cox-regression analysis the hazard for every centimeter of occlusion is 1.02 (95% CI 1.00 to 1.04, p = 0.049). Thus, a patient in whom the length of the angioplasty is 50 cm has a risk of occlusion 1.02^50 = 2.69, and compared to a patient with a 20 cm length of angioplasty, there is a risk of occlusion of 1.02^50−20 = 1.81. By using the median value of length of occlusion (30 cm) as a cut-off point we can divide the patients in two groups: those in whom the length of the recanalization was less than 30 cm and those in whom it was more than 30 cm. Using univariate analysis, the patency rates in the two groups were significantly different (Log-rank test, p = 0.005, hazard ratio = 3.1 with 95% CI 1.4 to 7.2).

According to Life-table analysis the patency rate among the patients that had a short length recanalization (<30 cm), 12 months after the procedure was 66% while in patients with a long recanalized segment (>30 cm) 33% (Fig. 4).

**Discussion**

This prospective clinical study shows that among the factors that can affect the patency rate of lower limb infrainguinal subintimal angioplasty (SA), the most important are the number of patent run-off crural vessels after the procedure and the length of angioplasty. Neither gender nor any risk factor of atherosclerosis such as diabetes mellitus, arterial hypertension, coronary artery disease and history of smoking, affect the outcome. Also, the distal point of angioplasty (above or below the knee level) is not a predictor of patency.

**Table 4. Univariate analysis of angioplasty patency for each risk factor examined**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Male/Female)</td>
<td>0.70 (0.31–1.56)</td>
<td>0.36</td>
</tr>
<tr>
<td>Arterial hypertension (Yes/No)</td>
<td>1.21 (0.54–2.70)</td>
<td>0.62</td>
</tr>
<tr>
<td>Coronary artery disease (Yes/No)</td>
<td>0.92 (0.41–2.06)</td>
<td>0.83</td>
</tr>
<tr>
<td>Diabetes mellitus (Yes/No)</td>
<td>1.41 (0.61–3.30)</td>
<td>0.38</td>
</tr>
<tr>
<td>Smoke (Yes/No)</td>
<td>0.83 (0.37–1.84)</td>
<td>0.62</td>
</tr>
<tr>
<td>Run-off vessels (More than one/one)</td>
<td>0.22 (0.10–0.48)</td>
<td>0.00</td>
</tr>
<tr>
<td>Length of angioplasty (&gt;30 cm/&lt;30 cm)</td>
<td>3.10 (1.42–7.16)</td>
<td>0.00</td>
</tr>
<tr>
<td>Site of angioplasty</td>
<td>0.48 (0.21–1.08)</td>
<td>0.06</td>
</tr>
<tr>
<td>(Femoropopliteal/Distal)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(HR = hazard ratio, CI = confidence intervals).

**Table 5. Cox regression analysis of time to occlusion on presence of predictor variables “Run-off vessels” and “Length of occlusion”**

<table>
<thead>
<tr>
<th>Variables</th>
<th>b</th>
<th>SE</th>
<th>z</th>
<th>p</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run-off vessels</td>
<td>−1.194</td>
<td>0.539</td>
<td>−2.22</td>
<td>0.027</td>
<td>0.30 (0.11–0.87)</td>
</tr>
<tr>
<td>Length of occlusion (cm)</td>
<td>0.022</td>
<td>0.011</td>
<td>1.97</td>
<td>0.049</td>
<td>1.02 (1.00–1.04)</td>
</tr>
</tbody>
</table>

Cox-regression analysis (Chi-square = 6.32, df = 2, p = 0.042).

The variable “Run-off vessels” is a binary one and its values can be either 0 (one vessel run-off) or 1 (more than one vessel run-off). The variable “Length of occlusion” is a quantitative one (centimeters of occlusion). (b = coefficient, SE = standard error of coefficient, df = degrees of freedom, HR = hazard ratio, CI = confidence intervals).
The technical success of SA is generally high and varies between 78 and 90% in different reports, something that was also found in our study. According to the literature, infrapopliteal occlusions have a less favorable technical success rate when compared to the femoropopliteal occlusions.3,4,14

The mortality rate at 1 year in our study was 18% which is similar to the results of our earlier studies.5,14 The perioperative mortality rate (30 days post-intervention) was zero which is similar to the results reported by Nydahl et al.5 Also, Adar et al. reported a 0.8% perioperative mortality rate in claudicant and critically ischemic patients who had a femoropopliteal transluminal angioplasty.17 Tisi et al. reported a 3% mortality rate in patients who had SA for chronic lower limb ischemia.8 It is obvious that angioplasty carries a low incidence of perioperative mortality something which is important especially when compared to lower limbs bypass procedures that usually have higher mortality rates.16,17

The primary patency rate in our series on an intention-to-treat basis was 50% at 12 months which is similar to the results reported in the literature. There are various studies on SA that deal with either femoropopliteal or infrapopliteal lesions or both and report primary patency rates that vary between 53 and 74%.4,5,18 In contrast, Laxdal et al. recently reported a 37% primary patency in femoropopliteal subintimal angioplasties.5 These results are low compared to bypass operations where patency rates are reported to be between 80 and 98% at the same time interval.6,7,20 However, the limb salvage rate in critically ischemic patients that had a subintimal angioplasty does not seem to be different than in patients that had a bypass operation. In our series, the overall limb salvage rate at 12 months after the angioplasty was 92% despite the 50% primary patency rate. Obviously, an occlusion of the angioplastied segment is not equivalent to limb loss. According to Leicester experience, an occlusion of a SA does not definitely imply a critically ischemic leg. It is not yet clear why there is such a difference between patency and limb salvage rate. We believe that collaterals are the key point. In SA, collaterals remain intact while in a bypass operation they are often sacrificed during the arteries dissection. Furthermore, SA has the advantage of the repetition as long as it is necessary. Also, the possibility of a femoropopliteal or a femorodistal bypass operation always exists.

With regard to the possible factors that might determine the patency rate of SA, we found that the number of patent crural vessels after the procedure and the length of angioplasty are the most important. According to our study, patients with 2 or 3 patent run-off vessels after the angioplasty have a 3.30 (95% CI 1.4 to 7.2) risk of occlusion compared to those with one patent run-off vessel (p = 0.027). London et al.21 reported a similar result in patients with only femoropopliteal occlusion treated by SA. Similar results have also been reported by other investigators for percutaneous transluminal infrainguinal angioplasty22–24 or stenting.25 Univariate analysis in our series has shown that the patency rate of SA with more than one patent run-off vessels at 12 months is 81% compared to the 25% of SA with one run-off vessel. This could be a very important observation as it is usually possible to recanalize more than one occluded crural arteries using the SA technique and we consider this safe as little harm can be caused by trying to recanalize an occluded crural vessel.

The length of the occluded arterial segment recanalized was also found to be related to the patency rate of SA by a hazard ratio of 1.02 (95% CI 1.00 to 1.04, p = 0.049) for every occluded centimeter. Thus, for every 10 cm of recanalized occlusion there is about 1.0210 = 1.22 risk of reocclusion after the angioplasty. Vraux et al. have also reported that the length of the occlusion (>10 cm) is a predictor of SA technical success and patency.4 Also, London et al. consider that the risk of reocclusion of a femoropopliteal SA increase by 1.73 for every 10 cm of occlusion length.21
The end point of the angioplasty was not a significant factor affecting the outcome of SA. Despite the event that the univariate analysis showed an almost statistically significant effect of this variable to angioplasty patency (Table 4), the multivariable Cox regression model did not prove it. Possibly, a larger number of observation may be useful in precisely identify the effect of this variable to the outcome. However, based on our results we concluded that whether a femoropopliteal or an infrapopliteal angioplasty was performed they both had almost the same outcome. Vraux et al. have also found that the location of distal reentry point after SA is not a predictor of technical success.4

None of the factors predisposing to atherosclerosis was found to affect the SA outcome in our series. Arterial hypertension has been reported to increase the risk of occlusion in claudicants who have invasive treatment (endovascular or surgical),26 although research on outcome of percutaneous transluminal angioplasty (PTA) for CLI did not show any statistical significance with any associated atheromatous disease.27 With regard to coronary artery disease, there are some investigators,22,28 who associate it negatively with the long-term patency of PTA but this is not unanimous.27 As far as diabetes mellitus is concerned Laxdal et al.3 and Vraux et al.4 believe that this is an independent factor for reocclusion of femoropopliteal and tibial SA. In contrast, Ingle et al. reported that although the rate of CLI is significantly higher in diabetics than non-diabetics, neither survival nor amputation rates are different.14 However, it is likely that the effects of diabetes and CLI are confounded by run-off status and the extent of the occlusive disease. Diabetic patients with good run-off fare better than those with poor run-off after femoropopliteal PTA.29 Diabetics in whom run-off can be restored by tibioperoneal PTA also fare well.30 A history of smoking is not related to the angioplasty outcome27 but the continuation of smoking after the procedure is related to a higher reocclusion rate.21 It is well known that the progression of peripheral arterial disease from asymptomatic to claudication and finally to ischemic rest pain is associated with cigarette smoking.31 In patients with severe disease, graft patencies are clearly improved by stopping smoking, both for vein as well as prosthetic graft material.7 Therefore, in patients with severe end-stage disease, smoking cessation is highly beneficial.

Sex was not found to be a significant risk factor in our study. In the literature, there are controversial thoughts on this. Timaran et al. believe that female gender is an independent factor for decreased primary iliac stent patency2,33 while Marzelle et al. have reported a statistically higher incidence of restenosis of infrainguinal endovascular revascularization procedures among men.34

As a weakness of this study, it could be considered the relatively small number of patients that does not permit a further stratification of the results. This is the reason why we have just remained on the distinction between one and more than one run-off vessels and have not studied further down the difference between two and three run-off vessels.

Subintimal angioplasty is a different technique to transluminal angioplasty; not only are there technical differences but also because SA achieves recanalization of long arterial occlusions which PTA cannot. In transluminal angioplasty selection on anatomical ground is important because the ideal patient will be the one with focal disease. Unfortunately, because of the presence of diffuse disease in chronic CLI, transluminal angioplasty is only applicable in a small proportion of CLI patients. In contrast, SA due to its effectiveness in long occlusions can be applied to most patients with CLI. Thus SA can be considered as an alternative to open surgery for these patients. The treatment is relatively atraumatic, complications are rare8 and in most cases treated by endovascular techniques.3,35 Our data suggests that the number of run-off vessels and the length of occlusion are the main determinants of SA patency. This knowledge could alter on SA technique as a recanalization of more than one vessel is often achievable. By recanalization of more than one run-off vessels when possible during SA, patency rates could be raised to bypass levels.

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