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What is the secondary patency of thrombosed bypasses of the lower limbs cleared by fibrinolysis in situ?

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ABSTRACT

Objectives: In case of acute thrombosis, lower limbs bypasses can, in certain cases, be cleared by local intra-arterial fibrinolysis (LIF). The aim of this study was to evaluate the secondary patency of thrombosed bypasses after fibrinolysis.

Methods: This retrospective study includes all patients hospitalized for thrombosed bypasses of the lower limbs that were treated with in situ fibrinolysis using urokinase, between 2004 and 2013, in two French university hospital centers. Fibrinolysis was indicated in case of recent thrombosis (< 3 weeks) provoking acute limb ischemia without sensory-motor deficit and in the absence of general contraindications. The secondary patency of the grafts was defined as the time after fibrinolysis without a new thrombotic event.

Results: There were 207 patients, hospitalized for recent thrombosis of 244 bypasses. The LIF was efficient in 74% of the cases (n=180). Secondary patency of these bypasses, was 54.2% and 32.4% overall, 68.3% and 50.3% for the suprainguinal bypasses and 48.3% and 21.5% for the infra-inguinal bypasses, at 1 year and 5 years respectively. There is a significant difference (p = 0.002) regarding the permeability of the suprainguinal and infra-inguinal bypasses. The survival rate was 75% (± 6.4%) at 5 years and the limb salvage rate was 89% (± 3.3%), 78.2% (±5.1%) and 75% (±5.8%) at 1 year, 3 years et 5 years respectively. The only independent factor influencing the secondary patency of infra-inguinal bypasses that was significant in a multivariate analysis was the infragenicular localization of the distal anastomosis (p=0.023).

Conclusions: LIF is an effective approach that often allows the identification of the underlying cause, permitting elective adjunctive treatment of the underlying cause. Although LIF is at least as effective as its therapeutic alternatives described in the literature, the secondary patency of the bypasses remains modest and encourages close monitoring, particularly in patients with an
infragenicular bypass.

INTRODUCTION

Acute limb ischemia might occur during the evolution of lower extremity arterial occlusive disease, caused by a thrombosis in native arteries or bypasses, but also by emboli. The most appropriate strategy for the management of thrombosis of bypasses in case of acute limb ischemia is still debated by vascular surgeons. Local intra-arterial fibrinolysis (LIF), a technique described since the 1980s, has a particular place in this strategy, for patients with thrombosis of bypasses provoking acute limb ischemia without sensory-motor deficit. In that respect the goal of LIF is to reestablish the arterial patency and to unmask the underlying cause of the thrombosis. It allows the consecutive treatment of the underlying cause in order to prevent recurrence of the thrombosis. The use of this technique has since been the subject of numerous publications that report a percentage of success of clearance of bypasses of over 70%. In our centers a specific protocol for LIF, established and unchanged since more than 25 years, has similarly demonstrated its effectiveness. Primary patency of different bypasses of the lower limbs has already exhaustively been reported in the literature. The primary patency rate of aorto-bi-iliac and aorto-bifemoral bypasses are 91% and 87% at 5 and 10 years respectively for patients with claudication and 87% and 82% at 5 and 10 years respectively for patients with acute ischemia (12,13). The primary patency rate of infra-inguinal bypasses at 5 years varied from 55 to 64% for venous bypasses and from 37-57% for prosthetic bypasses (14,15). However few data are available in the literature describing secondary patency at long term follow up of thrombosed bypasses that have been cleared with LIF.

The primary end point of this retrospective study was to determine the long-term secondary patency of thrombosed bypasses of the lower limbs, which underwent successful fibrinolysis. The secondary end points of this study were to investigate the morbidity associated with LIF and to research the possible factors influencing the permeability of the bypasses after LIF.

MATERIALS AND METHODS

Population:
This retrospective study includes all patients presenting at two university hospital centers (Angers and Lyon) between January 2004 and December 2013, with acute lower limb ischemia without sensory-motor deficit, provoked by acute thrombosis of a bypass, that have benefited from a successful clearing by LIF.

Acute ischemia without deficits or subacute ischemia of the lower limbs is defined by the sudden onset of lower limb pain or degradation of the patient’s maximum walking distance. In order to be eligible for fibrinolytic treatment, the duration of the symptoms of ischemia has to be less than 21 days and the ischemia should be classified as Rutherford Categorie IIa.

The protocol for fibrinolysis in situ was similar in both centers. The fibrinolytic agent used in our study is urokinase (Actosolv®, Eumedica sa, Belgium), which is delivered intra-arterial in situ. After an optional bolus of urokinase, a continuous infusion of 2500 IU/kg/h urokinase was administered via a thrombolysis catheter, placed within the recent thrombus in combination with 100 IU/kg/12h heparin via a peripheral venous line.

Daily radiological monitoring was performed to verify the progression of the thrombolysis and the achieving patency of arterial tree, and to allow the eventual repositioning of the catheter. The criteria for stopping fibrinolysis were: success (complete clearance of the bypasses), the occurrence of clinical complications (death, bleeding or hematoma requiring discontinuation of LIF, acute renal failure (elevations of creatinemia greater than 25μmol / L with or without clinical signs)) or biological complications (fibrinogen < 1g/L or a drop of more than 1g/L in 6hours, platelets < 100.000/mm³, hemoglobin decreases and < 8g/dL) or technical failure (absence of lysis of the thrombus after 72 hours of LIF).

The demographic data included: age, gender and cardiovascular risks factors. The following information has been collected for the bypasses: localization (supra-/infra-inguinal, supra-/infra-genicular), material (venous or prosthetic) and age.

Concerning the LIF procedure the following data have been collected: the duration of the ischemia before the start of the LIF, the duration of the LIF, its success or failure, the eventual complications, the etiology of the thrombosis if it was identified and the consecutive treatment of the underlying cause if performed.
Follow up:

A follow-up was set up with a clinical examination and a Doppler ultrasound at 3 months, 6 months and once a year. The follow up of each patient was stopped at the date of the latest doppler ultrasonography made to verify the permeability of the bypasses. For this purpose, a direct follow-up with the doctors or the angiologists in charge of the patients was performed in case of missing data. Eventual cases of recurrence of thrombosis or re-interventions on the same limb and eventual amputation or mortality of the patients were searched and retrieved when possible. The secondary patency of the grafts was defined as the time after fibrinolysis without a new thrombotic event. In case of iterative thrombosis of bypasses cleared several times with LIF, only the first LIF and the time until the following thrombosis were taken into account. For patients lost to follow up or deceased, the follow up was stopped on the date of the last ultrasound showing the patency of the bypasses.

Statistical Analysis:

The analyses were performed using the software Excel and SPSS (SPSSTM Inc, Chicago, Illinois) version 15.0. The continuous variables are described in terms of means and standard deviation or medians and extremes. The statistical link between two nominal qualitative variables were performed using the chi-square test. Data on the patency of the bypasses were analyzed using the Kaplan-Meyer method. Univariate and multivariate analysis of the factors influencing the patency were made using regression logistic model.

RESULTS

From the two centers participating in the study, between January 2004 and December 2013, 371 LIF procedures of the lower limbs were performed. 127 of these LIF procedures were carried out on native arteries or other specific circumstances and were therefore excluded from this study. The other 244 LIF procedures on bypasses in 207 patients were included in this study. The demographic characteristics are summarized in table I. The average age of the study population was 66 ± 13 years. The distribution of the types of bypasses was as follows: 73 supra-inguinal bypasses (30%) and 189 infra-inguinal bypasses (77,5%) (whereof 18 supra-inguinal with crural extension), 71 infra-genicular (29%), 79 venous bypasses (32%) and 192 prosthetic bypasses
The median primary patency of the bypasses before the first LIF was 4.5 years (2 months-24 years). The success rate of LIF was 74% (n=180). LIF was successful with complete clearance in 87.3% of the supra-inguinal bypasses and 70% of the infra-inguinal bypasses (p = 0.002). In the patients with successful fibrinolysis, an objective underlying cause for the thrombosis was found in 85% of the cases (n=153). More specifically in 31% distal anastomotic stenoses (n=56) and in 24% degradations of the arterial tree (n=43) were observed.

Etiological treatment, consecutive to the clearance was executed in 58% of the cases (n=104); endovascular treatment in 39% of the cases (n=70), with implantation of stents in 17% of the cases (n=30). Conventional direct surgical reparation was performed in 25% of the patients (n=45), including 9.4% (n=17) for distal anastomosis repair.

For 3.9% (n=8) patients lost to follow up, the follow up was stopped on the date of the last ultrasound showing the patency of the bypasses.

Secondary patency of the bypasses was 59% and 32% overall, 68% and 50% for the supra-inguinal bypasses and 48% and 21.5% for the infra-inguinal bypasses, at 1 year and 5 years respectively, with a significant difference between the latter two subgroups (p = 0.002). We have respectively, 54% and 42% one year patency for prosthetic bypasses and venous bypasses without statistically significant differences. Univariate analysis identified the infragenicular localization of the distal anastomosis (p = 0.006) and the time of ischemia before the start of the LIF < 48 hours (p = 0.049) as the only factors significantly influencing the secondary patency of the bypasses (Table II). The infragenicular localization of the distal anastomosis appeared as the only independent factor (p = 0.023) (OR = 2) influencing the secondary patency of the bypasses in a multivariate analysis (Table II).

At the end of the follow-up, the survival rate of patients successfully treated with fibrinolysis was 82% (± 5.2%) at 3 years and 75% at 5 years (± 6.4%). The limb salvage rate of patients successfully treated with fibrinolysis was 89% (± 3.3%), 78.2% (±5.1%) and 75% (±5.8%) at 1 year, 3 years et 5 years respectively.

The complication rate of LIF was 18.4% (n=45), whereof 12% (n=30) were bleedings or hematomas that necessitated discontinuation of LIF and 6% (n=15) were acute renal failures. Surgery was indicated for the management of the complication in 2% of the cases (n=5).
deaths (0.8%) occurred during the LIF treatment. One patient of 83 years with atrial fibrillation died of an ischemic stroke 3 hours after the start of LIF. Another patient of 60 years without history of ulcers or a digestive tumor, had hematemesis on day 1 of the LIF; the bypass was already cleared and the LIF was stopped. The patient died of hemorrhagic shock despite resuscitation. The average hospital duration of LIF and consecutive treatments was 10 ± 7 days. The mean follow-up of the patients after the procedure was 70 ± 39 months.

DISCUSSION

The management of patients with acute ischemia of the lower limbs without sensory-motor deficit caused by bypasses thrombosis remains a complex situation for vascular surgeons. The therapeutic strategy depends on the clinical status of the patient, the duration of the ischemia and the suspected etiology of the thrombosis. The treatment with LIF, which is usual practice in the university hospitals of Angers and Lyon, relies on a well-established longstanding protocol. The present study reports a 74% success rate of LIF, which is in line with what is found in the literature. This success rate decreases as the localization of the distal anastomosis in the lower limb descends. At the infra-inguinal level there is no significant difference between the prosthetic and venous bypasses regarding the success rate.

Although other fibrinolytic agents might be used, urokinase has several advantages, it represents a lower risk of general fibrinolysis, a shorter infusion time and less antigenicity than for example streptokinase.

Importantly, a constant protocol, with close clinical and biological surveillance of the patient, makes it possible to obtain an acceptable complication rate in comparison with other studies (hemorrhagic risk of about 10%) , with similar mortality rate found in the literature (0% to 5.2%).

Angioplasty with or without stenting of distal anastomotic stenoses was the most frequently used
adjunctive treatment. These results confirm those found in the data series of Van Holten (23). The endovascular treatment further limits the complications related to iterative surgical access. Nevertheless conventional surgical reinterventions remained indicated in 25% of the patients, mainly to establish extensions of the bypasses in case of important damage to distal arterial runoff or poor long-term results of an endovascular intervention.

The observed secondary patency of thrombosed bypasses treated with LIF is better than the secondary patency found after fibrinolysis in the study of Nehler et al (59% vs 32% at 1 year and 32% vs 19% at 5 years) (17). For infra-inguinal bypasses, the present study reports secondary patency of 48% at 1 year and 31% at 2 years; these figures are still superior to the data reported after LIF by Nackman et al (32% at 1 year and 25% at 2 years) (3). In addition the results of this study are included in the data ranges of 25%-60% secondary patency at 1 year found in other LIF studies (2,9). For venous bypasses we found a secondary patency of only 42% at one year and of 12.5% at 5 years, which may seem disappointing in comparison to the numbers of 65% at 5 years found after LIF by Conrad et al (18). However, this difference might be explained by the fact that in the current group of patients 72% of the venous grafts are infragenicular. As in the current group of patients the infragenicular position of the distal anastomosis is the main factor negatively influencing the secondary patency of the bypasses in multivariate analysis (OR= 2(IC95% 1.1-3.59)), the secondary patency of the venous grafts is thus majorly influenced by the localization of their local anastomosis (the higher the distal anastomosis is localized, the better the secondary patency is).

Factors that have been described in the literature to influence secondary patency after LIF are: primary patency longer than 1 year, the duration of the ischemia before the LIF, the localization of the distal anastomosis and the treatment of the underlying lesion (2-4,6,18). In the present study, distal bypasses showed a significantly worse secondary patency in univariate (p=0.006) and multivariate (p=0.023) analysis. This is in line with the data of Conrad (18) which found similar results in univariate analysis (p=0.02) but in their study the differences were not significant in multivariate analysis (p=0.73). These results encourage close surveillance of
patients with infragenicular bypasses, which have the worst prognosis.

The limb salvage rate in our data series are comparable to the one of Kühn and Conrad after fibrinolysis (19,18) and is better than the one presented in the LIF data series of Ouriel (5,7), however it is important to note that in our series we only took into account the patients that were successfully treated with fibrinolysis. The long-term mortality of the study population in our data series is also comparable to the one at 5 years of Conrad (18).

The design of this study does not allow the direct comparison of LIF with other therapeutic interventions for subacute limb ischemia. Nevertheless, the therapeutic alternatives for LIF for the treatment of subacute limb ischemia caused by thrombosis of bypasses of the lower limbs are: thrombectomy with a Fogarty catheter and revascularization with another bypass. Only few prospective randomized studies have compared the patency after LIF with immediate surgery (associated or not with thrombectomy) for the treatment of subacute limb ischemia caused by thrombosis of bypasses of the lower limbs, no clear differences could be found in these comparisons. In non-comparative studies the overall patency that has been described after thrombectomy with a Fogarty catheter was 20-30% at 5 years for venous bypasses and 30% at 2 years for prosthetic bypasses, the authors also found that early treatment of bypass is preferable (ideally within 24h to obtain the best secondary patency) (24,25). The patency that has been described after repetitive revascularization with bypasses was around 50% at 5 years for venous bypasses and 25% at 5 years for prosthetic bypasses, with 25% of complications related to the access points (7,8,9,26). The retrospective data series of Baril found a patency of 82% at 1 year for bypasses in the context of acute limb ischemia, but only 33% of the cases of acute limb ischemia were due to bypasses thrombosis (27).

Prospective, randomized studies that compare morbidity and mortality outcomes between LIF and alternative therapeutic strategies are limited to 1 year follow-up. The STILE trial (8) concluded after 1 year of follow-up that in the overall population, there was no significant difference between LIF and surgery. However, in subgroup analysis, this prospective, randomized study advocated the choice of LIF, for limb ischemia of less than 14 days and
surgery for limb ischemia of more than 14 days. For patients with limb ischemia of less than 14
days, the limb salvage rate was 87.7% for LIF and 62.5% for surgery and the survival rate was
94.4% for LIF and 90% for surgery at 6 months.

In non-comparative studies Baril (27) found 78% limb salvage and 79% survival rate at 1 year in
the data series of acute limb ischemia (whereof only 32.8% were on bypasses) revascularized
with bypasses in comparison to 89% limb salvage rate and 92% survival rate at 1 year, in
current data series. In a long-term follow-up, Barlett (26) found a 59% limb salvage rate at 5
years for repetitive revascularization surgery, in comparison with 75% in current data series and a
mortality similar to current data series at 5 years. Although LIF appears better than surgery in
terms of limb salvage, it is not pertinent to compare LIF with surgery, LIF must be an integral
part of the therapeutic arsenal of surgeons. In this way, it can delay or limit the need for urgent
conventional surgery. As a matter of fact, conventional surgery itself presents with its own
important complications, such as cutaneous complications or infections related to repetitive
access in sclerotic areas, major in hospital adverse events (27) and problems of material for the
establishment of repetitive bypasses in fragile patients.

Despite our large population, our data series has some limitations essentially because it is a
retrospective study that does not compare LIF with other therapies; nevertheless our data further
confirms the place of LIF for the clearing of thrombosed bypasses of the lower limbs.

CONCLUSION

Bypasses thrombosis remains a serious event in the evolution of arterial occlusive disease of the
lower limbs. In situ fibrinolysis of bypasses of the lower limbs is a safe and effective
pharmacological thrombus-removing approach that, if successful, often allows the identification
of the underlying cause, allowing elective adjunctive treatment of the cause of thrombosis. As
such it should be a part of the arsenal of vascular surgeons. Although LIF is at least as effective
as its therapeutic alternatives described in the literature, the secondary patency of the bypasses
remains modest and encourages close monitoring, particularly in patients with infragenicular
bypasses.
Declarations of interest: none

Author contributions
Conception and design: TK, JP, SH, PF, MA Analysis and interpretation: TK, JP Acquisition of data: TK, NDS Writing the article: TK, JP, MA

Critical revision of the article: TK, JP Final approval of the article: TK, JP Overall responsibility: TK, JP

Opinion of the ethics committee:
This study was submitted to the ethics committees of Angers and Lyon university hospitals and obtained a favorable opinion. It was conducted in accordance with the rules of ethics and the protection of medical confidentiality.

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Fig 1: Curve of secondary patency of supra-inguinal grafts (blue line) and of infra-inguinal grafts (green line) (p=0.002).
<table>
<thead>
<tr>
<th>Demography</th>
<th>n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>165(80)</td>
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<tr>
<td>Diabetes</td>
<td>50(24)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>186(90)</td>
</tr>
<tr>
<td>Active tobacco use</td>
<td>76(37)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>165(80)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>64(31)</td>
</tr>
<tr>
<td>Anticoagulant therapy</td>
<td>35(17)</td>
</tr>
<tr>
<td>Anti aggregate therapy</td>
<td>196(95)</td>
</tr>
</tbody>
</table>
**Tableau II:** Univariate and Multivariate analysis of factors and their influence on the patency of the bypasses

<table>
<thead>
<tr>
<th>Factors</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>p</td>
<td>n(%)</td>
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<tr>
<td>Infra-epigastric bypasses</td>
<td>0.006</td>
<td>57(81%)</td>
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<tr>
<td>Ischemia ≤ 48h</td>
<td>0.049</td>
<td>81(80%)</td>
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<td>Age of the bypasses &gt; 1 an</td>
<td>0.512</td>
<td>107(66%)</td>
</tr>
<tr>
<td>Identification of the underlying lesion</td>
<td>0.711</td>
<td>133(65%)</td>
</tr>
<tr>
<td>Treatment of the underlying lesion</td>
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<tr>
<td>Surgical treatment</td>
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<td>Chronic renal failure</td>
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<td>Tobacco</td>
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<tr>
<td>Coronary artery disease</td>
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<td></td>
</tr>
<tr>
<td>Cancer</td>
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