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Mortality after major amputation in diabetic patients with critical limb ischemia who did and did not undergo previous peripheral revascularization
Data of a cohort study of 564 consecutive diabetic patients

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Abstract

Background: To evaluate the survival after major lower limb amputation, at a level either below (BKA) or above (AKA) the knee, in diabetic patients admitted to hospital because of critical limb ischemia (CLI). **Methods:** From January 1999 to December 2003, 564 diabetic patients were consecutively admitted to our Foot Center because of CLI and followed up until December 2005. A revascularization procedure was performed in 537 patients (95.2%): in 420 with peripheral angioplasty, in 117 with peripheral bypass graft. Neither endoluminal nor surgical revascularization was practicable in 27 (4.8%) patients. **Results:** Major amputation was performed in a total of 55 (9.8%) patients. Among the clinical and demographic variables evaluated, age was significantly lower (67.3±10.1 vs. 76.7±10.4, *P*<.001), duration of diabetes was higher (17.1±11.1 vs. 13.4±10.0, *P*=.013), and current smoking was more frequent (38.5% vs. 25.0%, *P*<.001) in revascularized amputees. The amputation free median time for revascularized patients was 5.11 months, and for nonrevascularized patients, 0.33 months. The log-rank test for equality of survivor function without amputation between amputees with or without revascularization was 31.76 (*P*<.001). Among the 55 amputees, 11 (28.2%) out of the 39 revascularized patients and 13 (81.2%) out of the 16 nonrevascularized patients died. The log-rank test for equality of survivor function was 6.83 (*P*=.009). The Cox model performed to evaluate the association between the recorded variables and the mortality showed a significant hazard ratio only with age (hazard ratio for 1 year 1.11, *P*=.003, confidence interval 1.04–1.19). **Conclusions:** Our data suggest that the revascularization allows to postpone the major amputation, and that the survival of revascularized amputees is better than that of nonrevascularized amputated patients. All these data offer further encouragement to revascularize all diabetic patients with CLI.

Keywords: Diabetes; Critical limb ischemia; Major amputation; Revascularization; Survival; Age

1. Introduction

The survival of patients who have undergone major amputation is lower compared to patients in whom it has been possible to save the limb (Laakso & Lehto, 1997). In a case histories of 564 diabetic patients with critical limb ischemia (CLI), we recently found that the survival

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worsened with increasing gravity of the arteriopathy (Faglia et al., 2006). The recent study of Taylor et al. (2007) reports that the survival of patients who underwent amputation after peripheral percutaneous transluminal angioplasty (PTA) was worse than that of patients who underwent primary amputation. We were surprised by this data, as we thought that the survival of after revascularization amputees would be higher than that of non-revascularized amputees; however, we checked the results of our case histories, and we realized that this particular topic had not been not investigated. The aim of the present study was to verify any difference in survival and amputation level among diabetic patients admitted for CLI who underwent major amputation in our case histories.

2. Methods

2.1. Protocol

All diabetic patients referred to our Diabetic Foot Center for foot lesion or rest pain were assessed for the presence of critical limb ischemia (CLI) according to the 2000 edition of TransAtlantic Inter-Society Consensus criteria [TransAtlantic Inter-Society Consensus (TASC), 2000]. All patients were evaluated for posterior tibial and dorsalis pedal pulses, ankle-pressure by Doppler continuous wave technique, and transcutaneous oxygen tension ($TcPO_2$) tested on the dorsum of the foot. CLI was detected if one foot pulse was reduced or absent, if ankle pressure was <70 mmHg when assessable (foot arteries absent or not compressible because of medial calcifications), and if $TcPO_2$ at the dorsum of the foot was <50 mmHg. All patients with these parameters were referred to a duplex scanning examination and to an angiographic study, and if obstruction >50% of vessel diameter was present, PTA was performed as first-choice revascularization procedure in the same session of the angiographic study. In patients in whom PTA was attempted unsuccessfully, a bypass graft (BPG) was considered. The patients in whom PTA or BPG were not possible received a therapy with prostanoids and percutaneous chemical sympathectomy with phenol injection under computed tomography guidance, when possible.

2.2. Limb salvage

In patients complaining of rest pain without foot ulcer, the disappearance of pain with discontinuation of antalgic therapy was considered as successful limb salvage. In patients with foot ulcer, limb salvage was considered successful if the ulcer was healed and the patient was able to weight-bear through the plantar aspect of the foot—even if this was achieved by a tarsal–metatarsal amputation (Garbalosa et al., 1996; Reyzelman, Hadi, & Amstrong, 1999), and if the patient was able to walk the aid of without crutches or artificial leg. In patients in whom rest pain was not relieved, or in whom gangrene extended above the Chopart joint, an above-the-ankle-amputation was proposed and performed. Conversely, any above-the-ankle amputation was considered a major amputation.

2.3. Follow-up

After hospital discharge, all the patients with foot ulcer were examined weekly until ulcer healing. New above-the-ankle amputations, vital status, as well as date and cause of deaths were recorded.

2.4. Statistical methods

Data are presented as percentages of events in subgroups, and averages of recorded continuous variables are reported with their standard deviations. Student *t* test and Pearson chi-square test were applied when appropriate. The time to event median times were computed by Kaplan–Meier approach, and Log-rank test was used in order to assess the role of covariates on time to event and survival. The Cox survival model was also applied in order to assess the combined role played by covariates on time to event and survival.

The software used was the Stata 7.0 software package (Statistics/Data Analysis, Stata Corporation, 4905 Lakeway Drive, College Station, TX, USA, 800-STATA-PC).

3. Results

3.1. Patient population and treatment

From January 1999 to December 2003, 564 diabetic patients were consecutively admitted to our Foot Center because of CLI. A revascularization was performed in 537 (95.2%) patients: specifically, a PTA was successfully performed in 420 (74.5%) patients, and a BPG was carried out in 117 (20.7%) patients. In the remaining 27 (4.8%) patients neither PTA nor BPG was feasible: all these nonrevascularized patients received prostanoid therapy, and in five of them, a percutaneous chemical sympathectomy was also performed.

3.2. Follow-up

Of the 564 patients, 557 (98.8%) were followed up from January 1999 until June 2005: specifically, 415 of these patients belonged to the PTA group; 116, to the BPG group; and 27, to the nonrevascularized group. The mean follow-up was 3.4±1.3 years.

3.3. Major amputation

A total of 55 (9.8%) major amputations were performed. Twenty-three (4.1%) major amputations were

Table 1
Number of major amputations at the AKA (above-the-knee) or BKA (below-the-knee) level performed in the early and follow-up period in PTA, BPG and nonrevascularized patients

Patient's treatment	Number of major amputation		Total
	At 30 days	During follow-up	
Angioplasty (*n*=420)	6 (1.4%) 2 AKA - 4 BKA	16 (3.8%) 3 AKA, 13 BKA	22 (5.2%)
Bypass graft (*n*=117)	3 (2.6%) 3 AKA, 0 BKA	14 (12%) 10 AKA–4 BKA	17 (14.5%)
No revascularization (*n*=27)	14 (51.9%) 10 AKA–4 BKA	2 (7.4%) 2 AKA, 0 BKA	16 (59.3%)

carried out at 30 days. Two above- and 4 below-the-knee amputations (1.4%) were performed in PTA patients: in 5 of these patients the reason for the amputation was an extensive infection of surgical wound of a Chopart amputation, and in the remaining patient, the amputation was required due to an acute distal thrombosis after PTA that was not suitable for surgical revascularization. Three (2.6%) above-the-knee amputations were performed in BPG patients with infrapopliteal bypass because of an acute untreatable graft closure. Ten above- and four below-the-knee amputations were performed at 30 days in nonrevascularized patients because of rest pain and extensive gangrene.

During the follow-up, 32 (5.7%) major amputations were performed. Three above- and 13 below-the-knee amputations were performed in the PTA group because of untreatable restenosis. Ten above- and 4 below-the-knee amputations were performed in the BPG group because of untreatable occlusion of the graft. Two above-the-knee amputations were performed in non-revascularized patients because of worsening foot lesion. Table 1 summarizes the number and level of major amputations performed in the early and follow-up period.

The demographic and clinical data of amputated patients, with the differences between revascularized and nonrevascularized amputees, are reported in Table 2. Fig. 1 shows the Kaplan-Meier curves of major amputation in revascularized and non-revascularized amputees.

The amputation free median time for revascularized patients was 5.11 months, for nonrevascularized patients was 0.33 months. The log-rank test for equality of survivor function without amputation between amputees with or without revascularization was 31.76 (P<.001).

3.4. Amputation level

There was no statistically significant difference in the number of amputations at the above- or below-the-knee level between previously revascularized and nonrevascularized amputated patients: 21 BKA and 18 AKA in revascularized amputees, 4 BKA and 12 AKA in non-revascularized amputees (P=.075). However, the number of

Table 2
Demographic and clinical data of amputated patients who did and did not underwent previous revascularization

Variables	Revascularized amputees (*n*=39)	Nonrevascularized amputees (*n*=16)	*P*
Age (years)	67.3±10.1	76.7±10.4	.001
Females/males (n)	14 (35.9 %)/25 (64.1%)	10 (62.5%)/6 (37.5%)	.071
Insulin therapy (n)	38 (97.4 %)	14 (87.5%)	.069
Diabetes duration (years)	17.1±11.1	13.4±10.0	.013
Sensory-motor neuropathy (*n*)	34 (87.2%)	15 (93.8%)	.660
Retinopathy (*n*)	14 (35.9%)	6 (37.5%)	.911
Creatinine (mg/dl)	1.34±0.4	1.30±0.6	.814
Dialysis (*n*)	9 (23.1%)	–	.036
Antihypertensive therapy (*n*)	28 (71.8%)	11 (68.8%)	.821
Cardiac disease (*n*)	24 (61.5%)	12 (75.0%)	.533
Actual smoking (*n*)	15 (38.5%)	4 (25.0%)	.001
History of stroke (*n*)	2 (5.1%)	2 (12.5%)	.531
0	2 (5.1 %)	0 (–)	
1	0 (–)	2 (12.5%)	
2	4 (10.3%)	3 (18.8%)	.605
3	3 (7.7%)	1 (6.25%)	
4	30 (76.9%)	10 (62.5%)	
Infected ulcer (*n*)	31 (79.5%)	11 (68.8%)	.489
Rest pain	30 (76.9%)	13 (81.3%)	1.000
$TcPO_2$ at admission (mmHg)	9.74±11.0	8.62±10.1	.727

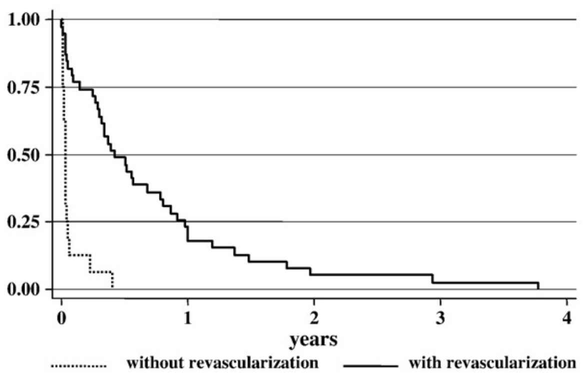

Fig. 1. Kaplan-Meier amputation free estimates in amputated patients, with (n=39) or without (n=16) previous revascularization.

AKA was significantly lower in amputated patients who had previously undergone PTA: 17 BKA and 5 AKA in PTA amputees, 4 BKA and 13 AKA in BPG amputees, 4 BKA and 12 AKA in nonrevascularized amputees (chi-square 12.6, P=.002).

3.5. Survival

Of the 55 amputated patients, 11 (28.2%) of the 39 revascularized and 13 (81.2%) of the 16 nonrevascularized died. Fig. 2 shows the Kaplan–Meier survival estimates in amputated patients with or without revascularization. The log-rank test for equality of survivor function was 6.83 (P=.009). Fig. 3 shows the Kaplan–Meier major amputation and death free estimates in the entire population: in the 420 patients who underwent revascularization with peripheral angioplasty, in the 117 patients who underwent peripheral bypass graft, and in the 27 nonrevascularized patients.

3.6. Prognostic determinants

The Cox model performed to analyze the association between the recorded variables and the mortality showed a significant hazard only with age: hazard ratio for 1 year 1.11, P=.003, confidence interval 1.04–1.19.

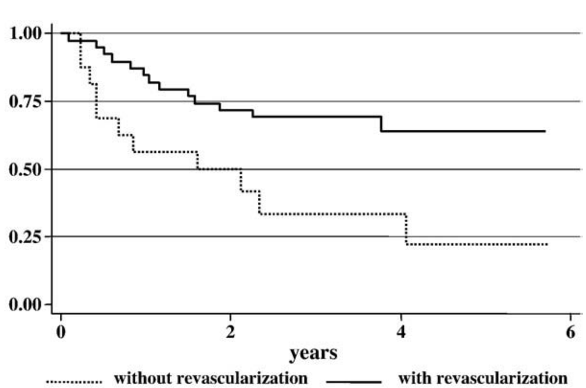

Fig. 2. Kaplan-Meier survival estimates in amputated patients with (N = 39) or without (N = 16) previous revascularization.

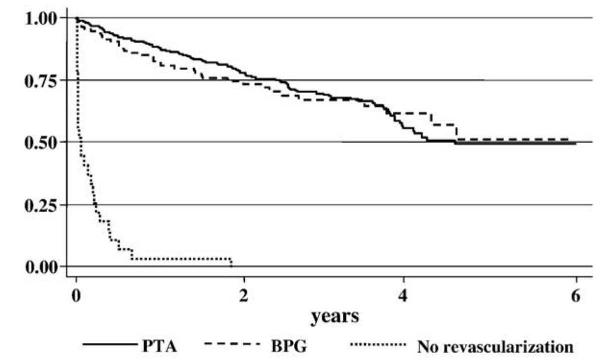

Fig. 3. Kaplan–Meier major amputation and death free estimates in the 420 patients who underwent revascularization with PTA, in the 117 patients who underwent BPG and in the 27 of nonrevascularized patients (no revascularization).

4. Discussion

Successful revascularization reduces the rate of major amputation in diabetic patients presenting with critical limb ischemia (LoGerfo et al., 1992). However, a certain risk of amputation still exists also in revascularized patients, both in the early and follow-up period, for several reasons: for instance, the revascularization may not succeeded in allowing the blood flow to reach the foot (Faglia et al., 2007), or gangrene may require the removal of a huge part of the foot (Pounds et al., 2005), or an untreatable restenosis in PTA patients (Ryer et al., 2006) or a graft closure in BPG patients may occur (Nowygrod et al., 2006).

Patients with CLI have a high risk of death (Tentolouris, Al-Sabbagh, Walker, Boulton, & Jude, 2004). Also in the recent TASC edition, it has been confirmed that the main purpose of the treatment of CLI is to increase the life quality and expectancy (Norgren et al., 2007). In our cohort of diabetic patients admitted to hospital because of CLI during 1999–2003, we extensively performed revascularization by means of PTA or BPG, and the incidence of major amputation in the early period was very low. The rate increased during a mean follow-up of about 4 years, when it reached almost 10%. On the contrary, the major amputation rate of nonrevascularized patients is very high in the early period but low during follow-up. The low percentage during the follow-up can be explained by the very low survival rate of these patients: as shown in the Fig. 3, about only one third of these patients survived for more than 1 year.

In this case histories we evaluated the differences in the survival between revascularized and nonrevascularized patients, but we did not analyze the survival of amputated patients who had or had not undergone previous revascularization: the study of Taylor et al. (2007) prompted us to investigate this topic. In our case histories, the survival of amputated patients who had previously undergone revascularization was significantly better than that of nonrevascularized amputees. These data conflict with that of Taylor: possible explanations for this discrepancy may be due to some differences in the studied population. Our case histories was composed entirely of diabetic patients, while diabetic patients in the study of Taylor represented about the 65% of a general population. We compared all patients admitted to our hospital because of CLI, including those revascularized by means of PTA or BPG and those nonrevascularized; instead, the study of Taylor only showed the outcomes of patients who underwent either primary amputation or PTA. However, the main difference appears to be the age of patients. The percentage of patients aged over 80 years was higher in the Taylor study than in our case histories. Age played a fundamental role in our study, as it appeared to be the only independent risk factor for death. We believe that also in the study of Talyor, the age, which was significantly higher in patients who underwent PTA, may have played an important role in influencing the kind of procedure that has been performed, as well as the mortality rate. We think that it is important to settle this issue: in fact, at this point, the question may arise as to whether an extensive use of revascularization procedures may be justified compared to primary amputation (Van Damme, 2004). We think that the revascularization is largely justified, as we already demonstrated that this procedure reduces the rate of major amputation. Data of this study demonstrated that the revascularization, even when unable to avoid major amputation, allowed for better patient survival than that of nonrevascularized patients. Moreover, our data indicated that the rate of below-the-knee amputation in PTA patients was significantly higher than that of nonrevascularized patients, as well as than that of amputated patients because of BPG closure. Our findings are in accordance with literature (Aulivola et al., 2004; Ploeg, Lardenoye, Vrancken, Peeters, & Breslau, 2005; Subramaniam, Pomposelli, Talmor, & Park, 2005)—although with some exceptions (Kulkarni, Pande, & Morris, 2006)—indicating that the outcomes of below-the-knee amputation are superior to those of the above-the-knee amputation.

Our data suggest that the revascularization allows to postpone the major amputation. Moreover, the incidence of below-the-knee amputation is higher in revascularized amputees, and it reaches the significance in PTA-amputated patients.

Also, the survival of patients who underwent major amputation after revascularization is better than that of patients who underwent an amputation without revascularization. Although we consider that these patients are older (Moulik, Mtonga, & Gill, 2003), the presence of a nonrevascularizable occlusive disease is a marker that represents a high risk not only for major amputation but also for their survival. This is true, however, when the revascularization feasibility is very high.

All these data offer a further encouragement to perform revascularization in all diabetic patients with CLI.

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