Does Peripheral Neuropathy Have a Clinical Impact on the Endovascular Approach as a Primary Treatment for Limb-Threatening Ischemic Foot Wounds in Diabetic Patients?

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**Introduction**

Approximately 15% of diabetic patients will develop a foot ulcer during their lifetime and among them, 14% to 43% will require amputation [1-3]. Peripheral neuropathy, such as chronic inferior limb ischemia, is a common complication of diabetes mellitus, affecting approximately 60% of diabetic patients and up to 80% of diabetic patients with foot ulcers [1-4]. Although the neuropathic etiology is dominant in 45% of diabetic foot ulcers, both ischemic and neuropathic risk factors are found in up to 35% of cases [1-4]. Current clinical management, focused on the endovascular approach as a primary treatment for critical limb ischemia (CLI), is highly feasible and shows low complication rates [5,6] and limb salvage rates comparable to surgery [5-8]. Although diabetic neuropathy has already been reported as an important risk factor for limb loss independently from limb-threatening ischemia, [1-4] there is little information on its direct effect on the outcome after surgical and endovascular reconstruction. Thus, the aim of the present study was to analyze the effect of concomitant peripheral neuropathy on critical limb ischemia in diabetic patients initially treated by endovascular methods. A retrospective design was used to assess clinical outcome in diabetic patients with ischemic foot wounds with and without concomitant peripheral neuropathy.

**Materials and Methods**

**Patients**

Between January 2005 and November 2010, below-the-knee (BTK) angioplasty was performed on a total of 152 ischemic limbs of 140 diabetic patients as a primary treatment for critical ischemic ulcers with or without neuropathic affection in two departmental hospitals of our institution. The medical records of these patients were retrospectively reviewed. The selection and follow-up of patients was uniformly carried out by a multidisciplinary “diabetic foot” team and approved by the local ethics committee. All patients presented with ischemic symptoms, revealed by clinical, duplex and transcutaneous oximetry (TcPO2) assessment. In all cases, revascularization for critical ischemia [2,3] and limb salvage was recommended [2,3,9] and clinical outcome was assessed. The 152 limbs were treated by subintimal (SA) and/or endoluminal (EA) primary angioplasty performed on selected diabetic CLI neuroischemic foot wounds. If the endovascular attempt failed, second-line surgical options were used. Twelve patients underwent staged bilateral revascularization surgery.

Eighty-six patients were men. A total of 132 ischemic limbs (87%) were associated with type 2 diabetes and 20 ischemic limbs (20%) were associated with type 1 diabetes. The mean age was 73.7 years (range 46-95). Ninety-six patients (62%) were under an insulin-based treatment regimen at the time of the surgery and 124 interventions (82%) were performed on patients who had diabetes for more than five years. Other patient characteristics and risk factors are summarized in Table 1. Foot ulcers, distal necrosis, swelling and local sepsis were present in different proportions in each case (Rutherford’s grade III, category 5 or Fontaine’s stage IV lesions) [2,3,9]. According to the UK screening test [10], there were 43 limbs (28%) without perceivable neuropathic affection (NN subgroup), 70 limbs (46%) (1p - 7p) with moderate neuropathic impairment (MN subgroup) and 39 limbs (26%) (6p -10p) with severe neuropathy (SN subgroup) (Table 2). The subgroups were matched for age, gender and type and duration of diabetes. Overall, there were 57 Wagner’s grade 1-2 (37%) and 95 Wagner’s grade 3-4 (63%) ischemic foot lesions [11] (Table 1). Patients with extended Wagner’s grade 5 [11] lesions, or equivalent Rutherford’s grade III category 6 major tissue loss [2,3,9], facing inevitable major amputation [1-3,11] were excluded from the study. Moreover, patients showing common femoral artery lesions, infragenicular atherosclerotic disease, recent occlusions with echolucent material (by systematic preoperative duplex evaluation) or acute lower limb ischemic symptoms were also not considered for this therapeutic approach. The endovascular procedures performed on the main arterial trunks of the leg consisted of 91 (60%) SA coupled to EA angioplasties, 29 (19%) SA angioplasties and 32 (21%) multilevel EA angioplasties (Table 2). Fifty-one of the 152 cases (33%) were insulin-dependent diabetic patients and most of them had multilevel arterial disease. The TASC type of lesions [2,3], the extent of infragenicular atherosclerotic disease and the spread of calcification are reported in Table 1. More than two thirds of the patients had diabetes longer than 10 years, while 109 out of 152 (72%) limbs presented different stages of peripheral neuropathy [10] associated with CLI features [2,3,9]. Other risk factors, comorbidities and local features of the treated limbs are summarized in Table 1 according to the NN, MN and SN subgroups of patients.

**Methods**

Considering a homogeneous distribution of clinical features in all subgroups (Table 1), the original protocol was designed to compare postoperative outcome in terms of patency rates, clinical success (ulcer healing) and limb salvage in the NN vs. MN and SN cohorts, after a similar primary treatment by angioplasty. The results were retrospectively recorded at equal time intervals. All patients had a similar follow-up schedule, with comparable multidisciplinary “diabetic foot”

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management and regular per- and postoperative assessment (between 2005 and 2010). The preoperative variables recorded in all cases were: initial clinical evaluation of the ischemic limb [2,3,9], clinical features of diabetes [10,11] ankle-brachial index (ABI) or toe pressure measurements (when technically feasible), Duplex scanning, TcPO2 and CT angiography or magnetic resonance imaging with detailed views of the main crural and pedal arteries. Postoperative assessment included specific follow-up variables, detailed in a further paragraph.

### Angioplasty technique

Patients with preoperative impairment of renal function were regularly hydrated and received N-acetylcysteine before the intervention. All interventions were preceded by routine preoperative antiplatelet therapy with daily administration of 160 mg of aspirin or 75 mg of clopidogrel, started at least 72 hours before the procedure. The SA and EA angioplasty procedures were performed according to previously published protocols [12-15] (Figure 1 and Figure 2).

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**Table 1:**

| PATIENTS CHARACTERISTICS / RISK FACTORS | Total Limbs (n = 152) | Group NN Limbs (n = 43) | Group MN Limbs (n = 70) | Group SN Limbs (n = 39) |
|----------------------------------------|-----------------------|-------------------------|-------------------------|-------------------------|
| Age > 70 years                          | n = 84 (55%)          | n = 25 (58%)            | n = 39 (56%)            | n = 20 (51%)            |
| Hypertension                           | n = 132 (87%)         | n = 39 (90%)           | n = 57 (81%)           | n = 36 (92%)           |
| Smoking                                | n = 65 (42%)          | n = 20 (46%)           | n = 27 (39%)           | n = 18 (46%)           |
| Coronary Disease                       | n = 128 (84%)         | n = 38 (88%)           | n = 56 (80%)           | n = 34 (87%)           |
| Chronic Renal Insufficiency            | n = 60 (39%)          | n = 17 (39%)           | n = 27 (38%)           | n = 16 (41%)           |
| End Stage Renal Disease/Dialysis       | n = 29 (19%)          | n = 6 (14%)            | n = 14 (20%)           | n = 9 (23%)            |
| Hypercholesterolemia                   | n = 96 (63%)          | n = 29 (67%)           | n = 44 (63%)           | n = 23 (59%)           |
| Cerebrovascular disease                | n = 33 (22%)          | n = 9 (21%)            | n = 15 (21%)           | n = 9 (23%)            |
| Retinopathy                            | n = 99 (65%)          | n = 15 (35%)           | n = 50 (71%)           | n = 34 (87%)           |
| LOCAL FEATURES IN TREATED LIMBS        | Total Limbs           | NN.                    | MN.                    | SN.                    |
| Diseased Artery > 10 cm                | n = 67 (44%)          | n = 20 (46%)           | n = 28 (41%)           | n = 18 (46%)           |
| Spread of Calcifications > 3 cm        | n = 57 (37%)          | n = 15 (35%)           | n = 26 (37%)           | n = 16 (41%)           |
| Associated Chr. Venuous Insufficiency  | n = 21 (14%)          | n = 5 (12%)            | n = 11 (15%)           | n = 5 (13%)            |
| Bed ridden                             | n = 15 (9%)           | n = 4 (9%)             | n = 7 (10%)            | n = 4 (10%)            |
| TASC "B" lesions                      | n = 13 (8%)           | n = 5 (12%)            | n = 6 (9%)             | n = 2 (5%)             |
| TASC "C" lesions                      | n = 62 (41%)          | n = 15 (35%)           | n = 31 (44%)           | n = 16 (41%)           |
| TASC "D" lesions                      | n = 77 (51%)          | n = 21 (48%)           | n = 33 (47%)           | n = 23 (59%)           |
| Wagner grade 1-2.                     | n = 57 (37%)          | n = 18 (42%)           | n = 25 (36%)           | n = 14 (36%)           |
| Wagner grade 3-4.                     | n = 95 (63%)          | n = 25 (58%)           | n = 44 (64%)           | n = 26 (66%)           |
| Ulcers < 10 mm2                        | n = 44 (29%)          | n = 14 (33%)           | n = 20 (29%)           | n = 10 (26%)           |
| Ulcers > 10 mm2                        | n = 108 (71%)         | n = 29 (67%)           | n = 50 (71%)           | n = 29 (74%)           |

Table 2:

| TYPE OF PROCEDURE | (Total limbs = 152) |
|-------------------|---------------------|
| **Group NN = 43 limbs (28%)** |
| Main axis         | SA + EA n = 25 (58%)   | SA alone n = 10 (23%)  | EA alone n = 8 (19%)  |
| Anterior Tibial + Dorsalis Pedis | n = 5              | n = 3                  | n = 2                  |
| Posterior Tibial + Plantar arteries | n = 17            | n = 5                  | n = 3                  |
| Peroneal artery   | n = 3                | n = 2                  | n = 3                  |
| Associate Iliac/ SFA or Popliteal (P1) SA/EA | n = 17           | n = 5                  | n = 4                  |
| Associate Inferopopliteal (P2+P3) or Tibio-Peroneal Trunk | n = 3             | n = 1                  | n = 4                  |
| **Group MN = 70 limbs (46%)** |
| Main axis         | SA + EA n = 43 (61%)   | SA alone n = 12 (17%)  | EA alone n = 15 (22%) |
| Anterior Tibial + Dorsalis Pedis | n = 10              | n = 4                  | n = 3                  |
| Posterior Tibial + Plantar arteries | n = 26            | n = 5                  | n = 7                  |
| Peroneal artery   | n = 7                | n = 6                  | n = 5                  |
| Associate Iliac/ SFA or Popliteal (P1) SA/EA. | n = 23           | n = 10                 | n = 4                  |
| Associate Inferopopliteal (P2+P3) or Tibio-Peroneal Trunk | n = 7             | n = 5                  | n = 1                  |
| **Group SN = 39 limbs (26%)** |
| Main axis         | SA + EA n = 23 (59%)   | SA alone n = 7 (18%)   | EA alone n = 9 (23%)  |
| Anterior Tibial + Dorsalis Pedis | n = 5              | n = 1                  | n = 2                  |
| Posterior Tibial + Plantar arteries | n = 13            | n = 3                  | n = 3                  |
| Peroneal artery   | n = 5                | n = 3                  | n = 4                  |
| Associate Iliac/ SFA or Popliteal (P1) SA/EA. | n = 6             | n = 2                  | n = 2                  |
|Associate Inferopopliteal (P2+P3) or Tibio-Peroneal Trunk | n = 12           | n = 5                  | n = 1                  |

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![Figure 1](image1.png) ![Figure 2](image2.png)
Access was typically achieved by ipsilateral antegrade femoral artery puncture, but also through the contralateral femoral artery in some cases. Retrograde access by popliteal or pedal puncture was not used in this study. The lesions were crossed endo- or extraluminally with hydrophilic 0.014-, 0.018- or 0.035-inch guidewires (Cook, UK or Cordis, USA). Small amounts of contrast agent were progressively injected to confirm the distal endoluminal localization. For the BTK tibial and foot arteries, a 2-3 mm low-profile balloon in a monorail 0.014-inch system (Savy, Cordis, USA) or a stiffer 0.018-inch "over-the-wire" system (ReekKross, Clear Stream Technologies Ltd., Ireland) assisted by a 50 or 70 cm 6F introducer sheath (Cook, UK or Cordis, USA) were specifically used. In 10 cases (7%), a cutting balloon (Boston Inc., USA) was used because of dense calcifications in the calf or ankle vessels. Selective stenting was performed in 39 cases (26%) for iliac, superficial femoral artery or popliteal (P) lesions. Synchronous staged angioplasty without stent placement in the supragenicular arteries was necessary in 34 cases (22%). In 79 specific cases (52%) presenting severe focal infragenicular arterial disease, below-the-knee EA and SA angioplasties confined to the distal popliteal (P+P) and tibial, pedal or plantar trunks were performed (Table 2). At the completion of each procedure, the vascular sheaths were removed and hemostasis was attempted by manual compression. Closure devices were rarely used. All patients were prescribed aspirin (160 mg/day) and clopidogrel (75 mg/day except in case of contraindication) for the first three months after the procedure, followed by aspirin (160 mg/day) indefinitely.

Wound healing approach

A standardized wound healing approach in accordance with the original study protocol was used in all three subgroups of patients, regardless of their enrolment period. The protocol included urgent debridement, expeditious revascularization, adapted wound dressings and eventual negative-pressure wound therapy, depending on the specific clinical indication. Off-loading devices were applied to patients depending on the location of tissue defects, to favor ulcer healing on the plantar, heel and side boundaries of the foot.

Follow-up

The patients were uniformly supervised by periodical clinical and duplex scanning evaluation and regular ABI, neuropathic and TcPO2 assessment. Follow-up was scheduled one month after discharge and every six months thereafter, with a mean duration of 32.3 months (range 1-52).

Definitions

Lower-limb ischemia was clinically graded according to the revised SVS/ISCVS criteria [9] and the TASC recommendations [2,3]. The other "diabetic foot" clinical findings were ranked with the revised Wagner’s classification [11] and the UK peripheral neuropathy screening score (0-2: normal, 3-4: mild, 5-6: moderate and 7-9: severe neuropathy) [10]. Sensory neuropathy was routinely quantified with the Semmes-Weinstein monofilament [10]. Technical success was defined as revascularization, allowing direct arterial flow from the aorta to the pedal arches, with maximal residual arterial stenosis under 25%. Patency was documented by periodic duplex scanning and in all cases by ABI and TcPO2 measurements. Clinical success was defined as a postoperative ABI increase > 0.10, with marked improvements in wound healing (at least two Rutherford categories) [2,3,9], with or without minor amputations (forefoot or toes). Limb salvage was considered successful if there was no major amputation and if the functional autonomy of the patient was recovered (walking or standing).

Statistical analysis

All results were included in an "intention to treat" analysis. The Kaplan-Meier life-table method was used to determine the outcome of
primary and secondary patency, clinical success and limb salvage rates [9]. These parameters were then compared among the NN, MN and SN subgroups using log-rank (Mantel-Cox) and Breslow-Wilcoxon tests. Additionally, specific risk factors were analyzed at one year as categorical variables with the two-sided Fischer’s exact test. A p-value < 0.05 was considered statistically significant. All data were analyzed with the Prism statistics software (Graph Pad, San Diego, CA, USA).

Results

Primary infragenicular angioplasty was successful in 120 of 152 cases (79%). Technical success was achieved in 35 of 43 cases (81%) in the NN subgroup, 56 of 70 cases (80%) in the MN subgroup and 29 of 39 cases (74%) in the SN subgroup.

Of the 32 initially unsuccessful interventions, 25 (78%) were performed with the SA technique and were unsuccessful because of a failure to re-enter the true lumen (n=15) or difficulties in initiating the subintimal dissection plane (n=10). The main SA-related limitations were found in the SN subgroup (41% of cases featured extended calcifications (Table 1). The other cases of technical failures were three cases of unsealed arterial perforations, one case of elastic recoil with collapsed extraluminal channel and early thrombosis and three cases of unsuccessful endoluminal angioplasties, due to the presence of extended annular wall calcifications. For all these initially failed procedures, five surgical recanalizations, 23 adjuvant endovascular interventions and four inevitable major amputations were required, the latter because of extended calf and foot arterial occlusions, with no other possible direct or indirect revascularization strategy, in a context of life-threatening sepsis.

The overall perioperative complication rate was 11.8% (18/152). In eight cases (5.2%), major complications were noted: two limbs with initial acute ischemia requiring prompt surgical revascularization, one early myocardial infarction, two patients with transient renal failure (contrast media-enhanced) and temporary dialysis and three groin hematomas requiring surgical hemostasis. In the other 10 cases (6.5%), minor complications with limited clinical repercussion were reported: five arterial perforations with flow restriction, three distal embolisms resolved by endo-aspiration and two superficial groin hematomas with spontaneous local resolution.

The 30-day survival rate was 99% (one case of myocardial infarction).

The cumulative primary and secondary patency rates (+/-SEM) (Figure 3 and 4) were: 57% (+/-7%) and 72% (+/-7%) for NN, 50% (+/-5%) and 66% (+/-6%) for MN with 38% (+/-8%) and 62% (+/-8%) for SN subgroups at 12 months; 46% (+/-8%) and 62% (+/-8%) for NN, 35% (+/-6%) and 54% (+/-7%) for MN and 27% (+/-7%) and 50% (+/-9%) for SN cohorts at 24 months, correlated to 39% (+/-9%) and 62% (+/-9%) for NN, 32% (+/-6%) and 49% (+/-7%) for MN and 26% (+/-7%) and 45% (+/-9%) for SN contingents at 36 months, respectively. The aggregate limb salvage and primary clinical success (Figures 5 and 6) showed: 90% (+/-5%) and 88% (+/-5%) for NN, 83% (+/-5%) and 77% (+/-6%) for MN and 72% (+/-9%) and 68% (+/-9%) for SN subgroups at 12 months; 85% (+/-7%) and 82% (+/-7%) for NN, 71% (+/-7%) and 68% (+/-7%) for MN, 64% (+/-9%) and 57% (+/-9) for SN contingents at 24 months, added to 85% (+/-7%) and 69% (+/-10) for NN, 66% (+/-8%) and 62% (+/-8%) for MN and 59% (+/-10%) and 46% (+/-10%) for SN populations, at 36 months, respectively.

Following the initial study protocol, the Log-rank (Mantel-Cox) test evaluation showed no statistical correlation between subgroups (with or without neuropathy), neither for primary (p=0.172, CI: 0.924-2.084, HR: 0.70, Chi square=1.85 for NN/MN and p= 0.152, CI: 1.310-2.390, HR: 0.62, Chi square=2.05 for NN/SN), nor for the secondary patency rates (p=0.335, CI: 0.372-1.401, HR: 0.72, Chi square=1.08 for NN/MN and p= 0.176, CI: 0.269-1.272, HR: 0.58, Chi square=1.83 for NN/SN). Using the same approach, there was a significant difference between NN/SN subgroups for limb salvage (p=0.041, CI: 0.135-0.960, HR: 0.36, Chi square=4.16), also for the primary clinical success (p=0.048, CI: 0.185-0.996, HR: 0.42, Chi square=3.87). However, we observed no statistical correlation when comparing the NN/MN tissue recovery results (p=0.411, CI: 0.314-1.403, HR: 0.62, Chi square=1.72), by the same method.

Specific risk factors (Table 1) were also analyzed as categorical variables at one year (average healing time three to 10 months), with the two-sided Fischer’s exact test. End-stage renal disease was a negative predictor in all subjects with or without peripheral neuropathy for primary patency (p=0.0146 and p=0.0163), clinical success (p=0.0001
and $p=0.0001$) and limb preservation ($p<0.0001$ and $p=0.0016$) at one year. Moreover, Wagner’s grade 3-4 and isolated infragenicular atherosclerotic disease also appeared to be negatively associated with limb salvage ($p=0.170$ and $p<0.0001$) and wound healing ($p=0.050$ and $p<0.0001$), but only in neuropathic patients (MN and SN) and at similar time intervals.

The mean increase in $\text{TcPO}_2$ was 24.2 mmHg (range 16-37 mmHg) in the NN subgroup, 21.4 mmHg (range 19-32 mmHg) in the MN subgroup and 17.8 mmHg (range 14-28 mmHg) in the SN subgroup. When comparing these data as categorical variables, a significant difference between the postoperative $\text{TcPO}_2$ values of the NN vs. MN subgroups at one year ($p=0.048$, CI: 1.032-1.444, RR: 1.22) and the NN vs. SN subgroups ($p=0.012$, CI: 1.068-1.733, RR: 1.36 and $p=0.0068$, CI: 1.094-1.946, RR: 1.45) was detected.

A total of 107 wounds (70%) showed complete healing after primary angioplasty. Thirty-two limbs (74%) in the NN subgroup and 75 (68%) in the MN+SN subgroups, including minor amputations, showed good recovery and regained ambulation. However, during the first year of follow-up, unchanged or incomplete ulcer healing was reported in 11 cases of 43 (26%) in the non-neuropathic and 34 cases (32%) in the neuropathic (MN+SN) groups of patients. A total of 48 limbs (31%) developed iterative ulcerations mainly between the fourth and tenth month after surgery. Nine cases (21%) were from the NN subgroup and 39 (36%) from the MN+SN subgroups. Seventeen of 48 limbs presented wound relapses (35%), in whom the initial arterial reconstruction was patent and only adjunctive local ulcer treatment was administered, in addition to strengthened dietetic measures.

Overall, there were 22 (14%) major amputations (four early failures, six short-term disappointing wound evolutions and 12 others throughout the entire follow-up period). The survival rates in this cohort were 91%, 73%, 49% and 41% at 12, 24, 36 and 48 months, respectively (Figure 7).

**Discussion**

Although surgery still plays a critical role in CLI revascularization [2,17], parallel endovascular techniques emerge as comparable alternatives in terms of limb salvage and clinical success. These techniques are feasible in most cases and provide low invasiveness and lower complication rates [5-7,17]. More specifically, for diabetic patients, primary angioplasty has become increasingly suggested as beneficial, providing low aggressiveness and applicability in challenging crural [8,14,15,18] and below-the-ankle atherosclerotic locations [19].

The literature shows that although most diabetic lower-limb ulcers appear neuropathic, there is ischemic involvement in more than 60% of cases [4,11,20]. The recently published “OPIDIA Study” [21] suggests that up to 87% of diabetic-infected foot wounds have a neuropathic background (among 291 patients) and 62% also have chronic ischemic presentation [21].

Among the multiple facets of “diabetic foot syndrome,” peripheral neuropathic affection currently encompasses distal symmetric sensorimotor neuropathy and synchronous autonomic peripheral denervation [20-22]. The former has been considered as the main initiating factor for foot ulceration [1,4,11,20-22]. It seems to affect approximately 30% of all diabetic people at any time and more than 50% of those having diabetes for more than 10 years [22]. Unlike sensorimotor components, autonomic peripheral neuropathy requires a more subtle clinical detection and stratification [4,21,22]. Neuropathy and chronic ischemia are increasingly described as entangled entities.
within the complex etiology of diabetic foot wounds [21-23]. They seem to present similar etiologic interactions within the wider group of functional diabetic microangiopathies [21-23]. The synchronous clinical presentation varying from subtle forms to more dominant pathologies [22-23] are defining the so-called “neuroischemic diabetic foot syndrome” [4,20].

The present study examined the potential efficacy of primary endovascular treatment for neuroischemic limbs. According to the initial protocol, despite non-significant \( p=0.172 \) primary assisted and secondary patency rates revealed in the NN (57% and 72% at 12 months) vs. MN (50% and 66% at 12 months) or SN subgroups (38% and 62% at 12 months), we observed a significant correlation between limb salvage and clinical success \( (p=0.048 \text{ and } p=0.041) \) in the NN (90% and 88% at 12 months, 85% and 69% at 36 months) vs. the MN (83% and 77% at 12 months, 66% and 62% at 36 months) and SN subgroups (72% and 68% at 12 months, 59% and 46% at 36 months). These data suggest a probable better tissue recovery in non-neuropathic diabetic CLI patients after successful hypoxic relief, even though the surveillance from the diabetic team was similar in all patients.

We also detected a significant difference between postoperative \( \text{TCPO}_2 \) values in NN vs. MN \( (p=0.048, \text{ CI: 1.032}-1.444, \text{ RR: 1.22}) \) and NN vs. SN patients \( (p=0.012, \text{ CI: 1.068}-1.733, \text{ RR: 1.36}) \) at one year. These results might reflect a better cutaneous irrigation after large tibial trunk angioplasty in the NN vs. MN and SN cohorts. However, this hypothesis should be considered with caution because of the dissimilar neuropathic affection of capillary microcirculation [15,16,23] and “patchy” \( \text{O}_2 \) redistribution to the skin [15,16,23].

Several variables were analyzed as risk factors for patency, ulcer healing and limb salvage. End-stage renal disease was negatively associated in all subgroups with or without distal sensorimotor neuropathy with primary patency \( (p=0.0146 \text{ and } p=0.0163) \), clinical success \( (p=0.0001 \text{ and } p=0.0001) \) and limb preservation \( (p<0.0001 \text{ and } p=0.0016) \) at one year. The extent of tissue defects (Wagner’s grade 3-4) was negatively associated with limb salvage \( (p=0.170) \) and wound recovery \( (p=0.050) \), but only in the neuropathic MN and SN subgroups. These results are in accordance with previous observations in the same field of research [4,11,15,18,20,23].

We also analyzed eventual concurrent risk factors that could affect technical success (81% in the NN, 80% in the MN and 74% in the SN subgroups) and primary patency after the initial angioplasty approach (Figure 3). Although the results were not statistically significant considering cumulative patency \( (p>0.05) \), we detected an increase in technical failures and precocious postoperative thrombosis in the SN subgroup (NN=19%, MN=20% and SN=26%). This was mainly attributed to the extensive (>3 cm) and bulky arterial wall calcifications (NN=35%, MN=37% and SN=41%) (Table 1), requiring more fastidious endovascular manipulations.

Following the same initial protocol, a significant difference in tissue healing and limb salvage was detected at one year between purely ischemic (NN) and neuroischemic (MN+SN) limb wounds \( (p<0.0001, \text{ CI: 0.321}-0.704, \text{ RR: 0.47 \text{ and } p<0.0001, \text{ CI: 1.942}-1.304, \text{ RR: 0.49})} \). As mentioned before, these cases were also frequently associated with extended and highly calcified TASC D lesions [3] (NN=48%, MN=47% and SN=59%) (Table 1). Although not assessing specific etiologic associations, some authors proposed a possible association between the severity of neuropathy and the extent of tibial calcifications in “diabetic foot syndrome” [20,22].

**Limitations**

Two limitations of this study are the small number of cases and its retrospective aspect. Moreover, the technical performance of the vascular interventionists and other professionals of the diabetic team have undoubtedly changed over the observation period, together with technical and technological advances in the field. Further data from prospective and larger multicenter studies are necessary to confirm these results and draw pertinent conclusions on the effects of diabetic neuropathy on limb salvage and revascularization.

**Conclusion**

Cumulative patency following first-line angioplasty in diabetic ischemic limbs seems to be unaffected by concomitant peripheral neuropathy. However, despite appropriate revascularization, severe diabetic neuropathy may impede correct postoperative wound healing and related limb salvage rates.

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