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## Predictive Values of Transcutaneous Oxygen Tension for Above-the-ankle Amputation in Diabetic Patients with Critical Limb Ischemia

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**Objective.** To assess the values of transcutaneous oxygen tension (TcPO<sub>2</sub>) capable of predicting above-the-ankle amputation in diabetic patients diagnosed for critical limb ischemia (CLI) according to the criteria of the TransAtlantic Inter-Society Consensus.

**Design.** Retrospective study.

**Methods.** From January 1999 to December 2003, 564 diabetic patients were consecutively hospitalized for CLI in one limb. Revascularization with angioplasty or bypass graft was performed when possible and, if not possible, prostanoid therapy was used. In patients in whom therapies did not relieve the rest pain or the gangrene was extended above the Chopart joint, an above-the-ankle-amputation was performed. After treatment TcPO<sub>2</sub> values were evaluated in all patients at the dorsum of the foot.

**Results.** Fifty-five (9.8%) patients underwent an above-the-ankle amputation: 22 of 420 patients who underwent angioplasty, 17 of 117 patients who underwent bypass (14.5%) and 16 of 27 patients in whom revascularization was not possible. Post-treatment TcPO<sub>2</sub>, measured by a receiver operating characteristic (ROC) curve, showed a value 34 mmHg as the best threshold for determining the need for revascularization, with an area under the curve of 0.89 (95%CI 0.85–0.94).

Using logistic regression analysis the probability of above-the-ankle amputation for this threshold is 9.7% and reduces to 3% for TcPO<sub>2</sub> > 40 mmHg.

**Conclusion.** TcPO<sub>2</sub> levels < 34 mmHg indicate the need for revascularization, while for values ≥ 34 < 40 mmHg this need appears less pressing, although there remains a considerable probability of amputation. TcPO<sub>2</sub> levels greater than 40 mmHg suggest that revascularization is dependent on the severity of tissue loss and possible morbidity caused by the procedure.

**Keywords:** Diabetic foot; Peripheral arterial occlusive disease; Critical limb ischemia; TransAtlantic Inter-Society Consensus parameters; Transcutaneous oxygen tension; Major amputation; Revascularization.

In June 2000, the TransAtlantic Inter-Society Consensus (TASC) defined the Critical Limb Ischemia (CLI) as the presence of chronic ischemic rest pain, ulcer or gangrene in the foot attributable to objectively proven peripheral arterial occlusive disease (PAOD).<sup>1</sup> For objective criteria for diagnosis of rest pain, ulcer or gangrene caused by the arterial occlusive disease the use of either ankle pressure <50–70 mmHg or toe pressure <30–50 mmHg, or transcutaneous oxygen tension (TcPO<sub>2</sub>) <30–50 mmHg has been suggested. In June 2007 a new version of TASC was edited.<sup>2</sup> In this edition the ankle and toe pressure thresholds

were confirmed while for TcPO<sub>2</sub> only a single value of 30 mmHg was proposed.

Ankle and toe pressure measurements are assessable readily in non-diabetic patients, and therefore they are regarded as optimal criteria for screening this population group.<sup>3</sup> In contrast, these measurements are not easily assessable in diabetic patients with critical limb ischemia and/or foot ulcer, where tibial arteries are often poorly compressible due to the presence of medial arterial calcifications (MAC) and both tibial arteries may be occluded: as a consequence of these anatomical abnormalities, the ankle pressure assessment becomes impracticable.<sup>4,5</sup> Moreover, ulcer or toe gangrene may frequently occur in diabetic patients, thus preventing toe pressure measurement. In our experience, ankle and toe systolic pressure investigations cannot be evaluated in

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almost 50% of diabetic patients with CLI and foot ulcer, similar to the rate reported by Gibbons *et al.*<sup>6</sup>

Unlike ankle or toe pressure, transcutaneous oximetry at the dorsum of the foot is easily assessable in all diabetic subjects and therefore it can be regarded as an useful parameter for diagnosis in the diabetic population.<sup>7,8</sup>

The aim of this study is to investigate the diagnostic efficacy of transcutaneous oxygen tension values in predicting above-the-ankle amputation in a cohort of diabetic patients consecutively hospitalized for rest pain and/or foot ulcer and diagnosed for CLI according to the TASC 2000 oxymetric criteria.

### Patients and Methods

All diabetic patients referred to our Diabetic Foot Center for foot lesions or rest pain were assessed for the presence of sensory-motor neuropathy, infection and peripheral arterial occlusive disease. Sensory-motor neuropathy was detected by means of vibration perception threshold  $>25$  V at biothesiometer, insensitivity in  $>5/9$  foot points at Semmes–Weinstein 10 g filament, and absence of Achille's tendon reflex. In patients with foot ulcer local cellulitis, erythema or purulence with positive swab culture was considered as being the indicators of the presence of an infection.

Peripheral arterial disease was diagnosed if one foot pulse was reduced or absent, ankle-pressure was  $<70$  mmHg when assessable (e.g. if foot arteries were not absent or poorly compressible due to medial calcifications), transcutaneous oxygen tension (TcPO<sub>2</sub>) at the dorsum of the foot was  $<50$  mmHg and obstructions were identified at duplex scanning.

In all patients presenting with absent or reduced pulses in at least one foot pulse, TcPO<sub>2</sub>  $<50$  mmHg, ankle-pressure  $<70$  mmHg and obstructions at duplex scanning, arteriography was performed and, when practicable, a percutaneous transluminal angioplasty (PTA) was performed concomitantly. In patients in whom PTA was attempted unsuccessfully, a by-pass graft (BPG) was considered. Patients in whom revascularization was not possible therapy with prostanoids or lumbar sympathectomy plus prostanoids was given when possible.

Above-the-ankle-amputation was considered and performed, with patient consent, if therapies did not relieve patients from rest pain or gangrene was extending beyond the Chopart joint. Limb salvage was considered successful if the plantar standing was maintained, even when achieved by tarsal-metatarsal amputation.<sup>9,10</sup> Conversely, any above-the-ankle amputation was deemed a failure. Only one limb was

considered: possible contralateral limb problems were not considered in this study.

*TcPO<sub>2</sub> measurement.* In all patients TcPO<sub>2</sub> measurements in the ischaemic limb were taken at hospital admission and then reassessed 5 days after PTA, BPG, medical therapy or sympathectomy. In patients who suffered an above-the-ankle amputation, the TcPO<sub>2</sub> level measured before the amputation procedure was the value considered for analysis.

All TcPO<sub>2</sub> measurements were taken at the dorsum of the foot in the peri-lesional site with the patient resting in supine position, in air-conditioned room maintained at 22 °C; the instrument used was a TCM<sup>TM3</sup> (Radiometer GMBH, Copenhagen, Denmark) equipped with a Clark electrode. The measuring site was cleaned carefully using saline solution. The transducer was fixed to the skin with double-sided adhesive rings and contact liquid supplied by the manufacturer. The calibration period was 10 min and the TcPO<sub>2</sub> signal was continuously recorded on paper for 30 minutes.

*Statistical methods.* Data are given as mean  $\pm$  standard deviation for continuous data, or as percentages for discrete variables. Major amputation was defined as an above-the-ankle amputation. The capability to predict the outcome of limb salvage and major amputation was assessed by the area under the Receiver Operating Characteristic (ROC) curve. The best cut-point was located via the Youden index.<sup>11</sup> The probability of above-the-ankle amputation on the basis of the TcPO<sub>2</sub> levels measured at the dorsum of the foot was evaluated with a logistic model. The validation of the indicator variables of high-risk of amputation was performed by resorting to the split sample technique. By using random numbers supplied by the statistical program, the cohort of patients was split into training and testing samples of equal size. On the training sample we tested a logistic regression model for amputation rate. In both training and testing samples the ability of the model in matching estimated amputation rate and observed amputation rate was evaluated by the Hosmer-Lemeshow goodness-of-fit statistics.<sup>12</sup>

Statistical analysis was performed using Stata 9.0 SE statistical package (Statistics/Data Analysis, Stata Corporation, 4905 Lakeway Drive, College Station, Texas 77845 USA, 800-STATA-PC).

### Results

From January 1, 1999 to December 31, 2003, a total of 564 consecutive diabetic patients with rest pain and/or foot ulcer, and with a pedal TcPO<sub>2</sub> value lower than

50 mmHg, were hospitalized at our Foot Center. Demographic and clinical characteristics of this study population are reported in Table 1. Fig. 1 reports the TcPO<sub>2</sub> values distribution by 10 mmHg classes at the entry in the study.

In all these subjects arteriography revealed the presence of a stenosis narrowing >50% of the vessel lumen in at least one artery of the ischemic limb. The obstructions were located exclusively in the iliac-femoral-popliteal arteries in 28 patients (5.0%), exclusively in the infrapopliteal arteries in 137 subjects (24.3%), in both iliac-femoral-popliteal and infrapopliteal arteries in 399 patients (70.7%).

A revascularization procedure was performed in 537 (95.2%) patients. Peripheral transluminal angioplasty (PTA) was carried out in 420 (74.5%) patients. Concomitant femoral-popliteal and crural PTA was performed in 151 patients: of these in 116 with angioplasty of one crural artery, more than one in 35 patients. Surgical bypass was performed in 117 (20.7%) patients. The bypass was axillo-femoral in one patient, femoral-popliteal (16 PTFE, 45 vein graft) in 61 patients, femoral-infrapopliteal (17 PTFE, 40 vein graft) in 57 patients. In 27 (4.8%) patients neither a PTA nor a bypass was possible due to high surgical risk or lack of outflow. In all these patients treatment with prostanoids and percutaneous chemical sympathectomy, under CT (computer tomography) scan guidance was performed, when possible.

During the study a major amputation was performed in 55 (9.8%) patients. Twenty-two amputations were performed in PTA patients, in 19 for gangrene extended above the Chopart joint, in 1 for acute distal thrombosis after PTA in a patient not suitable for further endoluminal or surgical revascularization, in 2 for gangrene of the heel. Seventeen

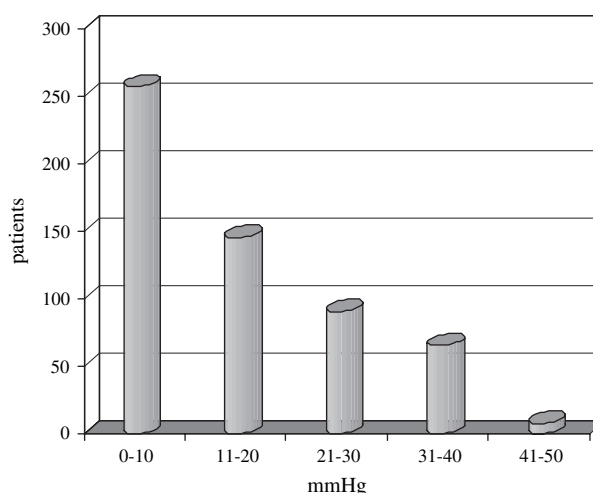


Fig. 1. TcPO<sub>2</sub> values distribution by 10 mmHg classes in study population at the study entry (N = 564).

amputations were performed in bypass patients following graft occlusion. Sixteen amputations were performed in non-revascularized patients for rest pain and extensive gangrene. These 55 subjects are referred as amputation patients. Fig. 2 describes the intervention, amputation, loss to follow-up and death of study population.

Table 1. Demographic and clinical characteristics of study population (N = 564)

Variable	
Age (years)	70.0 ± 9.6
Females/males (n)	198 (35.1%)/366 (64.9%)
Insulin/oral therapy (n)	342 (60.6%)/222 (39.4%)
Diabetes duration (years)	17.0 ± 11.1
Sensory motor neuropathy (n)	465 (82.4%)
Retinopathy (n)	212 (37.6%)
Albumin excretion (mg/l) (n = 532)	259.8 ± 529.7
Creatinine (mg/dl) (n = 532)	1.28 ± 0.56
Wagner grade (n)	
0	88 (15.6%)
1	83 (14.7%)
2	78 (13.8%)
3	55 (9.8%)
4	260 (46.1%)
Infected ulcer (n)	362 (64.2%)
TcPO <sub>2</sub> at admission (mmHg)	14.1 ± 11.8

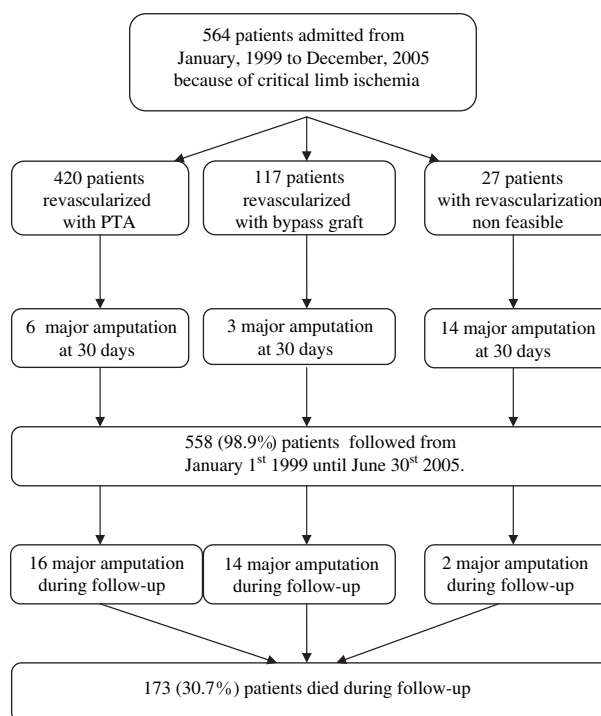


Fig. 2. Flow-chart of intervention, major amputation outcome and death in study population.

All non-amputated patients achieved pain relief with discontinuation of analgic therapy and regained autonomic walking capability with the help of with extra-deep rocker shoes provided with soft thermoformable leather and customized insoles.

The TcPO<sub>2</sub> values by classes of 10 mmHg after the therapy in cases of limb salvage or amputation are given in Fig. 3. The discriminatory ability of TcPO<sub>2</sub> values in patient selection for major amputation, measured by a receiver operating characteristic (ROC) curve, indicated a value of 34 mmHg as best threshold, on the basis of a Youden index of 160.6, sensitivity 78.6, specificity 83.0. The area under the curve was 0.89 (95%CI 0.85–0.94). Fig. 4 shows the ROC curve for TcPO<sub>2</sub>.

The results of the logistic regression analysis performed for the association of outcome in above-the-ankle amputation and TcPO<sub>2</sub> values showed an odds ratio of 0.90 (95%CI 0.87–0.93) for increase of 1 mmHg of TcPO<sub>2</sub>, *p* < 0.001. The results by classes of 10 mmHg are reported in Table 2. For TcPO<sub>2</sub> = 34 mmHg, which was the best threshold on the ROC curve, the logistic analysis indicated a 9.7% (95%CI 7.0–13.2) probability of above-the-ankle amputation. Fig. 5 shows the performance of the logistic model. The goodness-of-fit of this model was assessed by the Hosmer-Lemeshow test: the  $\chi^2$  was 10.36 with 8 degrees of freedom and *p* = 0.24 for the testing group, and  $\chi^2$  = 8.20 with 8 degrees of freedom and *p* = 0.41 for the training group.

**Discussion**

It is unquestioned that, in patients with CLI, the revascularization procedure is of paramount importance for achieving successful pain relief and healing of foot lesions.<sup>13,14</sup> The critical issues appear to be the parameters that are used to evaluate the CLI.

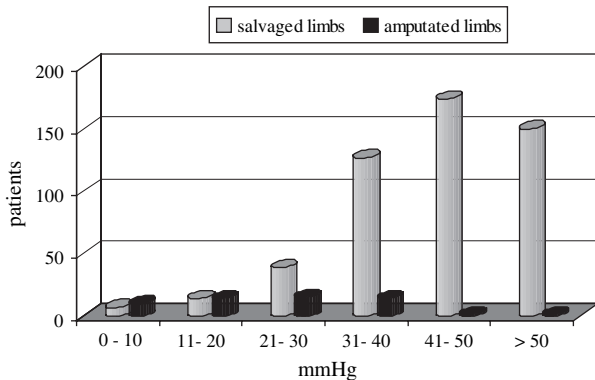


Fig. 3. TcPO<sub>2</sub> values by classes of 10 mmHg after therapy in salvaged or amputated limb.

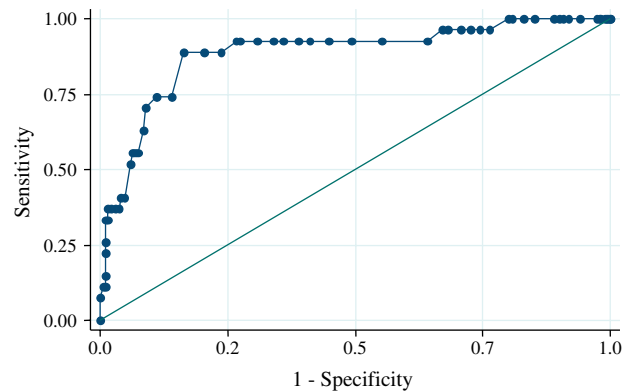


Fig. 4. ROC curve of TcPO<sub>2</sub> after therapy in study population (N = 564).

These parameters should identify patients who would with high probability of needing amputation in the absence of other adequate therapies. This becomes even more complicated in the diabetic population. Both morphological and clinical characteristics of diabetic patients with peripheral arterial occlusive disease deeply differ from those of non diabetic subjects.<sup>15</sup> The development of ischaemic pain often is attenuated or suppressed by a concomitant sensory neuropathy and therefore the reduced sensation of pain may underestimate the degree of the arterial occlusive disease. Medial arterial calcification and absence of the foot pulses, due to the occlusion of both tibial arteries, frequently occur in diabetic patients and prevent ankle or toe pressure measurements.<sup>16</sup> Moreover the toe pressure measurement was often prevented by presence of a lesion. For all these reasons, in our clinical practice we prefer to rely on the oxymetric parameters, which are easily detectable in all subjects.

By proposing the 30–50 mmHg interval, the TASC 2000 has indicated that a TcPO<sub>2</sub> value <30 mmHg might predict that healing will not occur. However, a range of 30–50 mmHg was also indicated as being useful in relation to the risk/benefit ratio of any procedure.

Table 2. Prediction probability of above-the-ankle amputation evaluated by logistic regression analysis of TcPO<sub>2</sub> values after the therapy

TcPO <sub>2</sub> values (mmHg)	Prediction probability of above-the-ankle amputation	Confidence interval
<10	68.0%	52.7–80.0
≥10 <20	44.0%	33.1–55.4
≥20 <30	22.5%	17.2–28.8
≥30 <40	6.1%	4.1–8.9
≥40 <50	2.6%	1.6–4.4
≥50 <60	0.8%	0.4–1.9

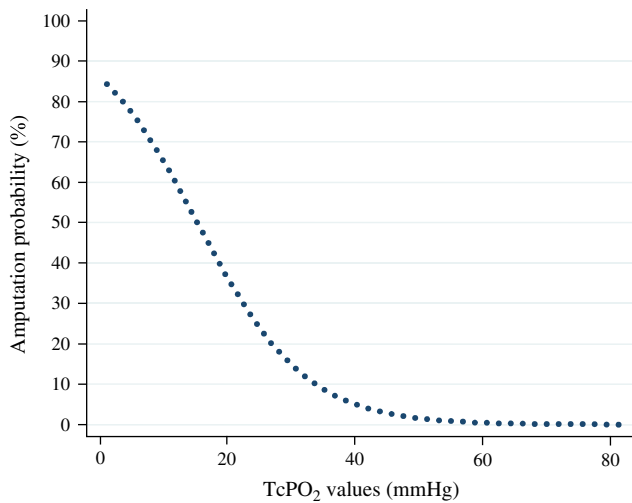


Fig. 5. Probability of above-the-ankle amputation according to TcPO<sub>2</sub> values after therapy.

In TASC 2007, the definition of Critical Limb Ischemia (Recommendation 16) no longer included instrumental parameters. TASC 2007 cited the TcPO<sub>2</sub> in D5.2 paragraph (Investigations) with just one value: “critical level <30 mmHg”. As a consequence 70 (12.4%) patients of our series, who were presenting with TcPO<sub>2</sub> values >30 < 50 mmHg and underwent revascularization (without complications, fortunately) on the basis of the TASC 2000 criteria, would have been exposed to a pointless risk on the basis of TASC 2007 criteria.

The parameters obtained in our study from the logistic analysis appear to be more articulate.

The ROC curve has indicated the TcPO<sub>2</sub> value of 34 mmHg as the best threshold. This value is somewhat higher than the value of 30 mmHg pointed out in TASC 2007. However, on logistic regression analysis this threshold was associated with a probability of amputation which was close to 10% and, in our opinion, accounts for the risk of a revascularization procedure. According to the logistic regression analysis, only for TcPO<sub>2</sub> values equal or higher than 40 mmHg did the probability of amputation fall below 3%. Therefore, for TcPO<sub>2</sub> > 40 mmHg the probability of amputation is low enough to make an attempt at revascularization non-mandatory: for a superficial, painless ulcer intervention can be avoided, while infected gangrene requiring surgical intervention may guide the clinician towards a revascularization strategy in order to ensure the best healing results of the surgical wound.<sup>17,18</sup> In such cases, a careful assessment of comorbidity, ulcer, and risk caused by the revascularization procedure can help in selection of the therapeutic choice.

In our analysis we considered the above-the-ankle amputation as a major amputation and the amputation at Chopart point as limb salvage with minor amputation. In the section “End Points/Outcome Reporting”, the TASC 2000 defines a major amputation as an “above the mid-forefoot amputation”. In the TASC 2007 in the D7.4 (Management of ulcers) paragraph only an above-the-ankle amputation was considered a major amputation. We agree with this new definition: we believe that patients who underwent a Chopart joint amputation and are able to ambulate for their daily needs (such as using the bathroom at night) without the need of crutches, prosthesis, or wheelchair, should be regarded as subjects in whom the walking capability is still maintained by a bipodalic support, even if the plantar standing is partially lost.

**Conclusions.** On the basis of our data TcPO<sub>2</sub> < 34 mmHg indicates an unquestionable need for revascularization, while for values ≥ 34 < 40 mmHg this need appears less pressing, although there remains a considerable probability of amputation. TcPO<sub>2</sub> levels greater than 40 mmHg suggest that the revascularization is optional, depending on severity of ulcer and possible morbidity caused by the procedure. Only for values >50 mmHg the amputation probability is lower than 1% and revascularization is not necessary.

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