Pilot Cohort Study Assessing the Efficacy of Endovascular Revascularization in the Restoration of Peripheral Sensory Disturbance in Patients With Critical Limb Ischemia

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Background: Sensory disturbance (SD) is a common consequence of peripheral nerve damage associated with diabetes and severe ischemia. Progression of SD places patients at high risk for lower extremity ulcers and amputations. SD has been thought to be progressive and irreversible, and possibly caused by microvascular dysfunction. The aim of this study was to determine whether endovascular revascularization (EVR) induces quantifiable changes in SD in chronic critical limb ischemia (CLI) patients with neuropathy.

Methods and Results: In all, 36 legs from 28 chronic CLI patients who underwent elective EVR were prospectively enrolled in this study (64% with diabetes and 54% on maintenance hemodialysis). The current perception threshold (CPT), an established diagnostic parameter for SD, was measured before and 3 months after EVR. Of the target lesions, 11%, 47%, and 81% were in the aortoiliac, femoropopliteal, and below-the-knee arteries, respectively, and 58% were totally occluded. Overall CPT in the target foot had improved significantly 3 months after EVR (from 53 to 30 µA; P=0.010); however, EVR did not change CPT in the non-target foot (from 44 to 33 µA; P=0.33). Patients with improved SD after EVR had a significantly higher 180-day survival rate (94% vs. 63%; P=0.040).

Conclusions: EVR improved CPT in target limbs of patients with CLI, and may be a promising option to improve SD associated with peripheral ischemic sensory neuropathy.

Key Words: Critical limb ischemia; Endovascular therapy; Neuropathy

Sensory disturbance (SD) is a common consequence of the nerve damage associated with diabetes mellitus (DM) and acute ischemia in patients with critical limb ischemia (CLI). Progression of SD with diminished sensation to touch, vibration, and temperature puts patients at high risk of lower extremity ulcers, amputations, and falls. SD has been thought to be progressive, irreversible, and possibly caused by microvascular dysfunction.

DM and severe ischemia chronically damage peripheral sensory nerves. The nerve damage initially appears as numbness, and may lead to skin ulceration and subsequently to gangrene. Most lower limb amputations are preceded by non-healing foot ulcers. Foot ulceration already reflects an advanced stage of CLI, and delayed intervention under the current clinical settings results in a very low rescue rate of ischemic legs. Foot ulcers begin with loss of protective sensation. Therefore, it is important to detect peripheral neuropathy at an early stage in the natural history of the disease to prevent the devastating complications associated with SD. SD in DM neuropathy has been investigated in depth, with numerous reports about its diagnosis and treatment. However, little is known about SD in patients with atherosclerotic limb ischemia.

Current perception threshold (CPT) is an established diagnostic indicator for SD in DM patients that can detect both clinical and subclinical large and small fiber neuropathy. A higher CPT indicates greater damage to peripheral sensory nerves. Using this simple, non-invasive test we can determine whether a patient has SD. However, to date this parameter has only been used for DM neuropathy. To the
best of our knowledge, no studies have evaluated the effect of endovascular revascularization (EVR) on SD using measures of CPT. Therefore, the aim of the present study was to determine whether EVR improves peripheral SD in patients with chronic CLI.

Methods

Study Population
In all, 36 legs from 28 chronic CLI patients who underwent elective EVR in a single cardiovascular center between September 2012 and April 2014 were prospectively enrolled in the study. The ankle-brachial index (ABI) and CPT were measured just before and then again 3 months after EVR and analyzed retrospectively. The study protocol was approved by the Ethics Committee of NishiHarai Heart Center Hospital. All participants provided written informed consent. Patients were enrolled according to the principles of the Declaration of Helsinki.

Treatment Protocols and Definitions
EVR was scheduled for patients who were clinically diagnosed with CLI and had proven angiographic stenosis or occlusion in a peripheral artery. All procedures were performed by a single operator. EVR that achieved at least ‘1 straight line’ to vascular beds below the ankle was defined as successful. In performing the EVR procedure, we primarily used a 6-Fr guiding sheath for target lesions from the aortoiliac to popliteal arteries, and a 4.5-Fr guiding sheath for isolated below-the-knee (BTK) lesions. Provisional stenting was performed for aortoiliac to popliteal lesions when major arterial dissections or flow limitations appeared after balloon angioplasty, and balloon angioplasty alone was used for BTK lesions. To prevent contrast-induced nephropathy, all patients with chronic kidney disease (CKD), except those with maintenance hemodialysis (HD), were given 1.0 mL/kg per h saline from at least 12 h before contrast administration. EVR sessions were separated by intervals of more than 3 months to treat the contralateral foot in the same patient.

For at least 3 months after EVR, all patients received 100 mg aspirin daily and/or 75 mg clopidogrel daily. Patients with a newly implanted stent received both aspirin and clopidogrel. The duration of antplatelet agent administration and other medical treatment regimens was at the discretion of the attending physician. Wound care and the decision for amputation were performed by independent plastic surgeons at regular clinic visits. CLI was defined as chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease. DM was defined as a fasting plasma blood glucose level ≥126 mg/dL on 2 separate occasions, or plasma blood glucose ≥200 mg/dL at any time, or receiving antihyperglycemic agents, including insulin.

The target limb was defined as the limb in which EVR was attempted in a given session. The non-target limb was the contralateral limb to the target limb. CPT values for the target limb were compared with those for the same region of the contralateral limb.

Endpoints
The primary endpoint was change in CPT from before to 3 months after EVR. Secondary endpoints were 180-day all-cause mortality and major adverse limb event (MALE) rates. MALE was defined as major amputation or any reintervention, including both surgical or EVR. Major amputation was defined as amputation above the ankle of the target limb.

Data Collection
CPT was recorded quantitatively before and 3 months after EVR using the painless PainVision PS-2100 electrical stimulation system (Nipro, Osaka, Japan). A disposable test pad was attached at the dorsum or ankle of the patient’s foot. Over a 5- to 10-min period of non-invasive examination, peripheral sensory nerve fibers were stimulated by 3 different frequencies (2,000, 250, and 5 Hz). Patients pressed a button if they felt electrical stimulation. The CPT value depends on a patient’s age, sex, and diabetic status, and can be in the range 0–256 µA (Figure S1).

In the present study, the dorsum and ankle of both sides of the feet were tested twice each, and the mean CPT value was calculated and used in subsequent analyses. If the CPT value exceeded 256 µA (over the CPT limit), it was recorded as 256 µA.

ABI and pulse wave velocity (PWV) were tested before and then 1 day and 3 months after EVR. Laboratory data (hemoglobin, C-reactive protein, lipid profiles, HbA1c, and eicosapentaenoic and arachidonic acids [EPA and AA, respectively]) and echocardiographic parameters (left ventricular ejection fraction and flow-mediated dilation) were evaluated before EVR. The Rutherford classification was recorded in the target limb at the time of EVR.

Statistical Analysis
In the text, values are expressed as the median [interquartile range] or as percentiles. Continuous parameters were compared between 2 groups using the independent Student’s t-test or the non-parametric equivalent Mann-Whitney U-test. Fischer’s exact test was used to evaluate categorical variables. Chi-squared tests were used to compare Rutherford classification and the severity of CPT between the DM and Non-DM groups. Comparisons among 3 sets of consecutive samples from 2 groups were evaluated by 2-way analysis of variance (ANOVA) with a Sidak post hoc test, whereas a multiple t-test with the Holm-Sidak method was used for 2 sets of samples from 2 groups. The Wilcoxon matched-pairs signed-rank test was used for comparisons of consecutive samples with baseline. Linear regression analysis was used to determine correlation coefficients between CPT and ABI at baseline, CPT and PWV at baseline, and baseline CPT and changes in CPT. Two-sided P<0.05 was considered significant. All-cause survival and MALE-free rates were evaluated using Kaplan-Meier curves, and differences between the groups were assessed with the log-rank test.

Results
Baseline Profiles
Baseline patient characteristics are given in Table 1. Patients were typically middle-aged (mean age 68 years) with a normal body mass index (22 kg/m²), and 71% were male. Among the cohort, 64% had DM and 54% were receiving maintenance HD. The DM patient group (n=18) included a significantly higher number of current smokers and those on maintenance HD, and had significantly lower total cholesterol levels than the Non-DM patient group (n=10). Of all patients, 14% were classified as Rutherford Stage VI, and the severity of clinical presentation was not significantly different between the DM and Non-DM groups.
Peripheral Sensory Recovery in CLI Patients

Technical success of EVR was achieved in 34 limbs (94.4%). No procedure-related adverse events, such as blue toe syndrome, pseudo-aneurysm, severe bleeding, and acute

### Table 1. Characteristics of Patients With or Without DM

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall (n=28)</th>
<th>DM (n=18)</th>
<th>Non-DM (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68±13</td>
<td>66±12</td>
<td>72±13</td>
<td>0.29</td>
</tr>
<tr>
<td>No. &gt;75 years old</td>
<td>9 (32)</td>
<td>5 (28)</td>
<td>4 (40)</td>
<td>0.51</td>
</tr>
<tr>
<td>No. males</td>
<td>20 (71)</td>
<td>14 (78)</td>
<td>6 (60)</td>
<td>0.32</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.1±3.4</td>
<td>22.3±3.5</td>
<td>21.7±3.2</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Obese**</td>
<td>4 (14)</td>
<td>3 (17)</td>
<td>1 (10)</td>
<td>0.63</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (64)</td>
<td>12 (67)</td>
<td>6 (60)</td>
<td>0.72</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18 (64)</td>
<td>18 (100)</td>
<td>0 (0)</td>
<td>–</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>20 (71)</td>
<td>12 (67)</td>
<td>8 (80)</td>
<td>0.45</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>5 (18)</td>
<td>3 (17)</td>
<td>2 (20)</td>
<td>0.83</td>
</tr>
<tr>
<td>Current smoker</td>
<td>6 (21)</td>
<td>1 (6)</td>
<td>5 (50)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>16 (57)</td>
<td>12 (67)</td>
<td>4 (40)</td>
<td>0.17</td>
</tr>
<tr>
<td>Prior MI</td>
<td>2 (7)</td>
<td>1 (6)</td>
<td>1 (10)</td>
<td>0.66</td>
</tr>
<tr>
<td>Prior PCI/CABG</td>
<td>9 (32)</td>
<td>6 (33)</td>
<td>3 (30)</td>
<td>0.86</td>
</tr>
<tr>
<td>CKD†</td>
<td>20 (71)</td>
<td>15 (83)</td>
<td>5 (50)</td>
<td>0.06</td>
</tr>
<tr>
<td>Maintenance hemodialysis</td>
<td>15 (54)</td>
<td>13 (72)</td>
<td>2 (20)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6 (21)</td>
<td>3 (17)</td>
<td>3 (30)</td>
<td>0.41</td>
</tr>
<tr>
<td>Rutherford classification (4/5/6)</td>
<td>12/12/4</td>
<td>8/8/2</td>
<td>4/4/2</td>
<td>0.81</td>
</tr>
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</table>

Laboratory data

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall (n=28)</th>
<th>DM (n=18)</th>
<th>Non-DM (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.5±2.7</td>
<td>11.6±2.0</td>
<td>13.8±3.1</td>
<td>0.13</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>0.64±0.63</td>
<td>0.66±0.72</td>
<td>0.61±0.52</td>
<td>0.91</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>170±42</td>
<td>157±43</td>
<td>194±27</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>96±38</td>
<td>88±39</td>
<td>110±33</td>
<td>0.11</td>
</tr>
<tr>
<td>LDL-C/HDL-C ratio</td>
<td>2.0±1.0</td>
<td>2.0±0.9</td>
<td>2.1±1.1</td>
<td>0.86</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.1±0.7</td>
<td>6.3±0.8</td>
<td>5.7±0.3</td>
<td>0.013</td>
</tr>
<tr>
<td>EPA (µg/mL)</td>
<td>81±89</td>
<td>67±42</td>
<td>104±135</td>
<td>0.77</td>
</tr>
<tr>
<td>EPA/AA ratio</td>
<td>0.54±0.82</td>
<td>0.41±0.32</td>
<td>0.74±1.3</td>
<td>0.69</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>56±11</td>
<td>58±12</td>
<td>54±10</td>
<td>0.42</td>
</tr>
<tr>
<td>FMD (%)</td>
<td>2.5±1.7</td>
<td>2.4±1.5</td>
<td>2.6±2.2</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Data are given as the mean±SD or as n (%). **Obesity was defined as a body mass index (BMI) >25 kg/m². †Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate <60 mL/min/1.73 m². AA, arachidonic acid; CABG, coronary artery bypass grafting; CRP, C-reactive protein; DM, diabetes mellitus; EPA, eicosapentaenoic acid; FMD, flow mediated dilation; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

### Table 2. Oral Medications at Discharge in Patients With or Without DM

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall (n=28)</th>
<th>DM (n=18)</th>
<th>Non-DM (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>2 (7)</td>
<td>1 (6)</td>
<td>1 (10)</td>
<td>0.66</td>
</tr>
<tr>
<td>Aspirin</td>
<td>24 (86)</td>
<td>17 (94)</td>
<td>7 (70)</td>
<td>0.08</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>19 (68)</td>
<td>11 (61)</td>
<td>8 (80)</td>
<td>0.31</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>21 (75)</td>
<td>13 (72)</td>
<td>8 (80)</td>
<td>0.65</td>
</tr>
<tr>
<td>Numbers of antiplatelet agents</td>
<td>2.4±0.9</td>
<td>2.3±0.8</td>
<td>2.4±1.1</td>
<td>0.60</td>
</tr>
<tr>
<td>Statin</td>
<td>13 (46)</td>
<td>9 (50)</td>
<td>4 (40)</td>
<td>0.61</td>
</tr>
<tr>
<td>EPA</td>
<td>11 (39)</td>
<td>7 (39)</td>
<td>4 (40)</td>
<td>0.95</td>
</tr>
<tr>
<td>β-blocker</td>
<td>9 (32)</td>
<td>4 (22)</td>
<td>5 (50)</td>
<td>0.13</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>5 (18)</td>
<td>4 (22)</td>
<td>1 (10)</td>
<td>0.42</td>
</tr>
<tr>
<td>CCB</td>
<td>10 (36)</td>
<td>8 (44)</td>
<td>2 (20)</td>
<td>0.20</td>
</tr>
<tr>
<td>ISMN</td>
<td>7 (25)</td>
<td>6 (33)</td>
<td>1 (10)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Data are given as the mean±SD or as n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; ISMN, isosorbide mononitrate. Other abbreviations as in Table 1.

Almost all patients received either aspirin or cilostazol in addition to clopidogrel. In addition, 46% received a statin and 39% received EPA at discharge (Table 2). There was no significant difference in prescriptions at discharge between the DM and Non-DM groups.

Technical success of EVR was achieved in 34 limbs (94.4%). No procedure-related adverse events, such as blue toe syndrome, pseudo-aneurysm, severe bleeding, and acute
or subacute stent thrombosis, were observed. In terms of angiographic profiles (Table 3), 58% of all lesions were de novo, and 64% were chronic total occlusions. Patients had multiple target lesions, and 83% of lesions were located BTK. Isolated BTK lesions comprised 42% of all lesions, and were present at a significantly higher rate among DM than Non-DM lesions (56% vs. 9%; P=0.011). Therefore, contrast volume during intervention was significantly lower in the DM group (125 [102–155] vs. 224 [130–272] mL; P<0.01).

CPT Kinetics

Of all patients included in the study, only 38% had a baseline ABI <0.9 (Figure 1A). In contrast, 64% had SD with impaired CPT before EVR, and 22% had a CPT higher than the upper limit of measurement (Figure 1B). At baseline, there was no association between CPT and ABI (r<0.01, P=0.99; Figure 1C). This lack of association was still observed after lesions were divided into DM and Non-DM groups (r=0.05 and r<0.01, respectively; Figure S2). In 56% of DM and 33% of Non-DM feet, ABI exceeded 0.9 at baseline.

EVR significantly improved CPT 3 months after the session (from 53 [29–89] to 30 [20–42] μA; P=0.010; Figure 2A). Two successful cases with baseline CPT higher than 256 μA did not show any improvement, and 2 unsuccessful cases showed worsening CPT values after EVR.

When comparing CPT values between the target and contralateral foot before and 3 months after EVR, EVR improved SD only in the target foot (non-target foot: from 44 [25–67] to 30 [20–42] μA; P=0.06; Figure 2B). The mean age of the study population was 68 years; therefore, the average cut-off value of normal CPT was approximately 46 μA.17 Mean CPT values in treated feet was restored to the normal CPT range.

In contrast, EVR did not significantly affect ABI of the target foot either at discharge or 3 months after the session, although there was a tendency for increased ABI at discharge (from 0.93 [0.54–1.08] to 1.05 [0.86–1.17] μA; P=0.053; Figure 2C,D). After excluding unsuccessful cases and patients with intact CPT or CPT over the limit at baseline, CPT was similarly decreased only in the target foot.
Peripheral Sensory Recovery in CLI Patients

Clinical Outcomes

Clinical presentations, including both numbness and ulceration, were improved to some degree after EVR in all feet except 2 unsuccessful cases. Among the entire study population, the all-cause and MALE-free survival rates 6 months after EVR were 83.9% and 87.4%, respectively. Twenty-four patients of 28 enrolled patients (86%) were observed at least 6 months after the session.

![Figure 4](image)

Figure 4. Kaplan-Meier plots of 180-day all-cause and MALE-free survival rates in patients whose CPT decreased to the intact range (improved CPT; n=20), as well as for patients whose CPT remained higher than the intact range (sustained high CPT; n=8) 3 months after EVR. Log-rank tests revealed a significantly higher all-cause survival rate in the improved CPT group (94% vs. 63%; P=0.040). MALE-free survival rate was higher in the improved CPT group than in the sustained high CPT group; however, this difference did not reach statistical difference (93% vs. 75%; P=0.11), primarily due to the small sample size. None of the parameters of patient profiles, including comorbidities, physiological findings, and medications, could discriminate between the sustained high and improved CPT groups (Table S1).

Comparison Between HD and Non-HD Patients

When comparing patients with and without regular HD, patient clinical profiles showed a significantly higher prevalence of DM and lower hemoglobin and total cholesterol values in HD patients (Table S2). Changes in CPT from baseline to 3 months after EVR were similar between the 23 feet in the HD group and the 13 feet in the Non-HD group (Figure S6A). CPT significantly improved after EVR only in HD feet. In contrast, ABI kinetics did not differ significantly between HD and Non-HD patients before or up to 3 months after EVR (Figure S6B).
The association of predominantly sensory neuropathy with chronic CLI has been reported previously. Peripheral blood flow is correlated with the degrees of neurological symptoms and electrophysiological testing. However, ischemic neuropathy without DM was thought to be less common, and its diagnosis can be challenging. Overlapping mononeuritis multiplex is a common presentation; distal symmetric polyneuropathy and monomelic neuropathy patterns can also be seen. Depending on whether the disease is associated with ischemic neuropathy, a mononeuropathy or a sensory motor, axonal-demyelinating peripheral neuropathy may also be seen.

Notably, the present study revealed that even Non-DM patients with CLI had a similar prevalence of SD to that seen in DM patients. Based on the results of the present study showing that SD was reversible by peripheral recirculation, EVR possibly affects ‘hibernating nerves’ in ischemic risk areas in both DM and Non-DM feet.

**Discussion**

To the best of our knowledge, the present study is the first to report restoration of damaged sensory nerves by EVR in both DM and Non-DM patients. The observations of worsened CPT in unsuccessfully treated cases and no change in CPT in non-target feet support the conclusion that EVR improved SD in the target foot.

These results suggest that CLI causes peripheral SD, SD can be reversed by EVR, and that SD in DM patients is not only due to DM neuropathy, but also due, in part, to CLI. The reversibility of SD in CLI patients further suggests that damaged peripheral nerves are partly ‘hibernated’ by severe ischemia, but not necrotized or regressed. This finding underscores the importance of clinicians understanding the modifiable risk factors associated with the development of neuropathy in order to delay or prevent its development.

**Sensory Nerve Disturbance in DM and Non-DM Patients**

Diabetic peripheral neuropathy (DPN) is a clinical diagnosis based on patient history and clinical examination, after the exclusion of other causes. Half of all patients with DPN may be asymptomatic. Among DM patients, it is difficult to clearly distinguish whether SD is caused by DM neuropathy, ischemia, or their combination.

The association of predominantly sensory neuropathy with chronic CLI has been reported previously. Peripheral blood flow is correlated with the degrees of neurological symptoms and electrophysiological testing. However, ischemic neuropathy without DM was thought to be less common, and its diagnosis can be challenging. Overlapping mononeuritis multiplex is a common presentation; distal symmetric polyneuropathy and monomelic neuropathy patterns can also be seen. Depending on whether the disease is associated with ischemic neuropathy, a mononeuropathy or a sensory motor, axonal-demyelinating peripheral neuropathy may also be seen.

Notably, the present study revealed that even Non-DM patients with CLI had a similar prevalence of SD to that seen in DM patients. Based on the results of the present study showing that SD was reversible by peripheral recirculation, EVR possibly affects ‘hibernating nerves’ in ischemic risk areas in both DM and Non-DM feet.

**Efficacy of CPT for Evaluating SD in CLI Patients**

The ABI is one of the classic indices for the detection of limb ischemia. However, the ABI level is not indicative of the degree of limb ischemia in some patients with DM or on HD, especially in the case of isolated BTK lesions, because of the presence of non-compressible vessels resulting...
Peripheral Sensory Recovery in CLI Patients

from calcified arterial walls.\textsuperscript{21,22} In addition, ABI cannot determine the presence of SD in CLI patients. Therefore, alternative parameters are needed for the appropriate evaluation of SD in such high-risk populations. Eventually, 78\% of limbs in the present study were classified as either DM or HD. CPT is an established indicator for evaluating SD in DM patients, whereas no such evidence has been reported in Non-DM patients with CLI. The present study included a large number of CLI patients with intact ABI at baseline, and found that CPT was not correlated with ABI in either DM or Non-DM feet. DM feet had higher CPT values at baseline with intact ABI, whereas Non-DM feet had lower CPT with impaired ABI. This suggests that CPT is more useful as an ischemic parameter in DM feet. In fact, CPT was clearly improved in DM patients with higher baseline CPT.

In contrast, CPT was strongly correlated with PWV at baseline. PWV represents atherosclerotic stage of ischemic legs well; therefore, CPT may have validity as an appropriate parameter for the evaluation of the severity of atherosclerosis. However, unlike CPT, PWV was not recovered by EVR. Collectively, PWV represents the severity of the atherosclerotic status of arteries; therefore, it was not affected by EVR. However, CPT purely represents the severity of sensory nerve damage, and thus parallels PWV at baseline and is reversible. The findings of the present study further suggest that ABI in DM patients is less reliable and appropriate than that in HD patients in terms of representing the ischemic status of CLI feet. The presence of HD did not affect CPT or ABI at any time point before or after EVR.

A limitation of CPT is that its measurable range is between 0 and 256\(\mu\)A; therefore, the degree of SD could not be evaluated in CLI feet with CPT values exceeding 256\(\mu\)A. However, in some cases, EVR decreased CPT values from >256\(\mu\)A down to the measurable range. This finding suggests that SD in cases of CPT values that are over the limit could be restored after revascularization, at least in a limited population.

Non-Target Feet

Baseline CPT values were similar between target and non-target feet, suggesting that the asymptomatic foot harbors latent risk for CLI. After EVR, CPT in the non-target foot was modestly improved. Although the improvement did not reach statistical significance on the non-target side, relief of pain or wound healing on the target foot after successful EVR enables CLI patients to exercise, which may exert favorable effects on SD in the non-target foot. EVR of the CLI foot at an early phase followed by daily exercise should be performed to increase the vessel bed and supply sufficient blood flow.

In contrast, tibial artery revascularization by balloon angioplasty was reported to result in restenosis or reocclusion rates as high as 70\% in 3 months.\textsuperscript{23,24} In light of these reports and the present results, persistent preservation of blood flow to the foot is not essential for the functional recovery of sensory nerves within 3 months after EVR.

Clinical Outcomes and Future Prospects

Endovascular intervention during the advanced phase of CLI results in very poor clinical outcomes. Clinical prognoses for the overall population of the present study were similar to those reported previously.\textsuperscript{25} However, the results of the present study suggest that successful recovery of SD may improve clinical outcomes. In addition, we found that the clinical prognosis of SD in patients with Rutherford Stage VI disease at baseline was not recovered by EVR. The findings of the present study establish that CLI leads to peripheral SD, ischemic SD is reversible, and that EVR may be a novel and effective treatment for ischemic SD. We are aware of the limitations of a retrospective analysis with no placebo control group. However, the substantial clinical improvement in feet with improved SD and the absence of improvement in untreated contralateral feet constitute strong data in support of the effect of EVR to improve SD.

We only evaluated short-term prognosis in the present observational study. Therefore, to verify whether restoration of SD in CLI patients brings about a clinical benefit, a larger-scale, outcome-oriented randomized trial with a longer observation period is needed. Furthermore, the benefit of endovascular intervention prior to ulcer formation should be examined in the future using CPT as a new indicator that accurately represents the ischemic status of the foot.

Study Limitations

First, this pilot study was a retrospective analysis of a small number of samples. Second, CPT is a subjective parameter of SD. Functional recovery of peripheral nerves was not confirmed by other objective parameters. Third, CPT values were not measured immediately after the session, because nerve regeneration was thought to require a substantial period after revascularization. CPT should be evaluated at different time points after EVR to identify functional recovery of hibernated peripheral nerves. Fourth, there is no angiographic evidence of target artery patency at 3 months after EVR because routine follow-up angiograms were not performed in the present study. Moreover, parameters that may represent microcirculatory status, including skin perfusion pressure and thermography, were not measured at any time point. This is the major limitation that prevents us from definitively concluding that EVR achieved neural improvement directly by increasing blood flow in the microvasculature of the target foot. Fifth, the target feet included de novo and restenotic lesions, and differences between these groups may have affected the results. Sixth, the present study included multiple target feet in the same patients. Although EVR sessions for the different feet in the same patients were separated by intervals of more than 3 months, this factor may have affected the results. Finally, diabetes duration could not be determined precisely in each patient; therefore, it was not considered when evaluating the effect of EVR on neurological improvement.

Conclusions

EVR may be a promising option to improve SD associated with peripheral ischemic neuropathy. This new concept suggests the advantage of earlier intervention on ischemic legs, prior to ulcer formation. However, further prospective trials with larger sample sizes and longer observational periods are warranted to confirm the findings of the present study.

Clinical Perspective

Damaged peripheral nerves are partly “hibernated” by severe ischemia. Chronic ischemia-inducing SD is reversible by EVR in both DM and
Non-DM patients. EVR improves SD associated with peripheral ischemic neuropathy. The benefit of endovascular intervention before ulcer formation should be examined by larger-scale, outcome-oriented randomized trials.

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References


Supplementary Files

Supplementary File 1

Supplementary Methods

Figure S1. CPT by age.

Figure S2. Relationship between baseline CPT and ABI in patients (A) with and (B) without DM.

Figure S3. Kinetics of CPT and ABI in feet with quantifiable SD.

Figure S4. Relationship between baseline CPT and changes in CPT after endovascular revascularization.

Figure S5. (A) Relationship between CPT and PWV at baseline.

Figure S6. Comparisons of (A) CPT and (B) ABI before and up to 3 months after endovascular revascularization in feet from patients undergoing HD or not.

Table S1. Baseline characteristics (sustained and improved CPT groups).

Table S2. Baseline characteristics in patients undergoing HD or not.

Please find supplementary file(s); http://dx.doi.org/10.1253/circj.CJ-17-0405