Critical limb ischemia (CLI) is a condition that represents the most advanced form of peripheral artery disease. According to the American College of Cardiology Foundation/American Heart Association and European Society of Cardiology Guidelines on the management of peripheral artery diseases, endovascular treatment (EVT) is now considered the acceptable therapy for patients with CLI attributable to infrapopliteal lesions.1–3 However, Iida et al4 reported that there was a high rate of reintervention in CLI patients and 25% amputations were observed according to the Endovascular Treatment for Infra-Inguinal Vessel, in Patients With Critical Limb Ischemia: A Prospective, Multi-Center, 12 Month Follow-Up Registry in Japan (OLIVE Registry). Therefore, bypass surgery is required in some patients with CLI.

In the coronary artery, coronary blood flow reserve (CFR) indicates the capacity of the coronary circulation to perform maximal hyperemic blood flow5 and reveals impaired coronary microvascular function.6 Despite achieving a sufficient blood flow in the epicardial artery after coronary intervention, some patients with acute myocardial infarction do not achieve adequate tissue perfusion. This inadequate tissue perfusion can be assessed by measuring CFR, and the impaired CFR after intervention was related to microvascular damage that led to increased morbidity and mortality.7,8

Background—The purpose of this study was to verify whether the concept of coronary blood flow reserve can be applied to patients with critical limb ischemia who are undergoing endovascular treatment (EVT) for isolated infrapopliteal lesions.

Methods and Results—Forty patients diagnosed with critical limb ischemia (Rutherford category 5) who were undergoing EVT for isolated infrapopliteal lesions were prospectively enrolled. All lesions were treated with conventional balloon angioplasty without stent placement. After successful EVT, a pressure/temperature sensor–tipped guidewire was positioned in the proximal popliteal artery. Using the thermodilution technique, the mean transit time (Tmn) was determined after bolus injections of 3-mL saline at baseline and at the onset of intra-arterial papaverine induced maximum hyperemia. Vascular flow reserve (VFR) was calculated as resting Tmn divided by hyperemic Tmn. Complete epithelialization of the reference wound (wound healing) was completely closed by either surgical or secondary intervention within 3 months after EVT. Wound healing was achieved in 22 patients after EVT (healing group) but was not achieved in 18 patients (nonhealing group). Postprocedural VFR was significantly lower in the nonhealing group than in the healing group (2.40; interquartile range, 2.00–3.08 versus 4.05; interquartile range, 3.60–4.60; \( P<0.0001 \)). Receiver operating characteristic analysis revealed postprocedural VFR >3.6 as the best threshold value for complete wound healing after EVT. Univariate analysis revealed that postprocedural VFR >3.6 was a predictor of wound healing (\( P=0.0002 \)).

Conclusions—Advanced lower limb clinical setting may be caused by a poor capability of microvasculature. VFR, which is easily assessable, is useful in clinical risk stratification for patients with critical limb ischemia after EVT in the catheterization laboratory.

Clinical Trial Registration—URL: http://www.umin.ac.jp/ctr. Unique identifier: UMIN000009313.

Key Words: catheterization ▪ microcirculation ▪ peripheral vascular diseases
The purpose of this study was to verify whether the concept of CFR can be applied to patients with CLI who are undergoing EVT for infrapopliteal arterial disease.

Methods

Study Design and Population
Between November 2012 and January 2014, a prospective and consecutive series of 62 patients who were scheduled for EVT of isolated infrapopliteal lesions were enrolled in this study. Patients diagnosed with CLI (nonhealing ulcers or gangrene, Rutherford category 5) and with CLI secondary to the iliac artery were included. Patients with iliac arterial disease were excluded from this study. Patients with Rutherford category 6 were also excluded from this study because their wound healing might have been affected by infections. Finally, 40 limbs of 40 patients were considered to be eligible for post-EVT physiological assessments. The ethics committee of the Hyogo College of Medicine (Nishinomiya, Hyogo, Japan) approved the protocols, and written informed consent was obtained from all the patients before performing all the procedures. This study was registered as UMIN000009313 at the University Hospital Medical Information Network Clinical Trials Registry (http://www.umin.ac.jp/ctr/), which is a public trial registry approved by the International Committee of Medical Journal Editors.

Study Protocol and Angiographic Analysis
Iliofemoral arteries were routinely evaluated by duplex ultrasound, and lower limb severity was hemodynamically assessed by using skin perfusion pressure (SPP). Angiography was performed before and immediately after EVT. Quantitative vascular angiography analysis using commercially available software (CAAS 5.9, Pie Medical Imaging, Maastricht, The Netherlands) was performed in a blinded manner to determine lesion severity and to evaluate the degree of residual stenosis in the artery subjected to intervention immediately after EVT. The tip of the guiding catheter was available as a calibration in the analysis because the movement of the catheterization table was required for angiographic evaluation of whole infrapopliteal lesions. Therefore, the diameters of the reference vessel, lumen, and lesion length were impossible to calculate, and only the percent diameter stenosis was calculated as follows: minimum lumen diameter divided by the average [(proximal+distal)×½] reference vessel diameter. EVT was recommended when the lesion indicated diameter stenosis >75% on digital subtraction angiography. All EVT procedures were generally attempted based on angiosome concept and the angiosome-based favorable target lesion was confirmed by digital subtraction angiography. Additional interventions for non-angiosome-based lesions were not attempted, even if digital subtraction angiography showed a high grade stenosis in the nontarget artery. The antegrade approach from the ipsilateral common femoral artery was selected for all patients. After insertion of a 4.5 Fr guiding sheath (Parent Plus 4.5, Medikit, Tokyo, Japan), unfractionated heparin (100 U/kg) was administered into the artery. Anticoagulation was accomplished by measuring the activated clotting time within 250 to 300 s during EVT. Dual antiplatelet therapy (aspirin at 100 mg/d and cilostazol at 200 mg/d, or clopidogrel at 75 mg/d) was initiated at least 1 week before EVT.

After a 0.014/0.018-inch guidewire was introduced into the lesion, conventional balloon angioplasty was performed using a balloon with a diameter equal to the reference vessel diameter according to visual estimation. Balloon inflation was held at nominal pressure for at least 3 minutes. If the residual stenosis was >30%, a repeat balloon angioplasty using the same balloon or another appropriately oversized balloon by 0.5 mm was performed for an additional 3 minutes. Procedural success was defined when the residual diameter stenosis was ≤30% on angiogram. After EVT, dual antiplatelet therapy was prescribed to all the patients for at least 3 months.

Infrapopliteal Physiological Measurement and Analysis
Physiological assessment was performed in all the patients before and after EVT. After the lesions were assessed by digital subtraction angiography, a 4.5 Fr guiding sheath was positioned in the proximal popliteal artery (Figure 1). A pressure/temperature sensor–tipped wire (Radi pressure wire Certus, St. Jude Medical, MN) was calibrated outside the body, equalized to the pressure reading from the guide catheter with the pressure sensor positioned at the ostium of the 4.5 Fr guiding sheath, and then the guidewire was positioned in the proximal popliteal artery (Figure 1). To accurately position the pressure/temperature sensor 3 cm from the tip of the guiding sheath, the distance from the Y-connector with the wire to the fastening torque device was 3 cm and advanced through the popliteal artery. With a commercially available software (CAAS 5.9, Pie Medical Imaging, Maastricht, The Netherlands) was performed in a blinded manner to determine lesion severity and to evaluate the degree of residual stenosis in the artery subjected to intervention immediately after EVT. The tip of the guiding catheter was available as a calibration in the analysis because the movement of the catheterization table was required for angiographic evaluation of whole infrapopliteal arteries.

Figure 1. Schematic representation of vascular flow reserve measurement. A 4.5 Fr guiding sheath was introduced from right femoral artery and positioned at the proximal popliteal artery (A). A pressure sensor, which was located 3 cm from the tip of the wire, was then advanced into the proximal popliteal artery (B and C). Injection of saline at the tip of the guiding catheter is registered by the temperature change of the shaft of the wire, acting as a second thermistor. SFA indicates superficial femoral artery.
available software (Radi Analyzer, St. Jude Medical), the shaft of this guidewire can act as a proximal thermistor by detecting changes in the temperature-dependent electric resistance. The sensor, located 3 cm proximal to the guidewire tip, simultaneously measures pressure and temperature and can thereby act as a distal thermistor. Popliteal arterial thermodilution curves were obtained by brisk manual injections of 3 mL of saline at room temperature for the determination of peak arterial flow, presented as mean transit time (Tmn). At baseline, triplicate measurements of the resting Tmn were performed and averaged. Papaverine was then administered intra-arterially in a dose of 30 mg through the guiding catheter to induce maximal hyperemia. Three injections of 3 mL of saline at room temperature were performed, initiating 30 seconds after papaverine administration. Thus, the triplicate measurements of hyperemic Tmn were averaged. Care was taken to keep the guidewire in a fixed position during the series of measurements. Vascular flow reserve (VFR) was calculated as resting Tmn divided by hyperemic Tmn (Figure 2).

Ulcer Assessment
Before EVT, lesions were photographed in patients with ulcers or gangrene from 3 different angles with a control-colored measuring tape applied near the wound. Ulcers were photographed from the same angles at each subsequent outpatient follow-up to monitor the healing process. Pictures were routinely taken before and after EVTs and after 1 and 3 months after the procedure. The assessor also determined the presence or absence of infection. All wounds were treated by an experienced plastic surgeon or dermatologist who was blinded to clinical and physiological information.

Primary End Points
The primary examination end point was the correlation between the VFR values and complete epithelialization of the reference wound, which was completely closed by either surgical intervention (skin graft, flap, and suture) or secondary intervention within 3 months.

Statistical Analysis
Continuous data were expressed as mean±SD, or medians and categorical data were expressed as numbers with percentages. Continuous variables were compared using the *t* test or Mann–Whitney *U* test, as appropriate. Categorical variables were compared by the maximum likelihood *χ*² test or Fisher exact test. Receiver operating characteristic curves were used to determine optimal sensitivity and specificity. The best threshold value was determined by the maximum sum of sensitivity and specificity. Univariate analysis based on the logistic regression analysis was used to examine individually multiple variables for a possible association with wound healing. The results were expressed as odds ratios with 95% confidence intervals. Univariate logistic regression analysis was performed to identify independent predictors of each variable on wound healing within 3 months after EVT. Two-sided *P*<0.05 was considered to be statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Shimotsuke, Tochigi, Japan), which is a graphical user interface for R (version 2.13.0; The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander (version 1.8–4) designed to add statistical functions frequently used in biostatistics.

Results
The study population comprised 25 men and 15 women with an average age of 73±10 years. Wound healing was achieved in 22 limbs after EVT (healing group) and not achieved in 18 limbs (nonhealing group). The patients’ baseline characteristics and angiographic findings are presented in Tables 1 and 2. No significant differences existed in patients’ baseline characteristics between the 2 groups. The most prevalent comorbidities were hypertension (92%; 37/40), dyslipidemia (75%; 30/40), hemodialysis (58%; 23/40), and diabetes mellitus (55%; 22/40). Lesion characteristics were similar in both groups. Median number of runoff vessels before and after EVTs were similar between the 2 groups (Table 2). All patients were treated with angiosome guidance. There was no significant difference in the proportion of patients who achieved wound healing when the patients were categorized by angiosome zone (Table 2). Median number of runoff vessels before and after EVTs were similar between the 2 groups (Table 2). All patients were treated with angiosome guidance. There was no significant difference in the proportion of patients who achieved wound healing when the patients were categorized by angiosome zone (Table 2).

### Table 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healing Group (n=22)</th>
<th>Nonhealing Group (n=18)</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>74±10</td>
<td>72±11</td>
<td>0.55</td>
</tr>
<tr>
<td>Body mass index</td>
<td>20.4±4.4</td>
<td>22.3±4.4</td>
<td>0.17</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>13 (59)</td>
<td>12 (67)</td>
<td>0.75</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>20 (91)</td>
<td>17 (94)</td>
<td>1.00</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>15 (68)</td>
<td>15 (83)</td>
<td>0.46</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>10 (45)</td>
<td>12 (67)</td>
<td>0.22</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>1 (5)</td>
<td>4 (22)</td>
<td>0.15</td>
</tr>
<tr>
<td>Hemodialysis, %</td>
<td>12 (55)</td>
<td>11 (61)</td>
<td>0.76</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE, %</td>
<td>10 (45)</td>
<td>6 (33)</td>
<td>0.53</td>
</tr>
<tr>
<td>ARB, %</td>
<td>10 (45)</td>
<td>10 (56)</td>
<td>0.75</td>
</tr>
<tr>
<td>Statin, %</td>
<td>12 (55)</td>
<td>7 (39)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Values are given as n (%) or mean±SD. ACE indicates angiotensin-converting enzyme inhibitor; and ARB, angiotensin II receptor blocker.

Figure 2. Thermodilution curves obtained at rest and in hyperemia. Thermodilution curves under resting conditions (blue lines) and during hyperemia induced by intravenous adenosine infusion (yellow and green lines). Graphical representation of thermodilution curves at baseline and hyperemia (seconds). In this case, mean transit time (Tmn) value measured 1.48 at rest (yellow circle) and 0.34 in maximum hyperemia induced by intra-arterial papaverine. Vascular flow reserve (VFR) was calculated as resting Tmn divided by hyperemic Tmn.
Peripheral Physiology in Critical Limb Ischemia

There was no statistically significant difference in the percentage diameter stenosis immediately after EVT between the 2 groups (17.79±6.84 versus 19.81±6.18; P=0.33, respectively). However, VFR values after EVT were significantly lower in the nonhealing group than that in the healing group (2.40; IQR, 2.00–3.08 versus 4.05; IQR, 3.60–4.60; P<0.0001; Figure 3B).

The optimal cutoff value for the detection of wound healing was determined by receiver operating characteristic curve analysis. The receiver operating characteristic curve analysis identified a VFR value >3.6 (area under the curve, 0.86; 95% confidence interval, 0.74–0.98; sensitivity, 77.3%; specificity, 88.9%) as the best threshold value for wound healing success within 3 months after EVT (Figure 4). Univariate logistic regression analysis revealed that postprocedural VFR >3.6 (odds ratio, 19.3; 95% confidence interval, 3.05–237.6; P=0.0002) was a predictor of wound healing within 3 months (Table 3).

Discussion

The main finding of the present study was that VFR assessed after EVT using the thermodilution technique with a pressure sensor/thermistor-tipped guidewire in patients with CLI was strongly associated with wound healing within 3 months. To the best of our knowledge, this is the first study to report the relationship between VFR analyzed by using a pressure sensor/thermistor-tipped guidewire and limb-threatening nonhealing ulceration and gangrene.

Although revascularization was successful, wound healing was not complete in some of the patients. We hypothesized that microvascular dysfunction was associated with the aforementioned conditions despite adequate artery reperfusion. SPP is currently available for the evaluation of microcirculation.\textsuperscript{10,11} Castronuovo et al\textsuperscript{10} reported that the measurement of SPP was useful for the evaluation of the microcirculatory condition after EVT in patients with CLI and that SPP values \(\geq 40\) mm Hg were associated with wound healing in critically ischemic limbs. SPP was useful in the assessment of microcirculation simplicity and reproducibility after EVTs. Risk stratification was difficult to use for patients’ outcomes because the SPP values could not be measured immediately after EVTs in the catheterization laboratory. In contrast, VFR is useful in clinical risk stratification of patients with CLI, because it can be measured immediately after EVT in the catheterization laboratory.

<table>
<thead>
<tr>
<th>Table 2.</th>
<th>Lesion Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healing Group (n=22)</td>
</tr>
<tr>
<td>Target lesions</td>
<td>Pop/ATA/PTA/PA</td>
</tr>
<tr>
<td>Run off vessels before EVT</td>
<td>0/1/2/3</td>
</tr>
<tr>
<td>Median run off vessels before EVT</td>
<td>1 (IQR, 0–1.75)</td>
</tr>
<tr>
<td>Run off vessels after EVT</td>
<td>0/1/2/3</td>
</tr>
<tr>
<td>Median run off vessels after EVT</td>
<td>2 (IQR, 2–2)</td>
</tr>
<tr>
<td>Percentage of lesion diameter stenosis before EVT</td>
<td>98.36±5.63</td>
</tr>
<tr>
<td>Percentage of lesion diameter stenosis after EVT skin perfusion pressure</td>
<td>19.81±6.18</td>
</tr>
</tbody>
</table>

Values are given as mean±SD. ATA indicates anterior tibial artery; EVT, endovascular treatment; IQR, interquartile range; PA, peroneal artery; Pop, popliteal artery; and PTA, posterior tibial artery.

no significant difference in median number of treated vessels between the nonhealing group and healing group (1; interquartile range [IQR], 1–1.75 versus 1; IQR, 1–1; P=0.50). There was no statistically significant difference in the percent diameter stenosis immediately after EVT between the 2 groups (17.79±6.84 versus 19.81±6.18; P=0.33, respectively).

Relationships Between VFR Values and Wound Healing

All procedures were successfully completed based on angiosome concept without complications. VFR was successfully measured immediately after EVTs in all patients without complications. There was no significant difference in VFR values before EVT between the nonhealing and healing group (2.95; IQR, 2.25–4.03 versus 3.4; IQR, 3.03–4.05; P=0.29; Figure 3A). Likewise, both resting and hyperemic Tmn values before EVT, which are inversely proportional to flow velocity, were similar in both groups (1.64; IQR, 1.13–1.95 versus 1.66; IQR, 0.78–2.13; P=0.66 and 0.44; IQR, 0.32–0.87 versus 0.43; IQR, 0.23–0.56; P=0.41, respectively). However, VFR values after EVT were significantly lower in the nonhealing group than that in the healing group (2.40; IQR, 2.00–3.08 versus 4.05; IQR, 3.60–4.60; P<0.0001; Figure 3B).

Figure 3. Pre–endovascular treatment (EVT) and post–EVT vascular flow reserve (VFR) values between nonhealing group and healing group. A, A comparison of the VFR value before EVT in patients with wound healing and those without wound healing. B, VFR value after EVT was significantly higher in patients with wound healing than those without wound healing.
Blood flow velocity was measured through a thermodilution technique such as the use of a Swan–Ganz catheter. The sensor near the tip of the wire simultaneously measures pressure and temperature and can thereby act as a distal thermistor. The transit time of room temperature saline injected down a limb artery can provide insight into the microvascular function immediately after endovascular therapy.

Table 3. Predictors of Wound Healing

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound healing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.44</td>
<td>0.06–2.39</td>
<td>0.46</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.42</td>
<td>0.09–1.79</td>
<td>0.31</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>0.77</td>
<td>0.18–3.21</td>
<td>0.92</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.17</td>
<td>0.01–2.00</td>
<td>0.16</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.37</td>
<td>0.32–6.26</td>
<td>0.87</td>
</tr>
<tr>
<td>Post VFR &gt;3.6</td>
<td>19.7</td>
<td>3.05–237.6</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Cl indicates confidence interval; OR, odds ratio; and VFR, vascular flow reserve.

Previous studies have suggested favorable EVT outcomes for CLI, but at the same time they have revealed contradictory results about the relative benefit of EVT in comparison with bypass surgery. Although the Bypass versus Angioplasty in Severe Ischemia of the Leg trial showed better long-term amputation-free survival outcomes after bypass surgery on autologous veins compared with EVT, a major amputation has been reported to be necessary in ≈10% of patients with ischemic ulcers of the lower limbs despite a patent bypass. In addition, the result of this study indicated that in the absence of an intact pedal arch, sufficient collateral pathways can revascularize the heel after the restoration of pulsatile flow to the forefoot circulation.

If the wound healing was not achieved through revascularization, the patients with low VFR values should have been treated using another therapy because of their poor microvasculature. However, it is still unknown how to avoid the major amputation in CLI patients. A recent study has reported therapeutic angiogenesis for CLI. Powell et al reported the safety and efficacy of gene therapy for the treatment of patients with lower extremity vascular disease. We also hypothesize that gene transfer therapy could be a good treatment of CLI, because angiogenesis is necessary to increase the blood volume, which affects wound healing. Measurement of VFR provides insight into the microvascular function immediately after EVT.

Study Limitations

First, this study was a single-center study with a relatively small study population. Further multicenter studies with large numbers of patients are required to confirm the present results. Second, VFR was measured using thermodilution techniques. In a small proportion of cases, thermodilution coronary flow reserve was shown to overestimate the true value of coronary flow reserve. Third, wound healing was affected by several factors such as the treatment technique used by plastic surgeons, infections, and reocclusion. Fourth, a follow-up study of the present patients should be considered to assess long-term outcomes. Fifth, the use of VFR has not been validated in the infrapopliteal artery in the clinical setting, although we have recently reported the ability for dilating the vascular bed exists in the lower limb during increased oxygen demand supply in response to a given hyperemic stimulation and can be assessed in the same manner. Finally, the pressure measurement distal to the lesion immediately after EVT was not attempted because residual dissections could be extended by advancing the pressure sensor into the artery undergoing EVT.

Conclusions

Advanced lower limb clinical setting may be caused by a poor capability of microvasculature. VFR, which is easily assessable, is useful in clinical risk stratification for patients with CLI after EVT in the catheterization laboratory.

Acknowledgments

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Disclosures

None.

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Vascular Flow Reserve Immediately After Infrapopliteal Intervention as a Predictor of Wound Healing in Patients With Foot Tissue Loss
Masashi Fukunaga, Kenichi Fujii, Daizo Kawasaki, Machiko Nishimura, Tetsuo Horimatsu, Ten Saita, Kojiro Miki, Hiroto Tamaru, Takahiro Imanaka, Yoshiro Naito and Tohru Masuyama

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