Pathophysiological Significance of Velocity-Based Microvascular Resistance at Maximal Hyperemia in Peripheral Artery Disease

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Aim: Maximal hyperemic response, leading to examination of microvascular resistance in lower-limb lesions is not well understood. This study aimed to investigate the infrainguinal arterial physiological response through a hyperemic condition and the pathophysiologic significance of microvascular resistance in peripheral artery disease.

Methods: Sixteen limbs with focal stenosis of the superficial femoral artery (SFA) and 16 control limbs were analyzed. We assessed the fractional flow reserve (FFR), vascular flow reserve (VFR), and hyperemic microvascular resistance (h-MR) of the SFA with a pressure/Doppler flow sensor-tipped combination guidewire before and after endovascular therapy (EVT). Skin perfusion pressure (SPP) on both the dorsal and the plantar sides of the foot was measured at baseline before and after the endovascular procedures.

Results: FFR ($p<0.05$) and VFR ($p<0.05$), but not h-MR, improved after EVT. There was no association between h-MR and FFR or VFR before EVT. h-MR was negatively correlated with the dorsal SPP before EVT ($r=-0.589, p<0.05$). h-MR in patients with high h-MR before EVT significantly decreased after EVT ($p<0.05$). Patients with high, but not those with low, h-MR before EVT exhibited a significant increase in dorsal and plantar SPP after EVT ($p<0.05$, each).

Conclusion: EVT for SFA stenosis improved FFR and VFR comprehensively, with no apparent change in h-MR. However, high h-MR before EVT may play a predictive role for limb perfusion improvement associated with h-MR reduction after EVT.

Key words: Combination guidewire, Endovascular therapy, Microvascular resistance, Skin perfusion pressure, Superficial femoral artery

Introduction

In case of the coronary circulation, coronary perfusion is under metabolic, endothelial, myogenic, and neurohumoral control¹,². Although real-world patients with peripheral artery disease (PAD) have coronary risk factors and comorbidities³, it is not clear whether the same regulatory mechanisms play a role in case of the lower-limb circulation. Furthermore, clinical significance of microvascular resistance in the lower legs is poorly understood till date and meeting challenges arising from this issue will offer a boon to patients with critical limb ischemia.

Potential mechanistic drivers of claudication, in addition to artery obstruction, include vascular dysfunction, microvascular flow and altered skeletal muscle function⁴. In pathophysiologic conditions such as a long-lasting stenosis of the superficial femoral artery (SFA), an increase in microvascular resistance may occur, because putative regulatory mechanisms may become progressively exhausted and blood supply may decrease relative to demand. Skin perfusion pressure (SPP) is widely used to predict clinical outcomes such as the probability of lower-limb wound healing⁵,⁶.
However, accurate assessment of altered lower-limb microvascular resistance before and after endovascular therapy (EVT) for SFA stenosis and its relation to the alterations of SPP of the foot remain to be seen.

**Aim**

We aimed to clarify the pathophysiological significance of lower-limb microvascular resistance at maximal hyperemia before and after EVT, and the relationship between high or low microvascular resistance before EVT and the changes in dorsal and plantar SPP of the foot after EVT in patients with diseased SFA. We assessed a velocity-based index of hyperemic microvascular resistance (h-MR) by using a dual-sensor (Doppler velocity and pressure)-equipped guidewire before and after EVT to elucidate the indexed issues stated above.

**Methods**

**Evaluation of Hyperemic Response in the Lower Limbs**  
The study population consisted of 16 subjects (10 men, 6 women) who underwent EVT for mid- or distal-SFA lesions. We excluded subjects with the following manifestations: ostial lesions in the SFA, difficult to measure lower-extremity hemodynamics, limbs associated with aorto-iliac inflow lesion and/or popliteal arterial lesion, <50% angiographic stenosis by visual estimation, critical limb ischemia with tissue loss, low left ventricular ejection fraction (<40%) on echocardiogram, atrial fibrillation, and end-stage renal disease maintained on hemodialysis. Patients without tolerance to papaverine were also excluded. For the examination of control data, we included other 16 subjects who did not have any stenotic lesions in their limbs when they performed coronary angiography for the evaluation of their symptoms. The study protocol adhered to the Declaration of Helsinki and was approved by the institutional review board of Yao Municipal Hospital. Written informed consent was obtained from all the subjects.

| Table 1. Baseline clinical characteristics |
|------------------------------------------|
| **Control group (n = 16)** | **EVT group (n = 16)** | **p Value** |
| --- | --- | --- |
| **Age, y** | 68.9 ± 10.5 | 75.4 ± 6.6 | 0.046 |
| **Men, n (%)** | 9 (56) | 10 (63) | 0.719 |
| **Body mass index** | 26.7 ± 4.2 | 24.1 ± 4.1 | 0.087 |
| **Arteriosclerosis risk factors, n (%)** |  |  |  |
| **Hypertension** | 10 (63) | 15 (94) | 0.087 |
| **Dyslipidemia** | 14 (88) | 7 (44) | 0.009 |
| **Diabetes mellitus** | 8 (50) | 11 (69) | 0.280 |
| **Chronic kidney disease** | 0 (0) | 1 (6) | 0.325 |
| **Current smoking** | 1 (6) | 9 (56) | 0.002 |
| **Coronary artery disease, n (%)** | 12 (75) | 13 (81) | 0.669 |
| **Cerebral artery disease, n (%)** | 1 (6) | 7 (44) | 0.014 |
| **Rutherford category (2/3/4)** |  | 3/1/2 |  |
| **Lesion length, cm** |  | 9.9 ± 6.5 |  |
| **TASC II classification (A/B/C/D)** |  | 8/5/3/0 |  |
| **Below the knee runoff (0/1/2/3)** | 0/0/0/16 | 1/4/5/6 | <0.001 |
| **Ankle-brachial index** | 1.12 ± 0.09 | 0.84 ± 0.14 | <0.001 |
| **Skin perfusion pressure** |  |  |  |
| **Dorsal, mm Hg** |  | 58.9 ± 20.1 |  |
| **Plantar, mm Hg** |  | 72.2 ± 15.4 |  |
| **Intravascular ultrasound data** |  |  |  |
| **EEM area, mm²** |  | 27.3 ± 5.7 |  |
| **Minimum lumen area, mm²** |  | 5.8 ± 2.9 |  |
| **% Area stenosis** |  | 78.8 ± 9.2 |  |

Values are mean ± SD or numbers (%).  
EVT, endovascular therapy; EEM, external elastic membrane.

EVT Procedure and Physiological Measurement  
After local anesthesia induction, a 6-Fr guiding sheath (Destination, Terumo, Tokyo, Japan) was adv-
distal to the stenotic SFA were obtained from the pres-

sure curve and Doppler wave. Then, 20 mg intra-arte-

rial papaverine was administered to the lower limb via

a guiding catheter, with each next measurement at least

3 min apart from the previous administration after

returning to baseline hemodynamic conditions. Saline

was flushed after each administration. The 20 mg pap-

averine bolus caused maximal infrainguinal hyperemia

in the SFA of normal subjects (data not shown). The

fractional flow reserve (FFR) was obtained as MDP/

mean proximal pressure at hyperemia. The vascular

flow reserve (VFR) was obtained as hyperemic APV/

baseline APV. h-MR was obtained as hyperemic MDP/

hyperemic APV. Control data for VFR, FFR, and

anced to a point of the common femoral artery through

a contralateral femoral approach. An intra-arterial bolus

of 5000 IU heparin was injected. A 0.014-in pressure/

Doppler sensor-tipped guidewire (Combo Wire; Vol-

cano, Rancho Cordova, CA, USA) was calibrated out-

side the body and equalized to the pressure of the com-

mon femoral artery, with the pressure sensor positioned

at the ostium of the guiding catheter. Then, the pres-

sure/Doppler sensor was positioned from the guiding

catheter into the SFA. The intra-arterial pressure curve

and Doppler wave distal to the stenotic SFA were

obtained in a similar manner, as is usually done for

measurements of the coronary flow reserve. The mean

distal pressure (MDP) and average peak velocity (APV)

Fig. 1. Correlation between baseline average peak velocity (APV) and log hyperemic

microvascular resistance (h-MR) before (A) or after (B) endovascular therapy (EVT).

A, A significant negative correlation was observed between baseline APV and log h-MR before

EVT ($r = -0.849$, $p < 0.001$). B, Even after EVT, a significant negative correlation was also pre-
served between baseline APV and log h-MR ($r = -0.861$, $p < 0.001$).
After balloon inflation for at least 1 min, stenting was done if there was flow-limiting dissection, a pressure gradient $\geq 5$ mm Hg, or $\geq 30\%$ residual stenosis. The endpoint of treatment for SFA lesions was trans-stenotic pressure gradient $\leq 5$ mmHg or $\leq 30\%$ residual stenosis. After ballooning and/or stenting, the VFR, FFR, and h-MR were repeatedly calculated. Patients received nitinol self-expandable stents (Lifestent; Bard, Murray Hill, NJ) with a diameter 1 mm larger than the reference vessel diameter.

h-MR were obtained similarly at the proximal or distal portion of the normal SFA in control subjects. The guidewire was advanced distal to the target lesion to perform intravascular ultrasound (IVUS) examination for recording the data on vessel characteristics after wire crossing and at the end of the procedure. A commercially available IVUS catheter (Eagle Eye Gold, Volcano) was used to examine the minimum lesion area (MLA), external elastic membrane (EEM) area, and percent area stenosis. The indication for revascularization was symptomatic disease (Rutherford category 2–4) with $\geq 70\%$ diameter stenosis on angiography. The lesion was dilated using a balloon catheter with a diameter equal to the reference vessel diameter, determined by IVUS measurement. After balloon inflation for at least 1 min, stenting was done if there was flow-limiting dissection, a pressure gradient $\geq 5$ mm Hg, or $\geq 30\%$ residual stenosis. The endpoint of treatment for SFA lesions was trans-stenotic pressure gradient $< 5$ mmHg or $< 30\%$ residual stenosis. After ballooning and/or stenting, the VFR, FFR, and h-MR were repeatedly calculated. Patients received nitinol self-expandable stents (Lifestent; Bard, Murray Hill, NJ) with a diameter 1 mm larger than the reference vessel diameter. SPP is an index for cutaneous microvasculature blood flow. SPP (Nahri MV monitor; Nexis, Tokyo, Japan) on both

Fig. 2. Correlation between skin perfusion pressure (SPP) and hyperemic average peak velocity (h-APV) (A) or log hyperemic microvascular resistance (h-MR) (B) before endovascular therapy (EVT).

A, h-APV was significantly correlated with both the dorsal (blue rhombus; $r = 0.658$, $p = 0.014$) and plantar (red square; $r = 0.689$, $p = 0.009$) SPP before EVT. SPP was measured at baseline before hyperemia induced by papaverine administration. B, Log h-MR was negatively correlated with both the dorsal (blue rhombus; $r = -0.589$, $p = 0.034$) and plantar (red square; $r = -0.543$, $p = 0.054$) SPP before therapy.
the dorsal and the plantar sides of the foot ($n=13$) was measured at baseline before, and immediately after, the endovascular procedure in an air-conditioned, temperature-controlled operating room.

### Statistical Analysis

Continuous variables are reported as mean ± SD, and categorical variables as frequencies. An unpaired or paired $t$-test was appropriately performed to compare continuous variables between groups, and the chi-square test was used to compare proportions between groups. Linear regression was used to show the relationship between the groups. A $p$ value of < 0.05 was considered statistically significant. Multiple regression analysis was performed with each clinical datum as an explanatory variable and log h-MR as an objective variable.

### Results

#### Baseline Characteristics

The baseline clinical and pathophysiological characteristics of the study limbs are provided in Table 1. There were no differences in sex and body mass index between the control and EVT groups, although several coronary risk factors were significantly different between them. The isolated focal stenotic lesions of the mid- and distal-SFA were analyzed in this study. Although not shown, there was no difference in the vessel diameter of the mid-portion of the SFA between the control and EVT groups. Sixteen limbs with SFA focal stenosis were treated with balloon angioplasty. Seven limbs required stenting after balloon angioplasty.

#### Correlation among Hemodynamic Variables before EVT

h-MR in the target lesion vessel before EVT was significantly correlated with the baseline APV ($r = -0.807, p < 0.001$), MLA ($r = -0.544, p = 0.029$), and EEM area ($r = -0.519, p = 0.039$). The log h-MR and baseline APV were highly and negatively correlated ($r = -0.849$, Fig. 1A), and the correlation continued even after EVT ($r = -0.861$, Fig. 1B). When multiple regression analysis was performed using essential clinical factors, log h-MR was independently associated with only baseline APV ($p = 0.024$), and not with the MLA and EEM area (Table 2). Hyperemic APV before EVT was positively correlated with SPP on both the dorsal ($r = 0.658$) and plantar ($r = 0.689$) sides of the foot (Fig. 2A). Furthermore, log h-MR before the procedure was negatively correlated with the SPP on both sides ($r = -0.589$ and $r = -0.543$, respectively; Fig. 2B). However, the hyperemic MDP was not correlated with the SPP of the dorsal ($p = 0.412$) or plantar ($p = 0.068$) sides before EVT.

#### Changes in Hemodynamic Variables after EVT

EVT-induced hemodynamic changes were evaluated with a pressure/Doppler flow sensor-tipped combination guidewire (Table 3). The reduced VFR in target lesion vessels before EVT significantly improved after EVT and reached the level in control subjects. The FFR in target lesion vessels was 0.83 ± 0.10 before EVT, and it also significantly improved to the control level after EVT. On the other hand, h-MR was not apparently different among control subjects and the patients with SFA lesions before and after EVT. There was no association between h-MR and FFR or VFR before EVT. SPP significantly increased after EVT only on the dorsal side (dorsal side: from 58.9 ± 20.1 to 79.2 ± 21.6 mm Hg, $p = 0.033$; plantar side: from 72.2 ± 15.4 to 76.3 ± 14.4 mm Hg, $p = 0.542$). The increment of dorsal SPP was significantly larger than that of plantar SPP after EVT ($p = 0.001$).

When we divided our subjects into two groups according to their h-MR level before EVT ($n=8$ each), there were no differences in the age, sex, MLA, and EEM area between the high and low h-MR groups (Table 4). The h-MR in the low h-MR group significantly increased after EVT; however, it significantly decreased in the high h-MR group (Table 5). h-MR was conditionally convergent after EVT. FFR significantly increased after EVT in both the high and low h-MR groups, but VFR increased only in the high h-MR group. SPP was lower in the high h-MR group than in the low h-MR group before EVT on both the dorsal and plantar sides (Table 6). Importantly, both the dorsal and plantar SPP in the high h-MR group significantly increased after SFA angioplasty ($p = 0.012$

### Table 2. Multiple regression analysis for log h-MR before EVT as an objective variable

| Variable                   | Coefficient | $p$ Value |
|----------------------------|-------------|-----------|
| Age                       | -0.003      | 0.690     |
| Sex                       | 0.109       | 0.278     |
| Body mass index           | -0.004      | 0.729     |
| Lesion length             | -0.003      | 0.738     |
| Below the knee run off    | 0.018       | 0.787     |
| Ankle-brachial index      | -0.435      | 0.368     |
| Mean EEM area             | -0.008      | 0.443     |
| Minimum lumen area        | 0.013       | 0.466     |
| Baseline APV              | -0.019      | 0.024     |
| Baseline MDP              | 0.003       | 0.264     |

h-MR, hyperemic microvascular resistance; EVT, endovascular therapy; EEM, external elastic membrane; APV, average peak velocity; MDP, mean distal pressure.
Doppler flow sensor-tipped combination guidewire. The functional gain in SPP after a successful EVT was thus due to SFA revascularization resulting in h-MR reduction only in patients with high h-MR before EVT. In patients with low h-MR before EVT, h-MR slightly and reversely increased, and SPP did not change after EVT. There was no association between h-MR and FFR or VFR before EVT.

Flow Reserve and Microvascular Resistance after EVT

The increase in blood flow of the lower limbs during maximal hyperemia varied among subjects, and maximal hyperemia exhibited a wide range of values.

Table 3. Hemodynamic characteristics of control subjects and patients with a stenotic superficial femoral artery

|                      | Control vessel | Target lesion vessel: Pre EVT | Target lesion vessel: Post EVT |
|----------------------|----------------|-------------------------------|-------------------------------|
|                      | b-APV          | h-APV                         | b-MDP                         | h-MDP | h-MPP | FFR | h-MR |
| Value                |                |                               |                               |       |       |     |      |
| Age, y               |                |                               |                               |       |       |     |      |
| Values are mean ± SD.|                |                               |                               |       |       |     |      |
| Values are mean ± SD.| 19.8 ± 6.2     | 40.8 ± 13.6                   | 100.2 ± 10.3                  | 90.2  ± 9.9 | 88.8 ± 8.7 | 1.00 ± 0.01 | 2.46 ± 0.96 |
| Values are mean ± SD.| 20.1 ± 8.9     | 33.6 ± 13.8                   | 93.2 ± 15.9                  | 71.1  ± 15.8 | 86.0 ± 15.5 | 0.83 ± 0.10 | 2.54 ± 1.32 |
| Values are mean ± SD.| 21.8 ± 8.3     | 39.3 ± 10.2                   | 1.89 ± 0.36                  | 97.2  ± 16.6 | 80.6 ± 12.8 | 0.98 ± 0.04 | 2.22 ± 0.80 |

Values are mean ± SD. “b” indicates baseline; “h” indicates during hyperemia; APV, average peak velocity; VFR, vascular flow reserve; MDP, mean distal pressure; MPP, mean proximal pressure; FFR, fractional flow reserve; MR, microvascular resistance; EVT, endovascular therapy.

Abbreviations are as in Tables 1 and 2.

Discussion

This study demonstrates a unique change in lower-limb h-MR after EVT with an associated change in indexed vascular flow and perfusion pressure in patients with PAD. As far as we know, this study is the first to examine the pathophysiological significance of microvascular resistance in lower limbs using a pressure/
used clinically to predict the probability of wound healing, and postprocedural SPP correlates with clinical outcomes after EVT for patients with critical limb ischemia\(^5\). However, the differences in dorsal and plantar SPP between PAD patients with high and low h-MR before EVT remain to be seen. In our study, dorsal SPP was significantly lower than plantar SPP before EVT, and the increment of dorsal SPP was significantly larger than that of plantar SPP after EVT in patients with SFA lesions. Furthermore, dorsal SPP was more closely associated with h-MR before EVT, indicating that more reliable data could be obtained from measuring dorsal SPP as compared with plantar SPP in case of SFA stenosis, possibly owing to the augmentation of anterior tibial artery flow after EVT of SFA lesions. In other words, plantar artery flow would be preserved lastly to avoid wound occurrence in the toes. This issue needs to be confirmed in a large-scale study.

### Pathophysiological Significance of h-MR in Peripheral versus Coronary Circulation

On the basis of the pressure dependence of resistance of the maximally vasodilated coronary bed, it is possible that the pressure dependence of hyperemic infrapopliteal microvascular resistance contributes to functional gain after EVT. However, there were no differences in distal pressure of SFA before and after hyperemia, both of before and after EVT between pati-
ents with high and low h-MR before EVT, showing that under these conditions, flow velocity is critical for the determination of microvascular resistance in the limbs. The reason why association between h-MR and VFR is absent in peripheral circulation but is present in coronary circulation, may be due to the differences in active flow velocity-dependent in peripheral circulation and passive pressure-dependent in coronary circulation. h-MR before EVT was independently associated with the baseline APV, but not with the MLA and EEM area, showing that h-MR cannot be estimated by IVUS examination. A strong inverse association between baseline APV and h-MR before EVT, and even after EVT, may represent the differences in individual structural conditions in the infrapopliteal vascular bed and/or in the extent of dilation of peripheral arterioles among patients with diseased SFA.

The increased risk of myocardial ischemia in the presence of high h-MR demonstrates that h-MR is reflective of an increase in actual microvascular resistance in coronary circulation. Furthermore, h-MR is a strong predictor of long-term major adverse cardiovascular events in patients with ST-segment elevation myocardial infarction treated with primary coronary intervention (PCI). In contrast, the pathophysiological significance of h-MR in atherosclerotic limbs remains to be seen. VFR immediately after infrapopliteal intervention may be a predictor of wound healing in patients with foot tissue loss. In patients with PAD, although the overall h-MR was insignificantly reduced after a successful EVT, patients with low or high h-MR before EVT exhibited a significant increase or decrease in h-MR after EVT. Importantly, patients with high h-MR showing low dorsal and plantar SPP before EVT exhibited significant increases in SPP. Since patients with low h-MR showing only slight decreases in SPP before EVT did not change their SPP after EVT, and h-MR may be changed from low to high with time, h-MR before EVT may be a determinant factor for the change in SPP level after EVT and represent a future prognostic factor in the clinical setting. Assessment of the status of the infrapopliteal microcirculation by measuring the indexed microvascular resistance brings scientific insights into the pathophysiology and therapeutic strategies concerning individual microvascular inhomogeneity, which were thus far restricted clinically. A large-scale prospective study is needed to clarify the differences in clinical outcomes, such as the incidence of restenosis and critical limb ischemia between patients exhibiting high and low h-MR not only after EVT, but also before EVT.

**Study Limitations**

Our study has some limitations. This study has a small sample size and the possibility of Type I and II errors is undeniable. Data on SPP could not be measured in all subjects. As the patients with Rutherford 5/6 were not included in this study because of intolerance to papaverine, most of the patients exhibited SPP levels >40 mmHg. However, the changes in SPP levels after EVT were different between dorsal and plantar sides. No data were obtained about the relationship between h-MR before and after EVT and future clinical outcomes. There were some problems such as the variations in the evaluations of VFR and h-MR due to the differences in the experience and skill of the examiners. Several instances of papaverine infusion can cause a gradual increase in baseline APV, possibly due to accumulated vasoactive effects. Care should be taken to examine the reproducibility and accuracy of hyperemic Doppler flow.

It is a potential problem that needs to be defined on addressing the reproducibility and accuracy of the method for measuring these parameters.

**Conclusions**

EVT for SFA stenosis improved FFR and VFR comprehensively, with insignificant change in h-MR. A high h-MR before EVT may play a predictive role for limb perfusion improvement after EVT.

**Declaration of Interests**

There are no relationships, financial or otherwise, that constitute a conflict of interest.

**Acknowledgements**

None.

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