The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2018; 25: 1128-1136. http://doi.org/10.5551/jat.43117

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

Kuniyasu Ikeoka[1], Shiro Hoshida[1], Tetsuya Watanabe[1], Yukinori Shinoda[1], Tomoko Minamisaka[1], Hidetada Fukuoka[1], Hirooki Inui[1], Keisuke Ueno[1] and Yasushi Sakata[2]

[1]Department of Cardiovascular Medicine, Yao Municipal Hospital, Osaka, Japan
[2]Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

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 pathophysiological 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 control[1, 2]. Although real-world patients with peripheral artery disease (PAD) have coronary risk factors and comorbidities[3], 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 function[4]. In pathophysiological 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 healing[5, 6].

Address for correspondence: Shiro Hoshida, Department of Cardiovascular Medicine, Yao Municipal Hospital, 1-3-1 Ryuge-cho, Yao, Osaka 581-0069, Japan
E-mail: shiro.hoshida@hosp-yao.osaka.jp

Received: October 16, 2017 Accepted for publication: January 10, 2018

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)	–	3/11/2	–
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, mm^2	–	27.3 ± 5.7	–
Minimum lumen area, mm^2	–	5.8 ± 2.9	–
% Area stenosis	–	78.8 ± 9.2	–

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

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[5] 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.

EVT Procedure and Physiological Measurement

After local anesthesia induction, a 6-Fr guiding sheath (Destination, Terumo, Tokyo, Japan) was adv-

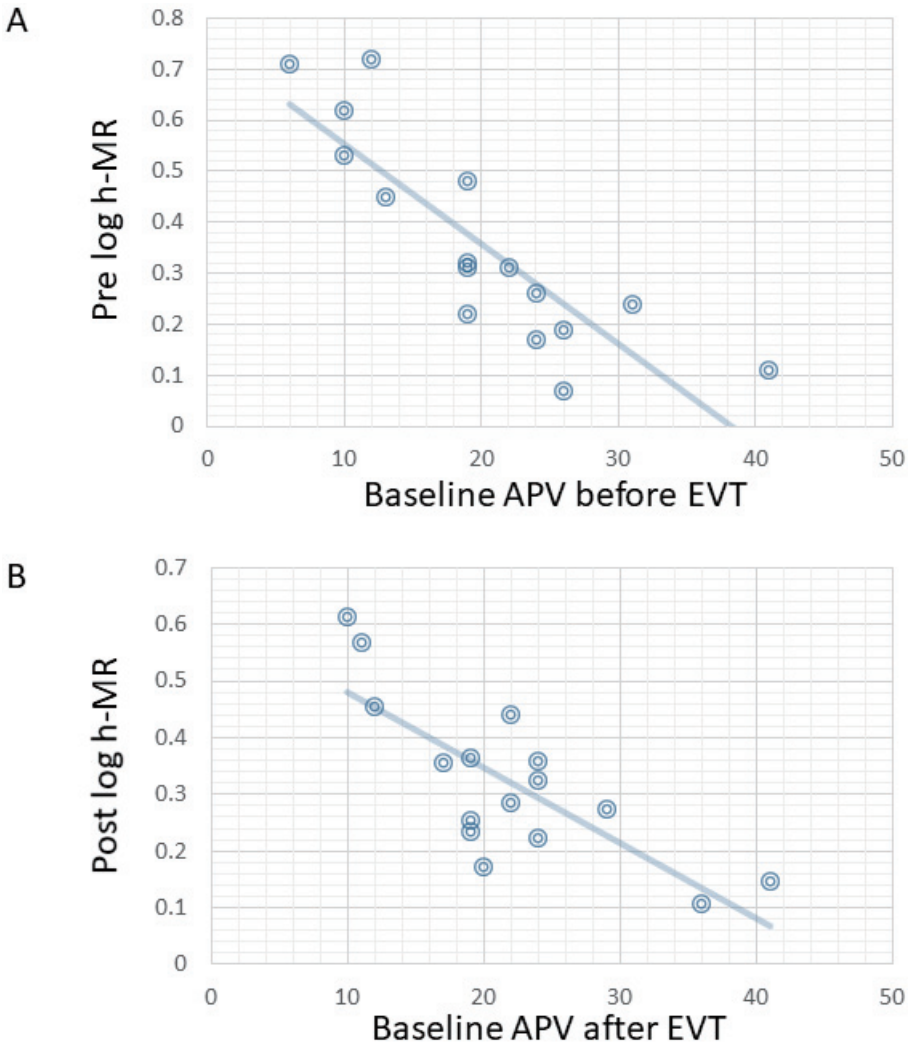

Fig. 1. Correlation between baseline average peak velocity (APV) and log hyperemic microvascular resistance (h-MR) before (A) or after (B) endovascular therapy (EVT).

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 preserved between baseline APV and log h-MR ($r = -0.861$, $p < 0.001$).

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; Volcano, Rancho Cordova, CA, USA) was calibrated outside the body and equalized to the pressure of the common femoral artery, with the pressure sensor positioned at the ostium of the guiding catheter[7]. Then, the pressure/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) distal to the stenotic SFA were obtained from the pressure curve and Doppler wave. Then, 20 mg intra-arterial 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[8]. Saline was flushed after each administration. The 20 mg papaverine 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

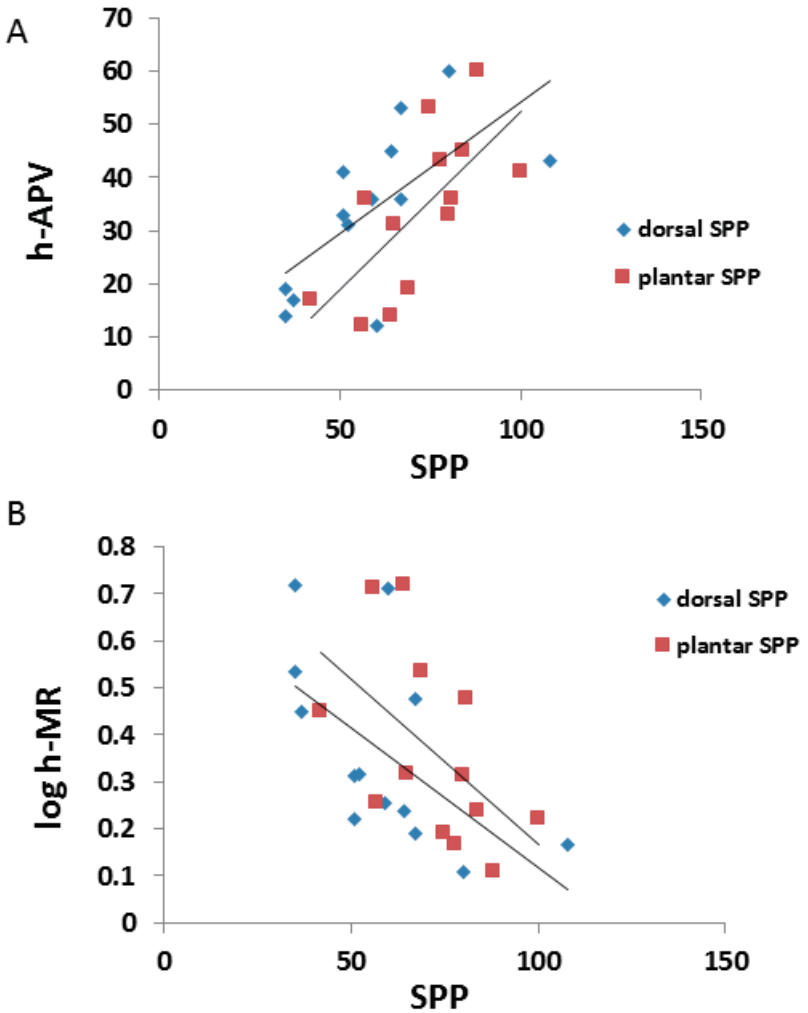

Fig. 2. Correlation between skin perfusion pressure (SPP) and hyperemic average peak velocity (h-APV) (A) or log hyperemic microvascular resistance (h-MR) (B) before endovascular therapy (EVT).

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.

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 ≥70% diameter stenosis on angiography[9]. 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 ≥5 mm Hg, or ≥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

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.

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

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

	b-APV	h-APV	VFR	b-MDP	h-MDP	h-MPP	FFR	h-MR
Control vessel	19.8 ± 6.2	40.8 ± 13.6	2.08 ± 0.33	100.2 ± 10.3	90.2 ± 9.9	88.8 ± 8.7	1.00 ± 0.01	2.46 ± 0.96
Target lesion vessel: Pre EVT	20.1 ± 8.9	33.6 ± 13.8	1.72 ± 0.33*	93.2 ± 15.9	71.1 ± 15.8*	86.0 ± 15.5	0.83 ± 0.10*	2.54 ± 1.32
Target lesion vessel: Post EVT	21.8 ± 8.3	39.3 ± 10.2†	1.89 ± 0.36†	97.2 ± 16.6	80.6 ± 12.8*†	82.6 ± 13.7	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.
*$p < 0.05$ compared with control vessel.
†$p < 0.05$ compared with target lesion vessel: pre EVT.

Table 4. Baseline clinical characteristics in the high h-MR and low h-MR groups

	High h-MR group	Low h-MR group	*p* Value
Age, y	77.2 ± 7.4	73.5 ± 5.4	0.266
Men, n (%)	7 (88)	3 (38)	0.121
Body mass index, kg/m^2	24.0 ± 4.1	24.3 ± 4.4	0.870
Arteriosclerosis risk factors, n (%)			
Hypertension	7 (88)	8 (100)	0.302
Dyslipidemia	3 (38)	4 (50)	0.614
Diabetes mellitus	6 (75)	5 (63)	0.590
Chronic kidney disease	1 (13)	0 (0)	0.302
Current smoking	4 (50)	5 (63)	0.614
Coronary artery disease, n (%)	6 (75)	7 (88)	0.522
Cerebral artery disease, n (%)	3 (38)	4 (50)	0.614
Rutherford category (2/3/4)	1/5/2	2/6/0	0.298
Lesion length, cm	10.4 ± 7.3	9.4 ± 5.9	0.769
TASC II classification (A/B/C/D)	3/3/2/0	5/2/1/0	0.597
Below the knee runoff (0/1/2/3)	1/1/3/3	0/3/2/3	0.314
Ankle-brachial index	0.83 ± 0.13	0.86 ± 0.16	0.735
Intravascular ultrasound data			
EEM area, mm^2	25.2 ± 4.1	29.4 ± 6.6	0.148
Minimum lumen area, mm^2	4.5 ± 2.7	7.1 ± 2.7	0.071
% Area stenosis	82.2 ± 9.3	75.5 ± 8.3	0.148

Abbreviations are as in Tables 1 and 2.

and $p = 0.039$, respectively); however, this was not so in the low h-MR group. Two patients with Rutherford category 4 having no tissue loss were included in the high h-MR group and their SPPs increased similarly after EVT.

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/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 5. Hemodynamic changes after EVT in the high h-MR and low h-MR groups

Group	Pre h-MR	Post h-MR	*p* Value (pre vs post)	Pre VFR	Post VFR	*p* Value (pre vs post)	Pre FFR	Post FFR	*p* Value (pre vs post)
High h-MR	3.49 ± 1.24	2.59 ± 0.95	0.037	1.73 ± 0.41	2.09 ± 0.37	0.024	0.82 ± 0.10	0.98 ± 0.05	0.002
Low h-MR	1.59 ± 0.29	1.85 ± 0.38	0.025	1.71 ± 0.27	1.69 ± 0.24	0.689	0.84 ± 0.11	0.98 ± 0.04	0.010
p Value (high vs low)	< 0.001	0.061		0.944	0.022		0.736	0.928	

Abbreviations are as in Table 3.

Table 6. Changes of skin perfusion pressure (SPP) after EVT in the high h-MR and low h- MR groups

Group	Dorsal SPP (mmHg)		*p* Value (pre vs. post)	Plantar SPP (mmHg)		*p* Value (pre vs. post)
	Pre EVT	Post EVT		Pre EVT	Post EVT	
High h-MR	47.7 ± 14.0	72.8 ± 14.5	0.012	62.8 ± 13.1	70.8 ± 14.6	0.039
Low h-MR	68.6 ± 20.1	84.7 ± 26.2	0.061	80.3 ± 13.1	81.1 ± 13.4	0.861
p Value (high vs. low)	0.055	0.346		0.035	0.211	

Abbreviations are as in Table 3.

(219−769%)[8]. The normalization of relative flow reserve provides evidence for the absence of significant microembolization after EVT. In our study, there was no association between h-MR and FFR or VFR, and no differences were observed in the FFR, VFR, and number of runoff vessels between patients with high and low h-MR before EVT, indicating that h-MR cannot be expected from the values of FFR or VFR. Since FFR, but not VFR, increased significantly after EVT in patients with low h-MR, these three indices reflect different aspects of pathophysiology of peripheral circulation of PAD patients. In PAD patients with low h-MR, stenotic SFA lesions may not largely affect peripheral vascular resistance. It would be important to clarify the differences in the possible determinant of VFR and h-MR in peripheral circulation.

Correlation between Microvascular Resistance and SPP

The skin microcirculation peripheral to the ankle probably depends on the macrocirculatory blood flow at the ankle level. The sum of the anterior tibial artery and the posterior tibial artery at the ankle level significantly correlated with the SPP on the foot[10, 11]. Successful EVT for SFA lesions leads to augmentation of vascular flow of both the anterior and posterior tibial arteries. SPP measurement by using laser Doppler is a noninvasive method that measures microcirculatory pressure of the artery at the skin level. SPP is widely 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, 6]. 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[12]. 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)[13]. 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[14]. 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.

References

1) Bassenge E and Heusch G: Endothelial and neuro-humoral control of coronary blood flow in health and disease. Rev Physiol Biochem Pharmacom, 1990; 116: 77-165
2) Chillian WM: Coronary microcirculation in health and disease. Summary of an NHLBI workshop. Circulation, 1997; 95: 522-528
3) Higashi Y, Miyata T, Shigematsu H, Origasa H, Fujita M, Matsuo H, Naritomi H, Matsuda H, and Nakajima M; SEASON Investigators: Baseline characterization of Japanese peripheral arterial disease patients−Analysis of surveillance of cardiovascular events in antiplatelet-treated arteriosclerosis obliterans patients in Japan (SEASON). Circ J, 2016; 80: 712-721
4) Hamburg NM and Creager MA: Pathophysiology of intermittent claudication in peripheral artery disease. Circ J, 2017; 81: 281-289
5) Utsunomiya M, Nakamura M, Nagashima Y, and Sugi K:

Predictive value of skin perfusion pressure after endovascular therapy for wound healing in critical limb ischemia. J Endovasc Ther, 2014; 21: 662-670
6) Okamoto S, Nakamura M, Yamauchi Y, Fukunaga M, Yokoi Y, Soga Y, Zen K, Hirano K, Suematsu N, Suzuki K, Shintani Y, Miyashita Y, Urasawa K, Kitano I, Yamaoka T, Ohura N, Hamasaki T, Uematsu M, and Nanto S; OLIVE Investigators: Postprocedural skin perfusion pressure correlates with clinical outcomes 1 year after endovascular therapy for patients with critical limb ischemia. Angiology, 2015: 66: 862-866
7) Siebes M, Verhoeff B-J, Meuwissen M, de Winter RJ, Spaan JAE, and Piek JJ: Single-wire pressure and flow velocity measurement to quantify coronary stenosis hemodynamics and effects of percutaneous interventions. Circulation, 2004; 109: 756-762
8) Miki K, Fujii K, Fukunaga M, Nishimura M, Horimatsu T, Saita T, Tamaru H, Imanaka T, Shibuya M, Ohyanagi M, and Masuyama T: Assessment of lower limb flow and adequate intra-arterial papaverine doses to achieve maximal hyperemia in elder subjects. Cardiovasc Interv Ther, 2015; 30: 227-233
9) Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, Machan LS, Snyder SA, O'Leary EE, Ragheb AO, and Zeller T; Zilver PTX Investigators: Durable Clinical Effectiveness With Paclitaxel-Eluting Stents in the Femoropopliteal Artery: 5-Year Results of the Zilver PTX Randomized Trial. Circulation, 2016; 133: 1472-1483
10) Kawarada O, Yasuda S, Nishimura K, Sakamoto S, Noguchi M, Takahi Y, Harada K, Ishihara M, and Ogawa H: Effect of single tibial artery revascularization on microcirculation in the setting of critical limb ischemia. Circ Cardiovasc Interv, 2014; 7: 684-691
11) Sekiya N and Ichioka S: Efficacy of ultrasonography at the ankle level for estimation of pedal microcirculation. Ann Vasc Dis, 2015; 8: 198-202
12) Nolte F, van de Hoef TP, Meuwissen M, Voskuil M, Chamuleau SA, Henriques JP, Verberne HJ, van Eck-Smit BL, Koch KT, de Winter RJ, Spaan JA, Tijssen JG, Siebes M, and Piek JJ: Increased hyperaemic coronary microvascular resistance adds to the presence of myocardial ischaemia. EuroIntervention, 2014; 9: 1423-1431
13) Jin X, Yoon MH, Seo KW, Tahk SJ, Lim HS, Yang HM, Choi BJ, Choi SY, Hwang GS, Shin JH, and Park JS: Usefulness of hyperemic microvascular resistance index as a predictor of clinical outcomes in patients with ST-segment elevation myocardial infarction. Korean Circ J, 2016; 45: 194-201
14) Fukunaga M, Fujii K, Kawasaki D, Nishimura M, Horimatsu T, Saita T, Miki K, Tamaru H, Imanaka T, Naito Y, and Masuyama T: Vascular flow reserve immediately after infrapopliteal intervention as a predictor of wound healing in patients with foot tissue loss. Circ Cardiovasc Interv, 2015; 8: e002412. DOI: 10.1161