ORIGINAL

Relationship between fluctuations in skin perfusion pressure values and wound healing in patients with chronic limb-threatening ischemia undergoing hemodialysis

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Abstract : Background : Patients with chronic limb-threatening ischemia are often on hemodialysis. It is unclear which skin perfusion pressure (SPP) values, i.e., those measured immediately after hemodialysis on a hemodialysis day or those measured on a non-hemodialysis day, reflect the actual wound healing course in chronic limb-threatening ischemia. Methods : Eighteen patients undergoing hemodialysis (49 measurements) who were treated for leg ulcers due to critical limb ischemia were included in the study. The SPP values were divided into two groups : those measured immediately after hemodialysis (HD day group) and those measured on non-hemodialysis days (non-HD day group). The wound healing outcomes were investigated. The cutoff SPP value for predicting wound healing was set to ≥35 mmHg. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of SPP in each group were measured. The relationship between SPP and blood pressure was analyzed by regression analysis. Results : Significant differences were observed in the positive predictive value (HD day : 100%, non-HD day : 50% ; P=0.002), The correlation coefficient was 0.698 in the HD day group and 0.292 in the non-HD day group. Diastolic blood pressure had a significant effect on SPP (P=0.039). Conclusions : The measurements are best taken immediately after hemodialysis for more accuracy. J. Med. Invest. 69 : 294-298, August, 2022

Keywords **:** *skin perfusion pressure, hemodialysis, critical limb ischemia, chronic limb-threatening ischemia, peripheral artery disease*

INTRODUCTION

Patients with chronic limb-threatening ischemia (CLTI) are often undergoing hemodialysis. Treating ulcers associated with CLTI is difficult (1-3). The skin perfusion pressure (SPP) test is important for predicting the course of wounds during CLTI treatment (4-8). Because the blood pressure during hemodialysis and the blood flow to the skin immediately after hemodialysis decrease, it is considered that the SPP value also decreases. However, it is unclear whether the SPP values measured immediately after hemodialysis and those measured on non-hemodialysis days reflect the actual wound healing course. Therefore, in this study, we investigated the SPP values that more accurately reflect wound healing in patients with CLTI.

PATIENTS AND METHODS

This retrospective study included 18 patients undergoing hemodialysis who were treated for ischemic ulcers at our department between January 2016 and March 2021. Among these patients, those in whom the course of ulcer was for 12 or more weeks were included in this study. A total of 49 SPP tests were performed on the lower limbs of these 18 patients during the observation period ; among these, 22 were performed immediately after hemodialysis (HD day group) and 27 were performed on non-hemodialysis days (non-HD day group). SPP was measured on the measurable skin closest to the ulcer or the surgical site. In the HD day group, SPP was measured within an hour from the end of the hemodialysis sessions in all cases. It was randomly determined who would undergo the SPP test immediately after dialysis. In the non-HD day group, SPP was measured more than 20 h after (range : 20–48 h) the end of hemodialysis. Patient characteristics such as sex, mean SPP value, mean blood pressure, diabetes mellitus status, ulcer or surgical site, and ulcer treatment methods were investigated and compared between the HD and non-HD day groups. An SPP of 35 mmHg was set as the cutoff value : SPP of ≥35 mmHg was used as a predictor of wound healing, while SPP of <35 mmHg was used as a predictor of healing failure. Ulcer treatments included major amputation, minor amputation, skin grafting, debridement, and conservative treatment according to the condition of the wound. When skin grafting, debridement, and conservative treatment were selected, healing was judged to have occurred when the ulcer area reduced to 10% or less 12 weeks after the start of the treatment. Conversely, healing was considered to have failed when more ulcer area remained or new necrotic tissue appeared after treatment (4, 5, 9). When major or minor amputation was selected for treatment, wound healing without additional treatment after surgery was defined as healing and wound dehiscence was defined as healing failure. Consent was obtained from the participants for the publication of their case details. Ethical approval for this study was obtained from the institutional review board of Tokushima University.

STATISTICAL ANALYSIS

We determined the differences in the SPP value, blood pressure, positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity, and accuracy between the

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HD and non-HD day groups. The outcomes were assessed using the *t*-tests and chi-square tests. The correlation between SPP and wound healing was determined for each group. The relationship between SPP and post-hemodialysis time and that between SPP and blood pressure were analyzed by regression analysis. Statistical significance was achieved at two-tailed P-values of <0.05. The correlation coefficient was calculated using the Pearson's test. Statistical analyses were conducted using SPSS version 16.0 (SPSS Inc.).

RESULTS

Baseline patient characteristics, including the sex, age, mean SPP value, mean diastolic and systolic blood pressure, site of the ulcers, and type of treatment, are presented in Table 1. The mean SPP and blood pressure were higher in the non-HD day group than in the HD day group. In the HD day group, the ulcer/surgery sites included the thigh (n = 1), lower leg (n = 5), foot (n = 9), heel (n = 4), and toes (n = 3). In the non-HD day group, the ulcer sites included the thigh (n = 2), lower leg (n = 1), foot (n = 13), heel (n = 8), and toes (n = 3) (P=0.413). In the HD day group, 7, 2, 7, 1, and 5 patients received conservative treatment, debridement, skin grafting, minor amputation, and major amputation, respectively. In the non-HD day group, 11, 4, 7, 2, and 3 patients received conservative treatment, debridement, skin grafting, minor amputation, and major amputation, respectively, (P=0.754). There were no significant differences in any of the items mentioned in Table 1 between the two groups. Wound healing was defined as a positive result, and healing failure was defined as a negative result. The PPV was 100% in the HD day group and 50% in the non-HD group (P=0.002). The NPV was 85.7% in the HD day group and 94.1% in the non-HD group (P=0.431) (Table 2). The sensitivity was 80% in the HD day group and 83.3% in the non-HD group (P=0.869). The specificity was 100% in the HD day group and 76.2% in the non-HD group (P=0.067) (Table 3). The accuracy was 90.9% in the HD day group and 77.8% in the non-HD group (P=0.216). The total accuracy for the HD day and non-HD day groups was 86.4% (Table 4). The correlation coefficient between SPP and wound healing was

Table 1. Baseline patient characteristics

	HD day group, n = 22	Non-HD day group, n = 27	P value
Sex	Male : 14 (63.6%) Female : 8 (36.4%)	Male : 19 (70.4%) Female : 8 (29.6%)	0.617
Mean age, years	63.14 ± 10.15	64.22 ± 5.54	0.245
History of diabetes mellitus	21 (95.5%)	27 (100%)	0.263
Mean SPP, mmHg	29.29 ± 14.67	34.48 ± 19.37	0.160
Systolic blood pressure, mmHg	125.45 ± 31.85	133.54 ± 33.40	0.183
Diastolic blood pressure, mmHg	62.35 ± 14.41	67.65 ± 13.31	0.081
Ulcer or surgical site	Thigh : 1 (4.5%) Lower leg : 5 (22.7%) Foot : 9 (40.9%) Heel : 4 (18.2%) Toe : 3 (13.6%)	Thigh : 2 (7.4%) Lower leg : 1 (3.7%) Foot : 13 (48.1%) Heel : 8 (29.6%) Toe : 3 (11.1%)	0.413
Treatment method	CT : 7 (31.8%) Debridement : 2 (9.1%) Skin grafting : 7 (31.8%) Minor amputation : 1 (4.6%) Major amputation : 5 (22.7%)	CT : 11 (40.7%) Debridement : 4 (14.8%) Skin grafting : 7 (26%) Minor amputation : 2 (7.4%) Major amputation : 3 (11.1%)	0.754

HD, hemodialysis ; n, number of measurements ; SPP, skin perfusion pressure ; CT, conservative treatment

Table 2. Comparison of PPV and NPV between HD day and non-HD day groups

	SPP ≥35 mmHg Positive predictive value	SPP <35 mmHg Negative predictive value
HD day	8/8 (100%)	12/14 (85.7%)
Non-HD day	5/10 (50.0%)	16/17 (94.1%)
P value	0.002*	0.431

PPV, positive predictive value ; NPV, negative predictive value ; HD, hemodialysis ; SPP, skin perfusion pressure
*P<0.05

Table 3. Comparison of sensitivity and specificity between HD day and non-HD day groups

	Healed Sensitivity	Failed Specificity
HD day	8/10 (80%)	12/12 (100%)
Non-HD day	5/6 (83.3%)	16/21 (76.2%)
P-value	0.869	0.067

HD, hemodialysis
*P<0.05

0.698 (P=0.000) in the HD day group and 0.292 (P=0.140) in the non-HD day group (Figure 1). SPP and post-hemodialysis time were not significantly causal in regression analysis (P=0.231). SPP and systolic blood pressure were not significantly causal in regression analysis (P=0.584). Diastolic blood pressure significantly affected SPP (P=0.039) (Figure 2).

Table 4. Comparison of accuracy between HD day and non-HD day groups

	Accuracy	Total Accuracy
HD day	20/22 (90.9%)	51/59 (86.4%)
Non-HD day	21/27 (77.8%)	
P-value	0.216	

HD, hemodialysis
*P<0.05

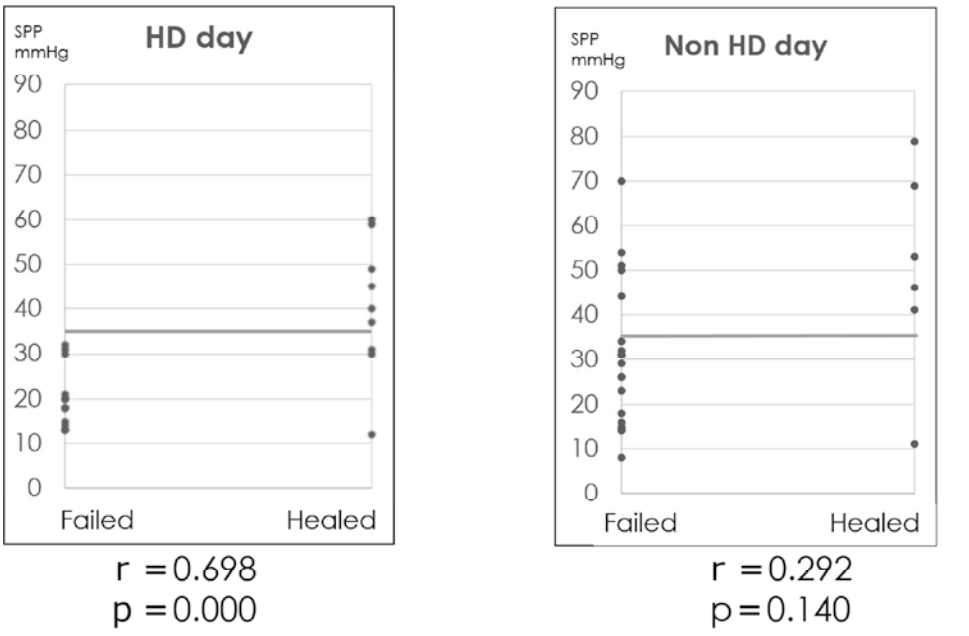

Figure 1. Correlation between wound healing and skin perfusion pressure (SPP, mmHg) distribution in the hemodialysis (HD) day group and the non-HD day group. The cutoff SPP value was considered to be 35 mmHg.

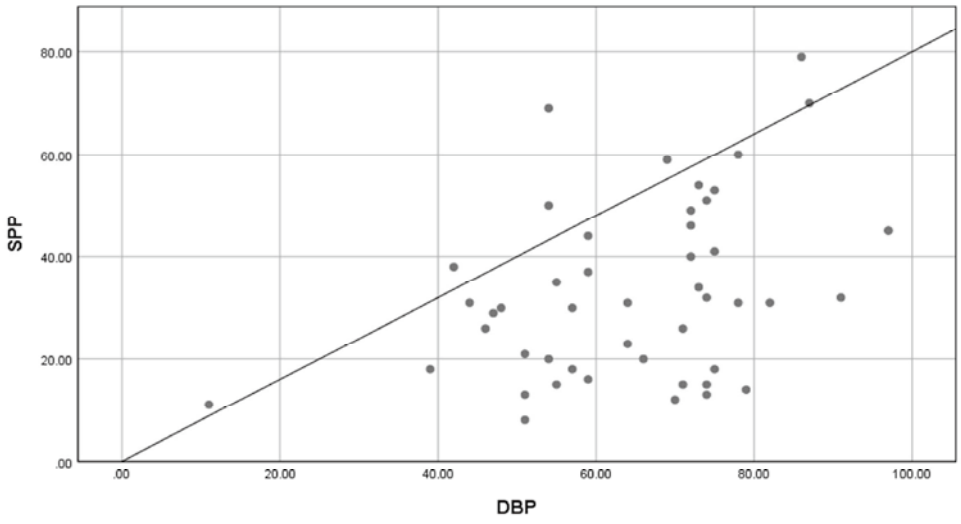

Figure 2. Scatter plot of regression analysis.
Diastolic blood pressure significantly affected skin perfusion pressure (SPP) in regression analysis.

DISCUSSION

In our study, the SPP value of patients undergoing hemodialysis measured immediately after dialysis more accurately reflected the course of the wound than the value measured on the non-dialysis day. SPP is as useful as the ankle-brachial index (ABI) for diagnosing peripheral arterial disease and predicting wound healing (10-12). The SPP is more useful than the ABI in identifying the extent of ischemia and determining the level of amputation and the extent of debris because the site of measurement can be selected (4-6). In previous reports, the cutoff value of SPP varied from 30 to 50 mmHg (4-7) ; however, Tsuji *et al*. reported that an SPP of 35 mmHg is the optimal cutoff value (13) that most accurately reflects whether the wound heals or not within 12 weeks. Based on this, we set the same SPP cutoff in this study. In some studies that investigated the relationship between SPP and wound healing, patients underwent conservative treatment, amputation, or debridement for their wounds (4-6, 13, 14), Plastic surgeons often treat CLTI cases with extensive necrosis and large ulcers. Therefore, skin grafting is often performed as a treatment option. Because skin grafts do not survive if there is ischemia, healing was considered successful in this study when the ulcer area was reduced to 10% or less after skin grafting. The wound healing period in this study was determined to be within 12 weeks ; this is because over a long period of time, the degree of blood flow in the lower limbs may change due to the development of new obstructions and progression of arteriosclerosis (15-17).

According to previous reports, there is a difference in the SPP levels measured before and immediately after hemodialysis (18, 19). This is attributed to the fluctuation in the blood pressure during hemodialysis (18, 20). The reduced blood pressure would not be able to adequately perfuse the stenotic arteries and injured tissues, thereby resulting in a low SPP value. In our study, this variation in the SPP value averaged 5 mmHg in both the HD day and non-HD day groups, although there were some patients with differences of ≥20–30 mmHg between the HD and non-HD days. This difference obscures the decision as to whether revascularization is necessary for the treatment of ulcers associated with CLTI. Therefore, it is important to determine which SPP value (i.e., the value in the HD day group or in the non-HD day group) is more credible. In our study, the SPP in the HD day group more accurately reflected the course of wound healing in terms of PPV, specificity and accuracy compared to that in the non-HD day group. The correlation between the SPP value and wound healing was also significantly higher in the HD day group. These results suggest that for patients undergoing hemodialysis, physicians should rely on the SPP value measured on the hemodialysis day, immediately after hemodialysis to predict wound healing.

The limitation of this study was that it was a retrospective study, so both groups were not completely controlled, and the number of patients in the HD day group was smaller than that of the non-HD day group. The novelty of this study is that we investigated the relationship between the SPP value, which fluctuates with hemodialysis and wound healing.

CONCLUSION

When SPP is measured on a non-hemodialysis day, its value tends to be higher than the value measured immediately after hemodialysis on a hemodialysis day. The SPP value is more accurate when it is measured immediately after hemodialysis. This timing is important to obtain an accurate prediction of the course of an ulcer in patients with CLTI undergoing hemodialysis, so that a revascularization strategy can be planned accordingly.

CONFLICT OF INTEREST DISCLOSURE

The authors declare that they have no conflicts of interest associated with this manuscript.

REFERENCE

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR, TASC Working Group : Inter-society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg 45 Supplement S : S5-67, 2007
2. Honda Y, Hirano K, Yamawaki M, Mori S, Shirai S, Makino K, Tokuda T, Takama T, Tsutumi M, Sakamoto Y, Takimura H, Kobayashi N, Araki M, Ito Y : Wound healing of critical limb ischemia with tissue loss in patients on hemodialysis. Vascular 25 : 272-82, 2017
3. Yoshikawa H, Iijima R, Hashimoto G, Hara H, Omae K, Yoshikawa Y, Suzuki M, Nakamura M, Sugi K, Yoshikawa M : Prediction of development of critical limb ischemia in hemodialysis patients. Ther Apher Dial 19 : 378-84, 2015
4. Adera HM, James K, Castronuovo JJ, Byrne M, Deshmukh R, Lohr J : Prediction of amputation wound healing with skin perfusion pressure. J Vasc Surg 21 : 823-8 ; discussion 828, 1995
5. Urabe G, Yamamoto K, Onozuka A, Miyata T, Nagawa H : Skin perfusion pressure is a useful tool for evaluating outcome of ischemic foot ulcers with conservative therapy. Ann Vasc Dis 2 : 21-6, 2009
6. Holstein P : Level selection in leg amputation for arterial occlusive disease : A comparison of clinical evaluation and skin perfusion pressure. Acta Orthop Scand 53 : 821-31, 1982
7. Okamoto K, Oka M, Maesato K, Ikee R, Mano T, Moriya H, Ohtake T, Kobayashi S : Peripheral arterial occlusive disease is more prevalent in patients with hemodialysis : Comparison with the findings of multidetector-row computed tomography. Am J Kedney Dis 48 : 269-76, 2006
8. Pan X, Chen G, Wu P, Han C, Ho JK : Skin perfusion pressure as a predictor of ischemic wound healing potential (Review). Biomed Rep 8 : 330-4, 2018
9. Tsuji Y, Hiroto T, Kitano I, Tahara S, Sugiyama D : Importance of skin perfusion pressure in treatment of critical limb ischemia. Wounds 20 : 95-100, 2008
10. Shimazaki M, Matsuki T, Yamauchi K, Iwata M, Takahashi H, Genda S, Ohata J, Nakamura Y, Inaba Y, Yokouchi S, Kikuiri T, Ashie T : Assessment of lower limb ischemia with measurement of skin perfusion pressure in patients on hemodialysis. Ther Apher Dial 11 : 196-201, 2007
11. Wang Z, Hasan R, Firwana B, Elraiyah T, Tsapas A, Prokop L, Mills JL, Murad MH : A systematic review and meta-analysis of tests to predict wound healing in diabetic foot. J Vasc Surg 63 : 29S-36S, 2016
12. Kawai M, Mihara S, Takahagi S, Iwamoto K, Hiragun T, Hide M : Evaluation of skin perfusion pressure to assess refractory foot ulcers. J Wound Care 26 : 267-70, 2017
13. Castronuovo JJ, Adera HM, Smiell JM, Price RM : Skin perfusion pressure measurement is valuable in the diagnosis of critical limb ischemia. J Vasc Surg 26 : 629-37, 1997
14. Brosi P, Baumgartner I, Silvestro A, Do DD, Mahler F, Triller J, Diehm N : Below-the-knee angioplasty in patients with end-stage renal disease. J Endovasc Ther 12 : 704-13, 2005

15. Iida O, Soga Y, Kawasaki D, Hirano K, Yamaoka T, Suzuki K, Miyashita Y, Yokoi H, Takahara M, Uematsu M : Angiographic restenosis and its clinical impact after infrapopliteal angioplasty. Eur J Vasc Endovasc Surg 44 : 425-31, 2012
16. Kawarada O, Fujihara M, Higashimori A, Yokoi Y, Honda Y, Fitzgerald PJ : Predictors of adverse clinical outcomes after successful infrapopliteal intervention. Catheter Cardiovasc Interv 80 : 861-71, 2012
17. Ishioka K, Tsutsumi D, Mochida Y, Oka M, Maesato K, Moriya H, Ohtake T, Hidaka S, Kobayashi S : Hemodialysis effect on SPP (skin perfusion pressure) : Study of changes in low extreme peripheral circulation before and after hemodialysis. J Jpn Soc Limb Salvage Podiatr Med 4 : 91-5, 2012
18. Matsuura R, Hidaka S, Ohtake T, Mochida Y, Ishioka K, Maesato K, Oka M, Moriya H, Kobayashi S : Intradialytic hypotension is an important risk factor for critical limb ischemia in patients on hemodialysis. BMC Nephrol 20 : 473, 2019
19. Holstein P, Lund P, Larsen B, Schomacker T : Skin perfusion pressure measured as the external pressure required to stop isotope washout. Methodological considerations and normal values on the legs. Scand J Clin Lab Investig 37 : 649-59, 1977
20. Shoji T, Tsubakihara Y, Fujii M, Imai E : Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. Kidney Int 66 : 1212-20, 2004