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PERIPHERAL VASCULAR DISEASE

Original Studies

Assessment of Macro- and Microcirculation in Contemporary Critical Limb Ischemia

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Objectives: A paucity of data exists regarding manifestations of macro- and microcirculation in contemporary critical limb ischemia (CLI). The aim of this study was (1) to evaluate the differences in foot circulation based on angiographic findings, (2) to clarify the relationship between macro- and microcirculation, and (3) to investigate the effects of postural changes on micro as well as macrocirculation between the supine position to the dependent position. **Methods:** A total of 40 critically ischemic limbs in 29 patients were included in this study. Noninvasive evaluation of macrocirculation, based on the ankle brachial index (ABI) and ankle pressure, and microcirculation, using skin perfusion pressure (SPP), was performed in both the supine and dependent positions. **Results:** There was no significant difference in macro- and microcirculations between any angiographical involvements. In the supine position, dorsal SPP correlated significantly with ABI ($P = 0.021$, $r = 0.363$) and ankle-pressure ($P = 0.001$, $r = 0.495$), whereas plantar SPP failed to correlate with ABI ($P = 0.198$, $r = 0.208$) or ankle-pressure ($P = 0.185$, $r = 0.214$). In the dependent position, however, SPP showed no significant correlation with ABI and ankle pressure. Postural change from the supine to dependent position yielded a significant increase in SPP (dorsal: 37.2 ± 16.2 to 77.9 ± 17.7 mm Hg, $P < 0.001$; plantar: 33.6 ± 17.3 to 75.7 ± 18.3 mm Hg, $P < 0.001$) as well as ABI and ankle-pressure (ABI: 0.70 ± 0.35 to 0.78 ± 0.42, $P = 0.003$; ankle-pressure; 108 ± 61 to 111 ± 60 mm Hg, $P = 0.038$). The effect of postural change on SPP showed no difference between patients with and without any clinical and angiographical complications. **Conclusions:** Of microcirculation assessed, only dorsal SPP correlated significantly with macrocirculation in the supine position. Furthermore, postural change from the supine to dependent position produced a dramatic improvement in microcirculation due to the effects of gravity.

Key words: critical limb ischemia; macrocirculation; microcirculation; skin perfusion pressure; gravity

INTRODUCTION

Macrocirculation, represented by the ankle-brachial index (ABI) and ankle pressure, is a traditional marker for limb ischemia. Recently, aside from the macrocirculation, increasing attention has been paid to microcirculation assessment such as skin perfusion pressure (SPP) in the field of interventional limb salvage, as it relates to the probability of healing of ischemic wounds in critical limb ischemia (CLI) [1–6]. However, the association between angiographic appearance and foot circulation and linkage of macro- and microcirculation remain unclear. Also, there is a paucity of data regarding the effect of postural change on foot

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Conflict of interest: Nothing to report.

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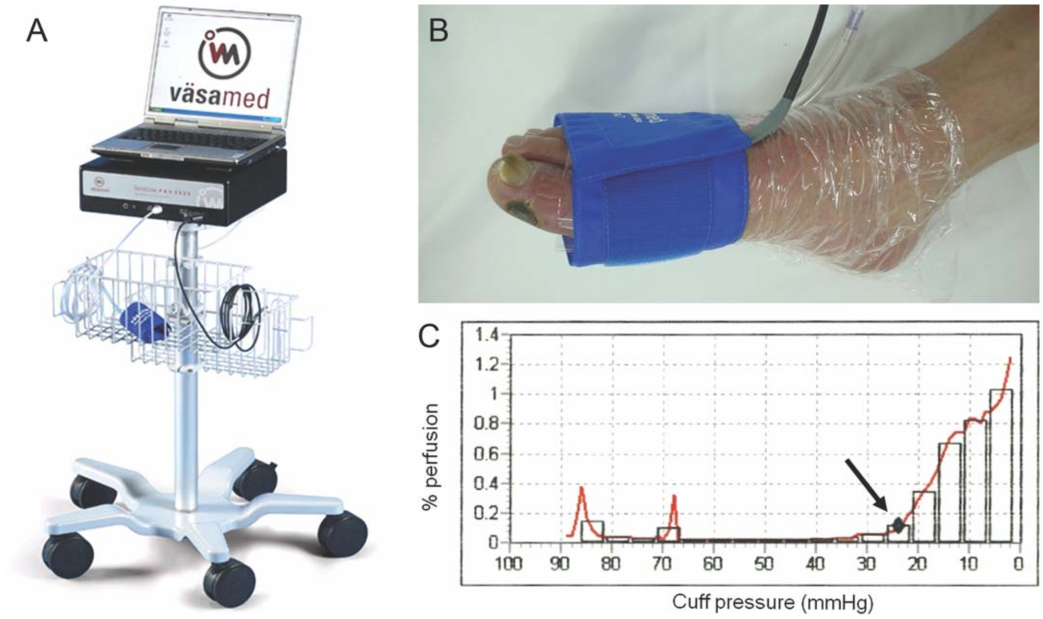

Fig. 1. Practical example of microcirculation examination. A: Device to automatically examine skin perfusion pressure, PAD 3000. B: Measurement of SPP. Note the gangrene of first toe of the right foot. C: SPP determination. Arrow indicates the point of the SPP value. The SPP in this case was 23 mm Hg.

circulation although postural change from the supine to the dependent position is of great help for the relief of ischemic rest pain in the clinical setting. Thus, the aim of this study was (1) to evaluate the differences in foot circulation based on angiographic findings, (2) to clarify the relationship between the macro- and microcirculation, and (3) to investigate the postural changes of the microcirculation as well as the macrocirculation from the supine position to the dependent position.

METHODS

Subjects

A total of 40 consecutive critically ischemic limbs in 29 patients (17 males) who underwent noninvasive evaluation of their foot circulation were included in this study. A noninvasive work-up was scheduled for clinical hard endpoints of wound healing and prevention of major amputation. Noninvasive evaluation of the macrocirculation (using ABI and ankle pressure) and of the microcirculation (using SPP) was performed sequentially in both the supine and dependent positions. All patients underwent diagnostic angiography after the noninvasive evaluations. Patients with a history of venous disease or signs and symptoms of venous insufficiency were excluded. All limbs met the CLI symptom of resting pain, with and without tissue loss, significant reduction of SPP $<$ 50 mm Hg at either the dorsal or plantar side [1], or lower extremity atherosclerotic occlusive disease, as established by angiography. This study was approved by the institutional review committee, and all patients gave informed consent before participation.

Measurement of ABI, Ankle Pressure, and SPP

The ABI and ankle pressure were measured using an oscillometric method [7]. SPP is the term used to denote a specific cuff pressure wherein microcirculatory perfusion is first detected following a period of occlusion. The essential technique of SPP measurements has been based on a previous study [1]. Using a Sensilase^{TM} PAD 3000 (Vasamed, Eden Prairie, MN), the SPP in the foot was measured, with the patient maintained at room temperature between 24° and 26°. A laser Doppler probe placed beneath a 8.0-cm-wide blood pressure cuff was wrapped at the dorsal and plantar region of the foot. At a high-cuff pressure, one would expect the cessation of skin perfusion. This is referred to as a baseline reading. The baseline pressure will sometimes decrease slightly during the initial portion of the deflation cycle, because the disappearance of capillary flow does not occur immediately in response to the counter pressure of the cuff. The SPP value is the cuff pressure at which the perfusion reading increases above baseline and is followed by further increases at the next several pressure levels (Fig. 1). For this study, the SPP was initially measured in a supine position and then in the sitting position with the legs dependent with continuous recording of the foot SPP.

TABLE I. Clinical Characteristics

Variables	
Number of patients (*n*)	29
Number of limbs (*n*)	40
Age (years)	67 ± 10
Male, *n* (%)	17 (59%)
Hypertension, *n* (%)	18 (62%)
Dyslipidemia, *n* (%)	10 (34%)
Diabetic mellitus, *n* (%)	23 (79%)
Chronic renal failure (>1.3 mg/dl), *n* (%)	24 (83%)
Current smoking, *n* (%)	14 (48%)
Rutherford category of ischemic limbs	
Class 4, n (%)	6 (15%)
Class 5, n (%)	26 (65%)
Class 6, n (%)	8 (20%)

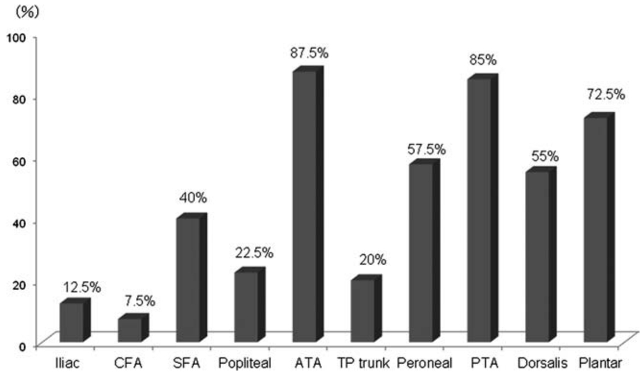

Fig. 2. Distribution of affected vessels. CFA, common femoral artery; SFA, superficial femoral artery; ATA, anterior tibial artery; TP, tibioperoneal; PTA, posterior tibial artery.

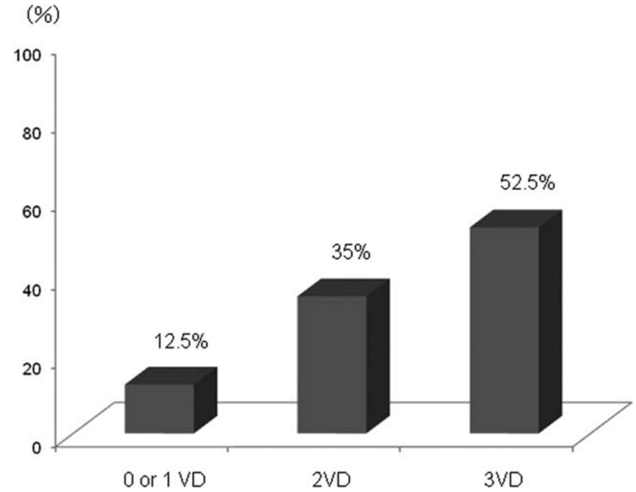

Fig. 3. Extent of crural artery disease. VD, vessel disease.

Diagnostic Angiography

Digital subtraction angiography (DSA) was performed with InnovaChase, Innova 3100 (GE Medical Systems, USA) via a contralateral femoral approach. Especially, DSA stepping facilitated the appreciation of the entire image of the lower limb artery. Infrapopliteal angiography was performed via the diagnostic catheter that was placed at the popliteal artery in order to achieve accurate evaluation of the distal tibial arteries, dorsalis pedis artery, and plantar arteries. Angiograms were assessed at an independent core laboratory (Cardiovascular Core Analysis Laboratory, Stanford University Medical Center, Stanford, CA). Significant disease was defined as stenosis ≥50%. Crural artery disease was defined as disease of one or more of the crural arteries, and the extent of crural artery disease was classified as one-, two-, and three-vessel disease.

Statistical Analysis

Data are expressed as a mean ± SD or a number and percentage. Categorical data were compared to the chi-square test. Distributions of continuous variables were determined using the Shapiro–Wilk test. Differences between two independent cohorts were evaluated with Student's *t*-test or Welch's *t*-test for continuous, parametric variables, or the Mann–Whitney test for continuous, nonparametric variables between the two independent groups. One-way analysis of variance was used to determine whether there were significant differences in hemodynamic data relative to the number of diseased crural vessels. Paired *t*-test and Wilcoxon signed rank test were used for continuous, parametric variables and continuous, and nonparametric variables, respectively, to evaluate posture-related differences in hemodynamic data. Linear regression was performed to investigate the correlation between the macro- and microcirculation. *P*-values <0.05 were considered significant. SPSS version 11.0 (SPSS, Chicago, IL) was used for all analyses.

RESULTS

The clinical and angiographic demographics are shown in Table I. The mean age was 67 ± 10 years (range, 46–82). Diabetes mellitus (DM) was the predominant complication in 79%, followed by chronic renal failure in 72%. Diagnostic angiography demonstrated a significantly ($P < 0.001$) different distribution of the affected segment in the lower limb artery with the crural artery being highly affected (39 limbs, 97.5%; Fig. 2). The infrapopliteal variant was not included in this study, except for one case of the type 2 variant [8]. In the region of the crural artery, a significantly ($P < 0.001$) specific distribution of the affected artery was observed, with anterior tibial artery (87.5%) being highly affected, followed by posterior tibial artery (85%; Fig. 2). The number of diseased crural arteries also showed a significant difference ($P = 0.002$; Fig. 3). In the region of the foot artery, the plantar artery showed a trend toward a higher occlusive lesion compared to the dorsalis pedis artery ($P = 0.104$). However,

TABLE II. Comparison of Foot Circulation Variables Based on the Extent or Location of Lesions

	Ankle-brachial index	*P* value	Ankle pressure (mm Hg)	*P* value	Dorsal SPP (mm Hg)	*P* value	Plantar SPP (mm Hg)	*P* value
Diseased segment		0.171		0.754		0.079		0.601
Single level disease ($n = 20$)	0.79 ± 0.27		147 ± 30		34.2 ± 13.8		33.8 ± 17.4	
Multilevel disease ($n = 20$)	0.64 ± 0.40		150 ± 26		44.1 ± 20.9		36.8 ± 19.5	
Number of crural artery disease		0.485		0.399		0.415		0.967
0 or 1 vessel disease ($n = 5$)	0.61 ± 0.39		89 ± 59		40.7 ± 23.1		37.2 ± 18.8	
2 vessel disease ($n = 14$)	0.78 ± 0.32		125 ± 51		42.2 ± 14.0		36.8 ± 19.9	
3 vessel disease ($n = 21$)	0.70 ± 0.37		104 ± 66		37.1 ± 20.2		33.8 ± 18.0	
Dorsalis pedis artery disease		0.496		0.205		0.422		0.129
Absence ($n = 18$)	0.61 ± 0.41		93.9 ± 68.2		35.7 ± 17.5		29.0 ± 19.6	
Resence ($n = 22$)	0.77 ± 0.28		118.6 ± 53.1		38.4 ± 15.5		37.4 ± 14.5	
Plantar artery disease		0.187		0.126		0.726		0.134
Absence ($n = 11$)	0.64 ± 0.38		88.8 ± 64.7		38.6 ± 15.7		40.3 ± 18.9	
Presence ($n = 29$)	0.72 ± 0.34		114.6 ± 58.9		36.6 ± 16.7		31.1 ± 16.3	

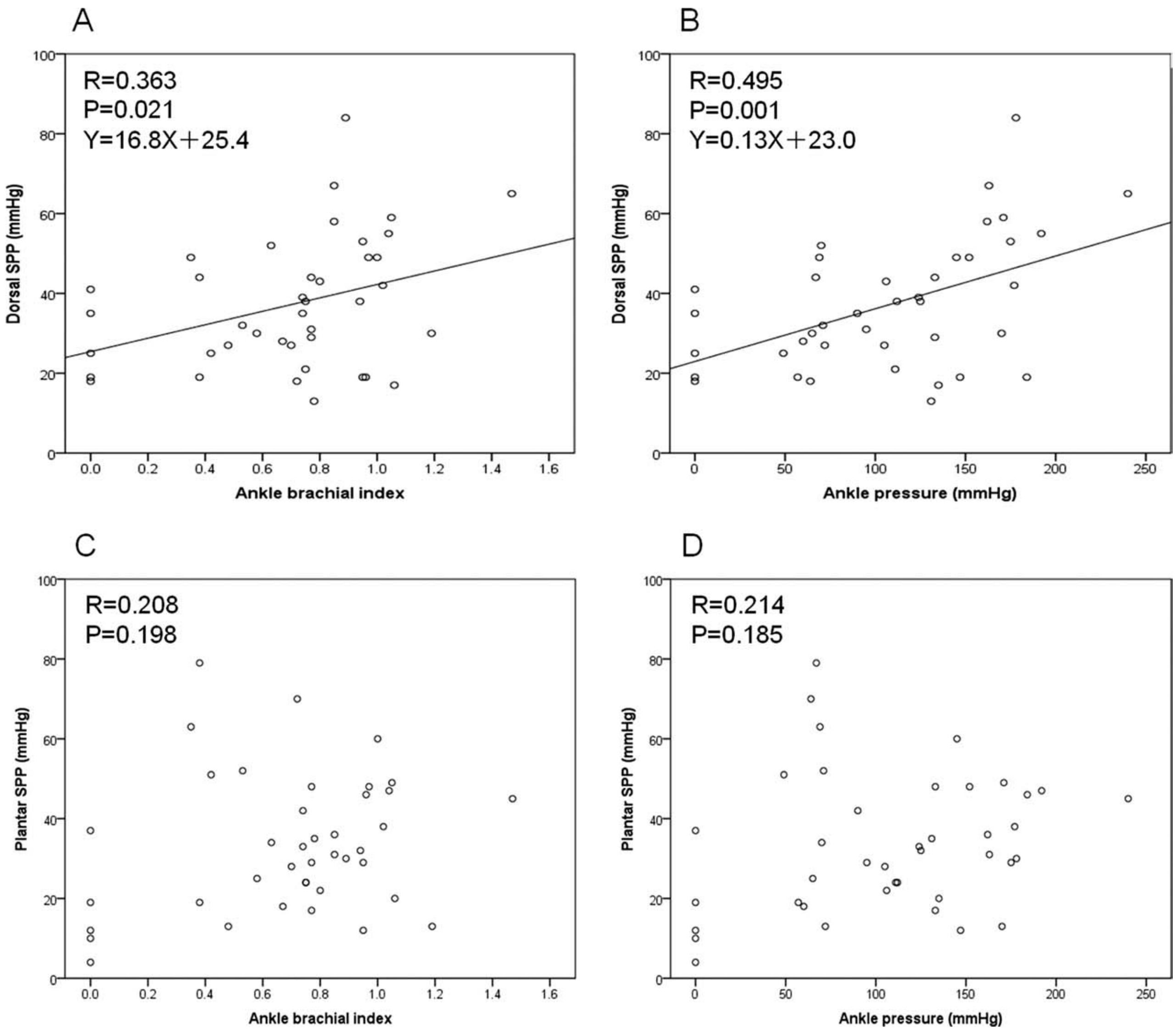

Fig. 4. Relationship between the macro- and microcirculation in the supine position. A: Dorsal SPP versus ankle-brachial index. B: Dorsal SPP versus ankle pressure. C: Plantar SPP versus ankle-brachial index. D: Plantar SPP versus ankle pressure.

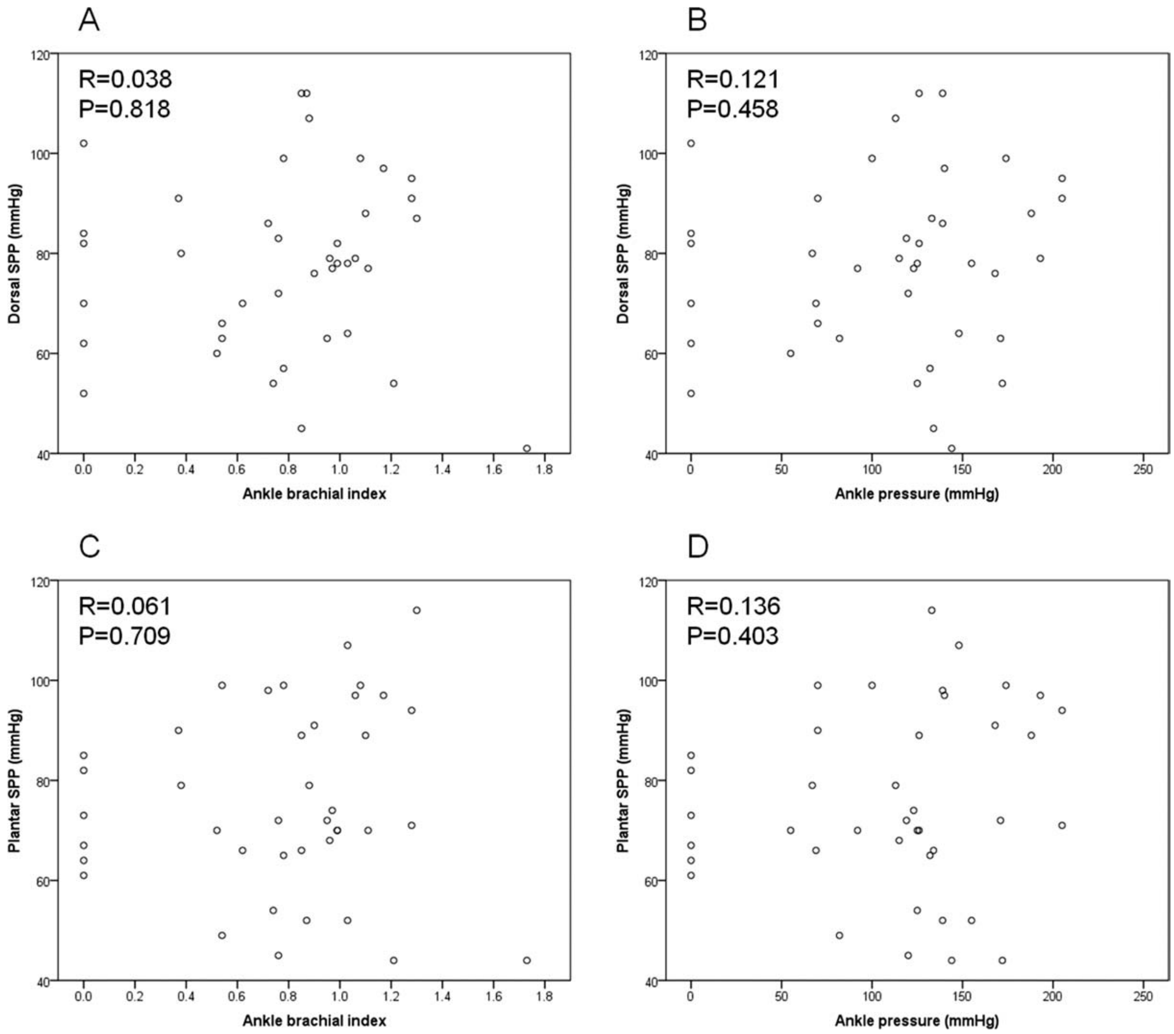

Fig. 5. Relationship between the macro- and microcirculation in the dependent position. A: Dorsal SPP versus ankle-brachial index. B: Dorsal SPP versus ankle pressure. C: Plantar SPP versus ankle-brachial index. D: Plantar SPP versus ankle pressure.

there was no significant difference in ABI, ankle pressure, and SPP (dorsal and plantar) between the angiographical extent of any of the lesions (Table II).

In the supine position, the dorsal SPP correlated significantly but mildly with ABI ($P = 0.021$, $r = 0.363$) and ankle-pressure ($P = 0.001$, $r = 0.495$; Fig. 4A and B), whereas the plantar SPP did not exhibit a significant correlation with either ABI ($P = 0.198$, $r = 0.208$) or ankle-pressure ($P = 0.185$, $r = 0.214$; Fig. 4C and D). In the dependent position, however, SPP did not correlate significantly with either ABI or ankle pressure (Fig. 5).

Postural change from the supine to the dependent position yielded a significant increase in SPP (dorsal: 37.2 ± 16.2 to 77.9 ± 17.7 mm Hg, $P < 0.001$; plantar: 33.6 ± 17.3 to 75.7 ± 18.3 mm Hg, $P < 0.001$) as well as ABI and ankle-pressure (ABI: 0.70 ± 0.35 to 0.78 ± 0.42, $P = 0.003$; ankle-pressure; 108 ± 61 to 111 ± 60 mm Hg, $P = 0.038$) (Fig. 6). The postural change of SPP did not differ regardless of the presence of any clinical complications, such as DM, renal failure, hypertension, or dyslipidemia. Also, the location and extent of the lesion was not associated with postural change of SPP.

DISCUSSION

To the best of our knowledge, the present study is the first to investigate the macro- and microcirculation in the setting of contemporary CLI using currently available hemodynamic and angiographic tools.

With changing demographics worldwide, an increasing number of CLI patients with DM and/or renal failure have emerged. In the present study, in which DM and renal failure were observed in 79% and 83%,

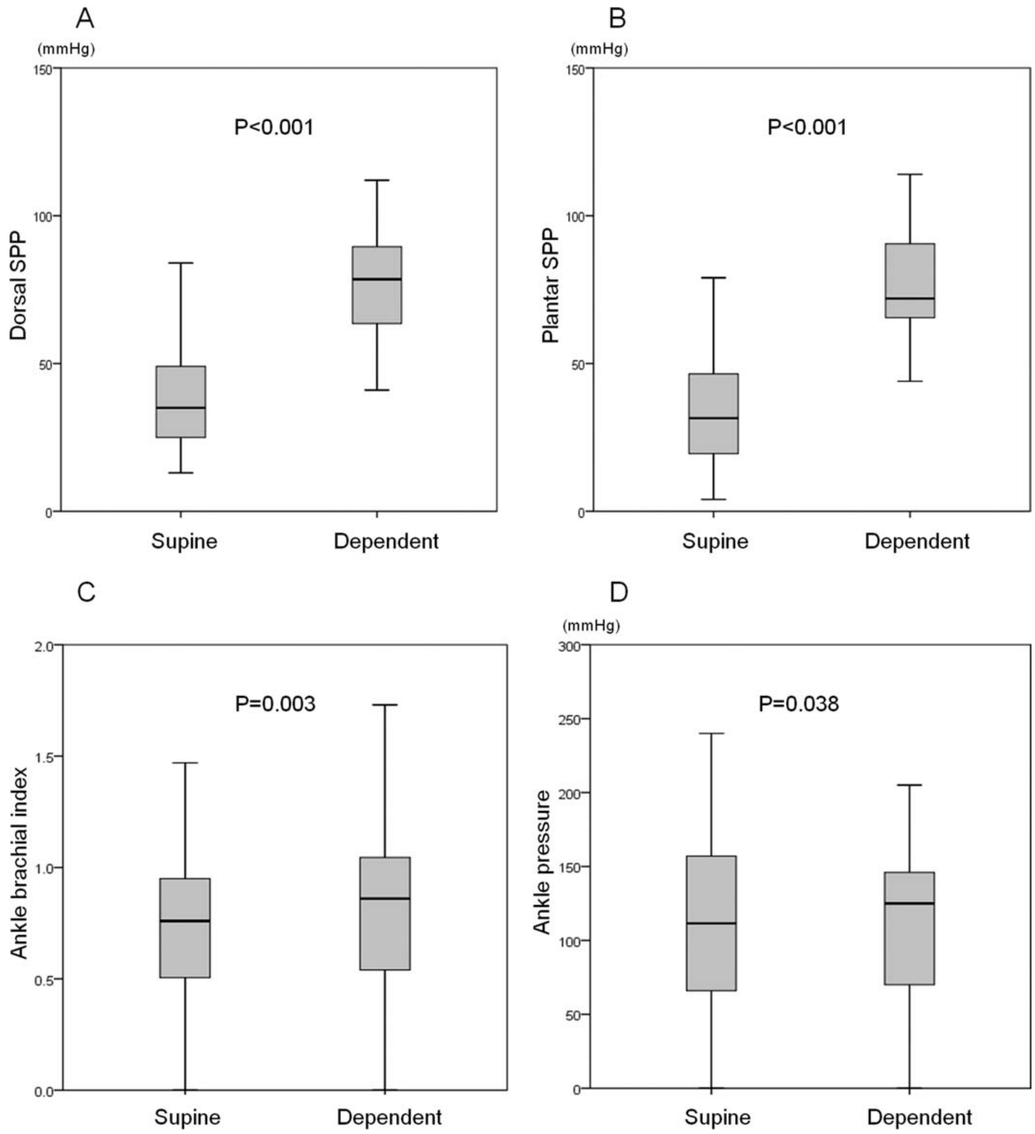

Fig. 6. Change of the macro- and microcirculation from the supine to dependent position. A: Dorsal SPP. B: Plantar SPP. C: Ankle-brachial index. D: Ankle pressure.

respectively, CLI patients had a significantly specific distribution of affected vessels. Indeed, crural artery disease was the mainstay of CLI, followed by superficial femoral artery. Moreover, the crural artery showed a significantly different extent of disease with three vessels predominantly affected, which is consistent with findings of previous studies [9]. Also, the present study showed that 73% of patients yielded plantar artery disease, whereas 55% exhibited dorsalis pedis artery disease. These findings suggest that contemporary CLI could be characterized by more distal and sole occlusive disease. Of great interest, even SPP, which is representative of the microcirculation, was not associated with any specific angiographic findings although there might be a potential lack of statistical power to detect significance. Therefore, the development of collateral vessels through branches of the main vessels could contribute to the supply of the blood flow to the foot threatened by critical ischemia.

Evaluation of the macrocirculation, through assessment of ABI and ankle pressure, can certainly translate to improve patient care for peripheral arterial disease [10,11]. However, these macrocirculation markers can cause a falsely high value, due to excessive calcification of the tibial artery [12]. Also, the macrocirculation cannot represent the blood flow below the ankle. Thus, with the limited utility of the macrocirculation assessment, enthusiastic investigation of the microcirculation appears to be mandatory in the setting of CLI [13,14] (Fig. 7). According to the recent studies [2,15], SPP is

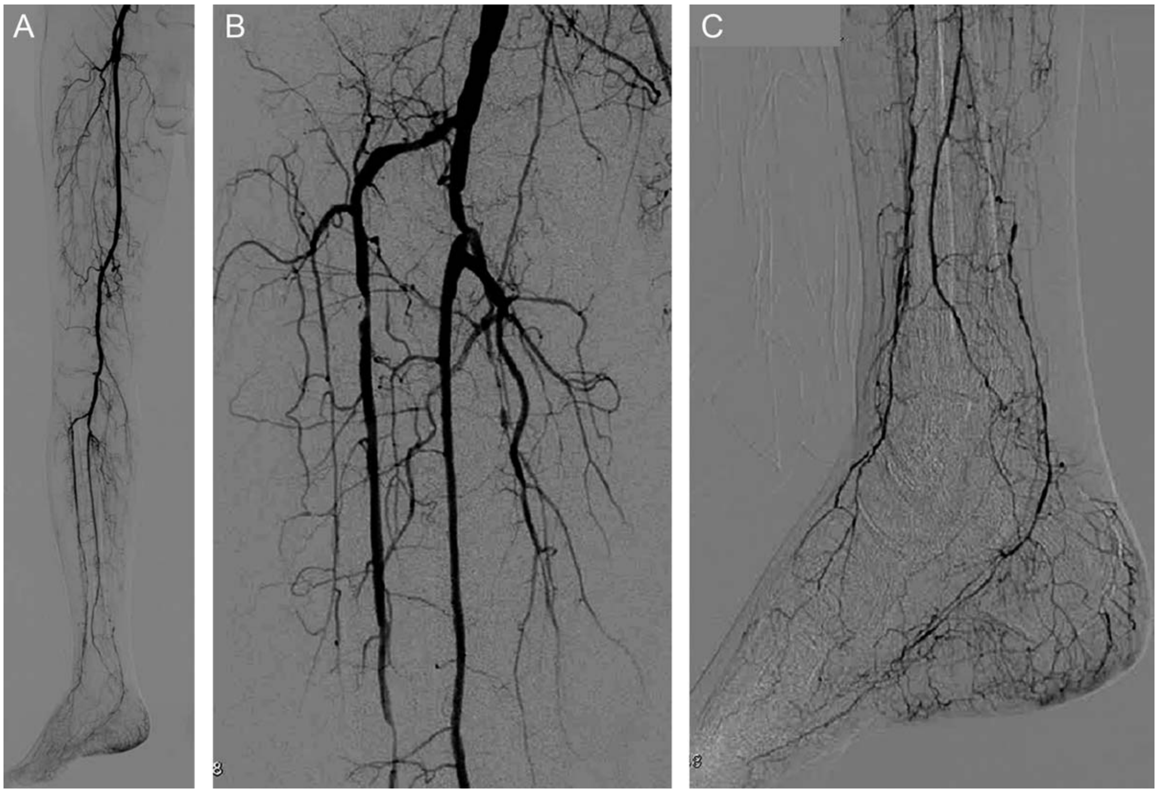

Fig. 7. Representative case of discrepancy between the macro- and microcirculation values. A: A 74-year-old male with tissue loss of Rutherford category 5 in the right foot, complicated by diabetic nephropathy. The entire image showing the severe single level disease of the infrapopliteal artery. The skin perfusion was 19/46 mm Hg (dorsal/ plantar) suggesting critical limb ischemia, whereas the ankle brachial index was 0.96 and ankle pressure was 191 mm Hg. B: Magnified view of the proximal crural artery showing significant stenosis in the anterior tibial and tibioperoneal arteries. Also, the posterior tibial artery is completely occluded. C: Magnified view of the distal crural and foot arteries showing severely affected distal anterior tibial and dorsalis pedis arteries. The reconstituted posterior tibial artery to medial and lateral plantar arteries were also severely diseased.

a more reliable tool to detect severe peripheral arterial disease with calcified vessels and to predict healing of ischemic wound than other macro- and microcirculation evaluation tools (ABI, ankle pressure, toe brachial index, toe pressure, and $TcPO_2$). Given the simplicity, accuracy, and reproducibility of SPP examination in clinical practice, SPP can be considered a modern noninvasive method in the evaluation of the foot circulation. In a few previous studies, "dorsal" SPP correlated significantly with toe pressure as well as ABI [2,16,17]. However, "plantar" SPP has been underappreciated. The present study showed that only the dorsal SPP correlated significantly but weakly with ABI and ankle pressure in the supine position, whereas plantar SPP did not. This finding suggests the need for better awareness of an uneven relationship between the macro- and microcirculation at the dorsal and plantar sides, presumably due to the higher frequency of occlusive lesions in the plantar artery compared to the dorsalis pedis artery, as shown in Figure 2. Also, in the present study, the dependent position showed no relationship between the macro- and microcirculation, suggesting that the effect of gravity when in the dependent position could elicit a different impact on foot circulation compared to the supine position.

In the "clinical" setting, ischemic rest pain generally worsens when the legs are elevated, such as when lying in bed at night. Relief from the pain occurs only when the feet are dangled. However, despite the advancement of noninvasive diagnostic tools, "hemodynamic" data are scanty regarding this gravity's favorable effects in CLI patients. The present study clearly demonstrated a dramatic improvement of microcirculation (SPP) by postural changes (37.2 ± 16.2–77.9 ± 17.7 mm Hg on the dorsal side and 33.6 ± 17.3–75.7 ± 18.3 on the plantar side), whereas a slight change of macrocirculation (ABI and ankle pressure) was observed. Also, this beneficial change of SPP was independent of any angiographical variables. These findings suggest that postural change from the supine to dependent position in CLI patients elicited ~40 mm Hg of SPP, due to the effect of gravity, and that the response of SPP as microcirculation index to postural changes could be achieved via the development of collateral vessels. Furthermore, the beneficial effects of postural change on microcirculation could represent a reasonable explanation for getting out of bed helps to relieve rest pain that occurs at night, when the patient is lying flat on the bed.

Limitations

There are some limitations of this study that should be taken into consideration.

First, the present study has a limited number of patients. Second, ABI and ankle pressure were used as markers of macrocirculation. However, these tools might not accurately reflect the degree of macrocirculation impairment due to the inherent potential for falsely high values, especially in CLI patients. Third, there is the possibility that SPP was not measured at the most ischemic site in the foot. Fourth, this study did not address the degree of collateral vessel involvement, which is challenging to determine objectively by angiographic investigation. With the advancement of vascular imaging, the "quantitative and qualitative" assessments of collateral vessels might be of great help in understanding how the development of collateral vessels could influence the foot circulation. Finally, as normal and claudication subjects are not included in this study, further investigations of foot circulation using contemporary available tools in non-CLI patients might also be required to compare with those in CLI patients.

CONCLUSIONS

Of microcirculation assessed, only dorsal SPP correlated significantly with macrocirculation in the supine position. Also, microcirculation was sensitive to postural changes due to the effect of gravity. Thus, the measurement of foot circulation in the supine position is clearly unrepresentative of the conditions to which the peripheral circulation must generally adapt, except during sleep. We emphasize the need for a better awareness of microcirculation in the setting of CLI, and a large outcome driven study on SPP-guided limb salvage could generate widespread use of SPP.

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