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Laser speckle flowgraphy can also be used to show dynamic changes in the blood flow of the skin of the foot after surgical revascularization

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Abstract

Objectives: Laser speckle flowgraphy is a new method that enables the rapid evaluation of foot blood flow without contact with the skin. We used laser speckle flowgraphy to evaluate foot blood flow in peripheral arterial disease patients before and after surgical revascularization.

Materials and methods: A prospective single-center study. Thirty-one patients with 33 limbs that underwent surgical revascularization for peripheral arterial disease were included. Pre- and postoperative foot blood flows were measured on the plantar surface via laser speckle flowgraphy and skin perfusion pressure. The laser speckle flowgraphy device was used to visualize the blood flow distribution of the target skin and processed the pulse wave velocity of synchronized heart beats. The mean blood flow, which was expressed as the area of the pulse wave as the beat strength of skin perfusion on laser speckle flowgraphy converted into a numerical value, was assessed as dynamic changes following surgery. Beat strength of skin perfusion was also investigated in non-peripheral arterial disease controls (23 patients/46 limbs).

Results: The suitability of beat strength of skin perfusion in non-peripheral arterial disease controls was achieved; the beat strength of skin perfusion value was significantly higher in every area of interest in non-peripheral arterial disease controls compared to that in peripheral arterial disease limbs at the preoperative stage (105.8 ± 8.2 vs. 26.3 ± 8.2; $P < 0.01$). Although the pulse wave before surgery was visually flat in peripheral arterial disease patients, the pulse wave was remarkably and immediately improved through surgical revascularization. Beat strength of skin perfusion showed a dynamic change in foot blood flow (26.3 ± 8.2 at preoperation, 98.5 ± 6.7 immediately after surgery, 107.6 ± 5.7 at seven days after surgery, $P < 0.01$ for each compared to preoperation) that correlated with an improvement in skin perfusion pressure.

Conclusions: Laser speckle flowgraphy is a noninvasive, contact-free modality that is easy to implement, and beat strength of skin perfusion is a useful indicator of foot circulation during the perioperative period. Further analysis with a larger number of cases is necessary to establish appropriate clinical use.

Keywords

Peripheral artery disease, laser speckle flowgraphy, beat strength of skin perfusion, foot blood flow, surgical revascularization, pulse wave

Introduction

The prevalence of peripheral arterial disease (PAD) continues to increase all over the world[1,2] due to the substantial increase in the frequency of diabetes mellitus (DM).[3–5] Revascularization, either via endovascular therapy (EVT) or surgical revascularization, is an

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essential technique to improve the ischemic symptoms with PAD, including intermittent claudication, rest pain, and gangrene.[6–9] Revascularization is particularly needed for critical limb ischemia (CLI) to improve foot blood flow for limb salvage. However, no device exists that can capture dynamic blood flow changes during revascularization, which demonstrates the need to develop new methods that can be easily and quickly implemented to accurately assess the effect of revascularization. Patients who have foot pain, extensive tissue loss, and/or infectious foot gangrene are sometimes difficult to evaluate with typical ischemia estimation measures such as the ankle brachial index (ABI), skin perfusion pressure (SPP), and transcutaneous oxygen ($TcPO_2$),[10,11] which have been widely accepted as noninvasive measurements for the assessment of the severity of PAD, including the evaluation of CLI. The former two measures involve skin-contact devices that can cause pain. SPP is also time-consuming method (5 min per measurement).[12] Although $TcPO_2$ is a noninvasive modality used to evaluate foot blood flow as well as wound healing potential, some problems still exist with its use, including lengthy test time and variable results.[13]

Laser speckle flowgraphy (LSFG) is a noninvasive technology based on the laser speckle phenomenon, which is an interference event observed when coherent light sources, such as lasers, are scattered by a diffusing surface (i.e., the scattered pattern varies rapidly depending on the movement of blood cells and choroid in the tissue), and has been used for the assessment of microcirculation in ophthalmology, especially for the evaluation of blood flow to the optic nerve head and the retinal vessels.[14] This was recently approved as a medical device to evaluate foot hemodynamics in Japan. Additionally, Nagashima reported that LSFG was a useful method for cutaneous blood flow evaluation compared to strain-gauge plethysmography, which is used to measure the absolute value of blood flow.[15] The advantages of LSFG technology are as follows: (1) the ultrashort time required for measurement (only 4 s), (2) contact-free measurements with no pain that permit the evaluation of blood flow in infected feet and individuals with extensive tissue loss, and (3) the acquisition of time-dependent blood flow images.

The aim of this study was to evaluate whether the new LSFG technology can capture dynamic changes in foot blood flow following surgical revascularization for PAD.

Materials and methods

This was a prospective single-center study that was approved by the regional ethics committee of Asahikawa Medical University. Patients, including non-PAD controls, provided informed consent for this research regarding the use of a new modality, LSFG, for the evaluation of foot blood flow. Between October 2015 and May 2016, 48 limbs from 46 PAD patients underwent infrainguinal surgical revascularization at Asahikawa Medical University Hospital. Limbs were excluded if ABI or SPP could not be measured, the patient was discharged from our institute within one week after surgery, there was an emergency, or the patient had early graft thrombosis or early death after surgery. Thirty-three limbs (from 31 patients) were included in this study. Data on patient risk factors, comorbidities were obtained preoperatively at admission. Comorbidities that were examined included coronary artery diseases, hypertension, tobacco use, DM, and cerebrovascular diseases.

Surgical procedures

Complete revascularization was performed. All bypasses for arterial lesions distal to the popliteal artery at the knee were performed using vein grafts except for the use of one Propaten prosthetic graft (Gore). EVT, endarterectomy with patch angioplasty, or bypass using vascular prosthesis was employed for inflow lesions. Completion angiography after surgical revascularization was performed. Bypass to the below-the-knee popliteal artery, crural artery, and pedal artery bypass were performed in 9 limbs (27.2%), 9 limbs (27.2%), and 14 limbs (42.4%), respectively. One limb underwent revascularization with infrainguinal endarterectomy.

Ischemia evaluations

ABI was measured only preoperatively. Postoperative ABI measurement was avoided due to fresh surgical wounds and graft compression immediately after distal bypass surgery. SPP was measured preoperatively, immediately three and seven days after surgical revascularization under uniform testing conditions; the ambient room temperature was set at 22–23°C. The core temperature was also measured each time. A laser Doppler probe beneath a 5.8-cm-wide blood pressure cuff (PHILIPS, Amsterdam, The Netherlands)[16] was placed on the medial and lateral sides of the plantar aspect of the foot; the probe was placed between the first and second toes for the medial side and between the fourth and fifth toes for the lateral side.

The LSFG technology

LSFG-PIE (Softcare Co., Ltd., Fukuoka, Japan) was used to evaluate foot hemodynamics. This device can visualize the blood flow distribution of the target skin

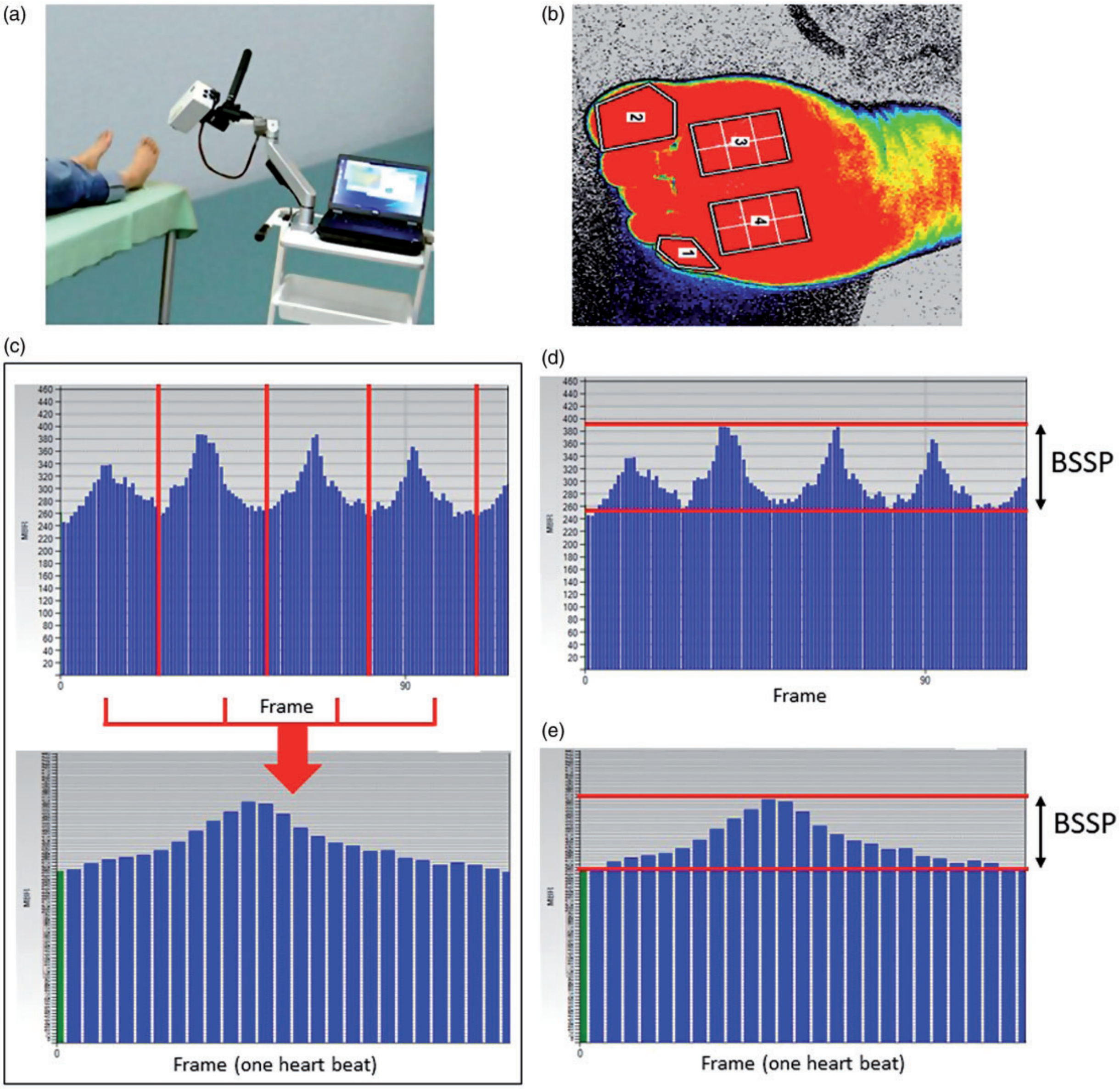

Figure 1. Photograph of the measurement of foot blood flow using laser speckle flowgraphy (LSFG) (a) and a 2-D color-coded map with the four regions of interest examined in this study (b). Processing of the pulse wave velocity (MBR in the y-axis) synchronized with 4.5 heartbeats for 4 s in one of the study subjects, whose heart rate was 68 heartbeats per minute. The red dotted line separates a heartbeat and shows four sections with approximately 27 flames in the x-axis (top) as well as a representative synthesized pulse wave (bottom) (c). The amplitude of the pulse wave is expressed as the beat strength of skin perfusion (BSSP) (d). A synthesized pulse wave with one heartbeat and averaged BSSP were also calculated (e).

on the foot in a 20 × 15 cm section from a working distance of 25 cm above with a map of 710 (width) × 480 (height) pixels (Figure 1(a)). The standard measuring time is 4 s, and data analysis is completed in 10 s, demonstrating that near real-time measurement is possible. A diode laser with an 830-nm wavelength emitted from the camera unit illuminates the entire foot area and reaches the dermis (1-mm depth), where it is mainly scattered by a number of moving red blood cells. The scattered light returns to the image sensor in the camera unit, and the interference produces a moving laser speckle field. The motion speed of speckles detected at each pixel point in the image field is proportional to the average velocity of the red blood cells moving at the corresponding objective point. The faster movement of blood cells causes more blurring in the capture process of the speckle pattern. The software calculates the mean blur rate (MBR) of the moving speckle image and displays the result with a series of 2-D color-coded maps (Figure 1(b)). The MBR values are recognized as the signal strength conducted by heartbeats, which is a quantitative index of relative blood flow velocity and have been widely used to observe retinal blood flow by ophthalmologists.[17,18] In the screen of the LSFG-PIE, the MBR maps are shown sequentially with 120 flame-shaped flows for 4 s to observe the blood flow change, providing the ability to chronologically and quickly grasp the pulse wave form. In addition, the software provides a display that the manufacturer calls the Heartbeat Map, which represents multiple blood flow maps by searching heartbeat timing in the 120 flames and averaging them into a form for a single heartbeat (Figure 1(c)) by setting region of interest (ROI) areas (max six areas) in the blood flow map, as shown in Figure 1(b). Using this approach, we can examine and compare the pulse wave forms for each area synchronized with the cardiac cycles. Thus, LSFG technology expresses blood flow as signal strength conducted by heartbeats at a cutaneous depth. Medical staff can use this device by following the instructions and without specific training.

In this study, LSFG tracked the measurement field at the first and fifth toe in addition to the two points of the plantar surface indicated in the SPP with the same time course under uniform conditions. For the dorsum, the LSFG exhibits the possibility for inaccurate measurement given the curved and rugged surface; thus, we omitted the dorsum data from our analysis.

Beat strength of skin perfusion (BSSP) as a new indicator in LSFG

BSSP is provided by the device manufacturer as a new parameter that shows an average amplitude of dynamic cutaneous blood flow change synchronized with heartbeats obtained from an ROI (Figure 1(d)). There are variations in the blood flow waves for each cardiac cycle, and the BSSP value is essentially calculated by averaging the variation and averaging the amplitude of the blood flow (Figure 1(e)). The BSSP value was calculated from the difference in MBR between the maximum and the minimum individual blood flow waves (arbitrary unit). MBR is automatically calculated and is displayed immediately after the measurement on the y-axis of the image. The calculation formula has been disclosed through the patent application (patentscope.wipo.int/search/en/detail.jsf?docId=WO2018003139). BSSP is a more detailed numerical value that demonstrates the signal strength by heartbeats that is conveyed to the cutaneous tissue of the foot.

Statistics

Data were reported as the mean and standard error of the mean or as percentage for dichotomous variables. Paired and unpaired *t*-tests were used to compare continuous variables between two groups. Comparisons of measures between two groups or between various time courses were performed using a repeated measures analysis of variance with Bonferroni correction as needed. A p value ≤ 0.05, assessed with SPSS version 24 (IBM, Chicago, USA) was considered statistically significant.

Table 1. Characteristics of patient population at preoperation.

	33 Limbs
Age	72.1 ± 1.7
Female gender	13 (39.4%)
Body mass index	23.5 ± 0.8
Hypertension	27 (81.8%)
Diabetes mellitus	19 (57.6%)
Hemodialysis	15 (45.5%)
Hyperlipidemia	10 (30.3%)
Cerebrovascular disease	6 (18.2%)
Ischemic heart disease	14 (42.4%)
Ankle brachial index	0.39 ± 0.8
Rutherford class	
3	7 (21.2%)
4	4 (12.1%)
5	17 (51.5%)
6	5 (15.2%)

Results

The demographic data of PAD and non-PAD limbs

The characteristics of the patients are listed in Table 1. PAD limbs included 7 limbs with intermittent claudication and 26 CLI limbs. Fifteen limbs (45.5%) were in chronic kidney disease patients who received regular dialysis. Twenty-three non-PAD patients (46 limbs) were enrolled as non-PAD control subjects to investigate LSFG use (mean age 67.4 ± 0.5 years, female sex 7 (30.4%), HD 1 (4.3%), DM 11 (47.8%), Rt. ABI 1.11 ± 0.1, Lt. ABI 1.13 ± 0.1).

Comparison of foot blood flow in PAD limbs and non-PAD controls with LSFG

Before applying the LSFG technology to PAD patients, we investigated non-PAD controls to assess whether the LSFG technology could provide evidence that the blood flow evaluation translated to transcutaneous measurements in the foot. Sharp pulse wave and speckles that moved quickly in a 2-D color-coded map were observed in a non-PAD control (Figure 2(a) and 2(b)). On the other hand, slow speckle movement with no pulse wave was seen in a 2-D color-coded map from a PAD patient with gangrene (Figure 2(c)

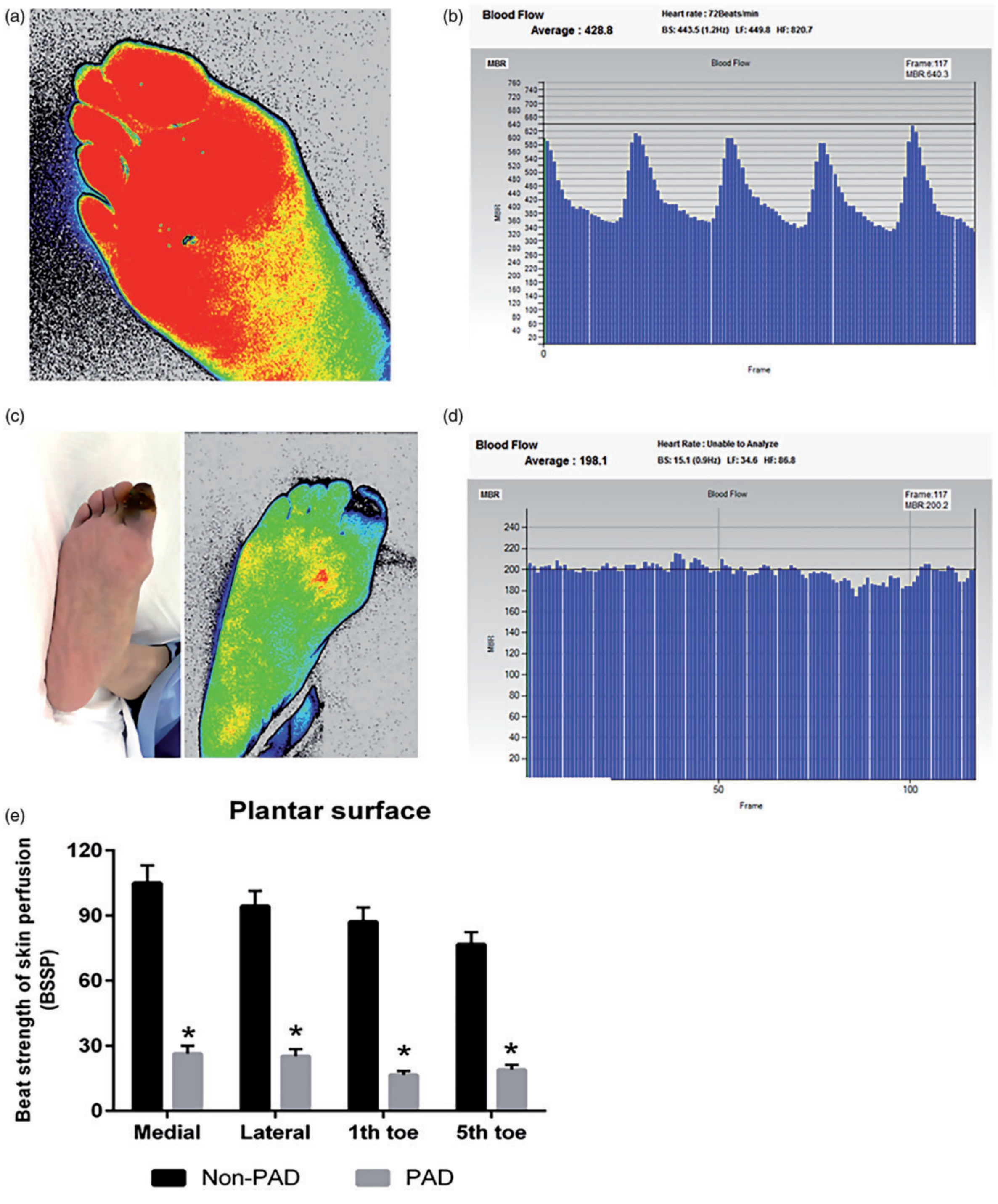

Figure 2. A 2-D color-coded map and a pulse wave velocity with heartbeats of a 77-year-old non-peripheral artery disease (PAD) control subject ((a) and (b)) and a 78-year-old PAD patient ((c) and (d)). The velocity at the medial side of the plantar aspect of the foot with the heartbeat is shown for both cases. The BSSP on LSFG in the foot is shown for all non-PAD controls ($N = 46$) and PAD limbs ($N = 33$). *$P < 0.05$ between the non-PAD control limbs and PAD limbs (e).

and 2(d)). BSSP was lower for PAD limbs compared to non-PAD controls (Figure 2(e)). Moreover, BSSP in the plantar aspect showed significant differences at every point examined: 105.0 ± 8.1 vs. 26.3 ± 3.7 at the medial foot, 94.2 ± 7.1 vs. 25.1 ± 3.3 at the lateral foot, 87.1 ± 6.7 vs. 16.5 ± 1.9 at the first toe and 76.7 ± 5.7 vs. 19.0 ± 2.1 at the fourth toe ($P < 0.01$ for each).

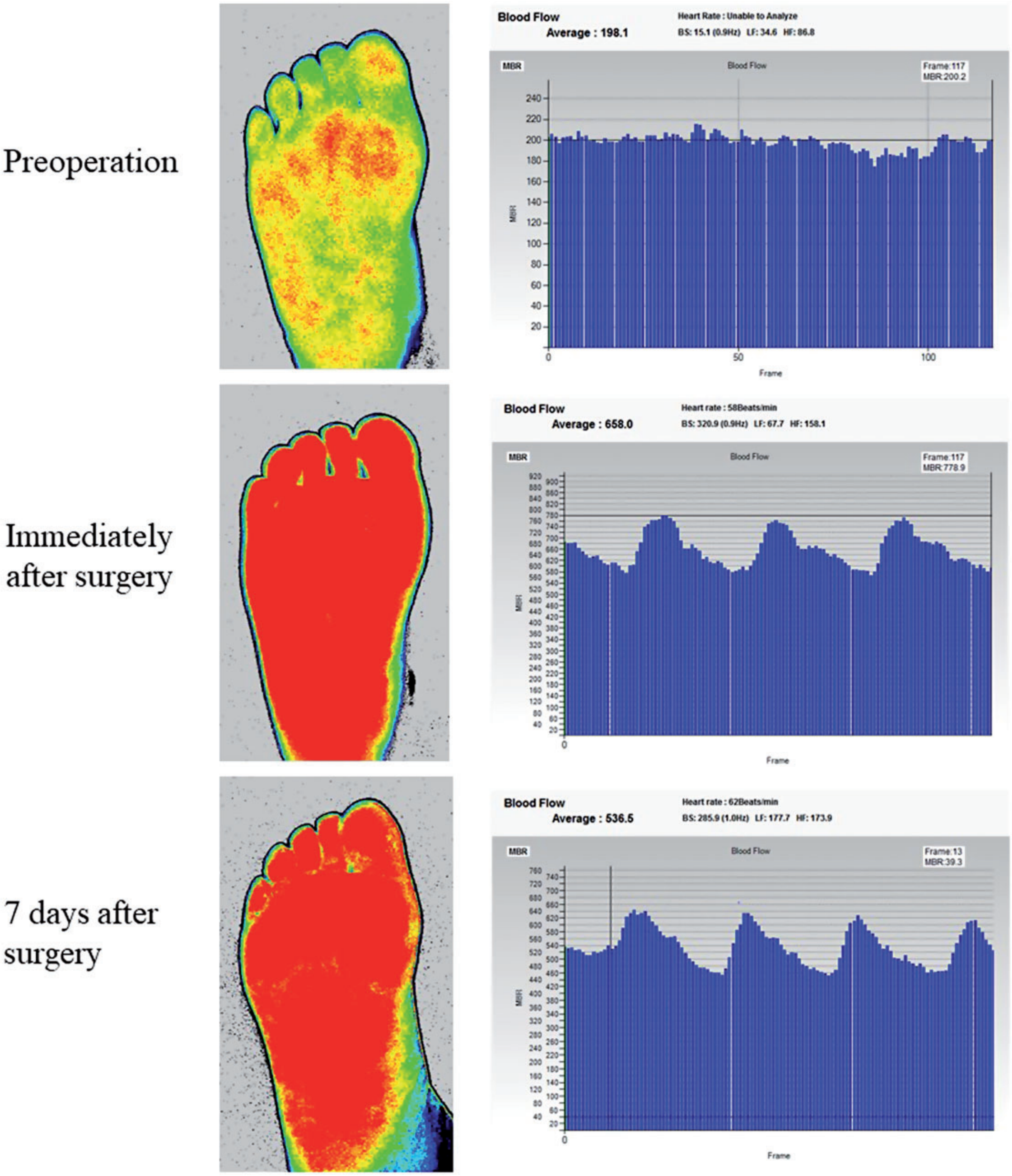

Figure 3. Pre- and postoperative color-coded maps and pulse wave velocity with heartbeats at the medial side of the plantar aspect of the foot of a 71-year-old female with critical limb ischemia who received a femoro-dorsalis pedis artery bypass.

Determination of the effect of surgical revascularization through the dynamic change in BSSP in PAD limbs

Based on the suitability in non-PAD controls, blood flow changes after surgical revascularization were evaluated. Based on the 2-D color-coded map, pulse wave and speckle movement were clearly shown to improve after surgical revascularization in a patient with CLI (Figure 3). BSSP for each point was significantly increased immediately after the procedure and reached a maximum on day 7 after revascularization

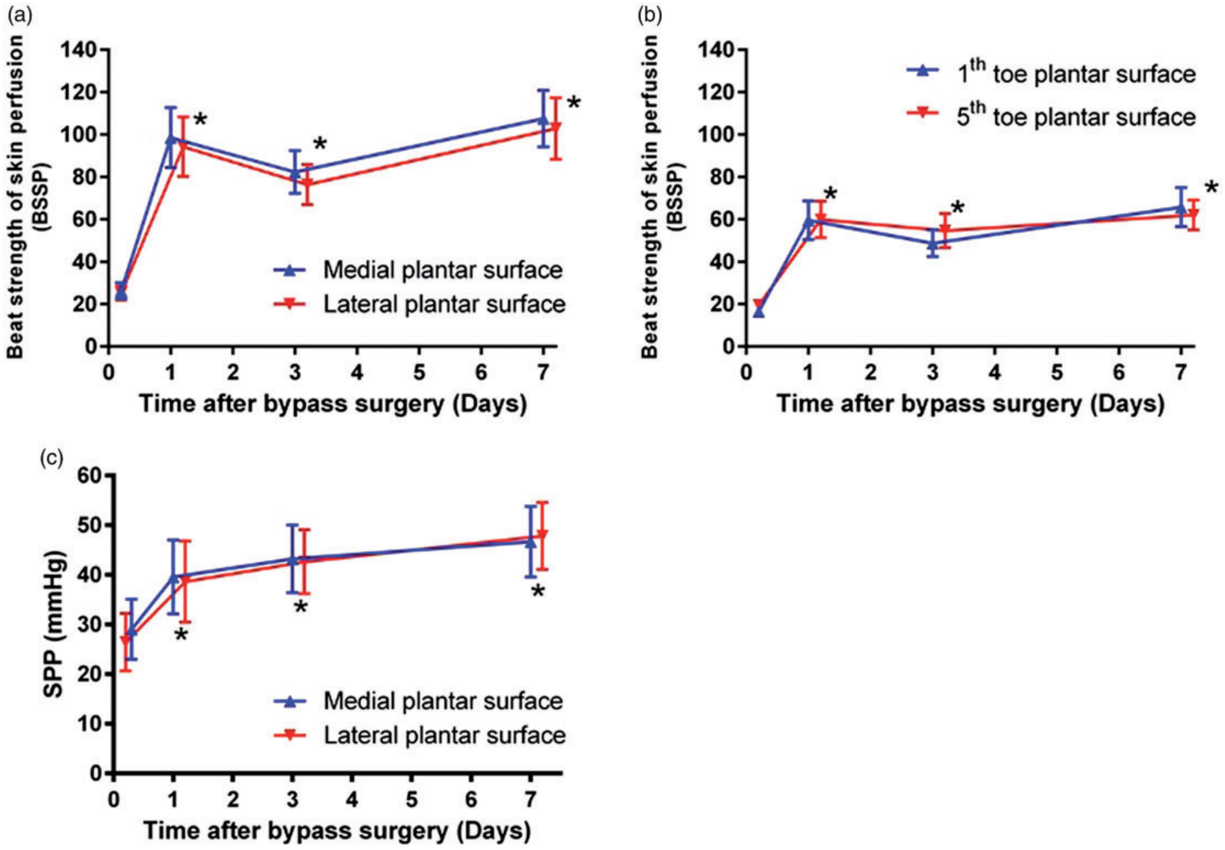

Figure 4. Blood flow changes in the feet that were evaluated ($N = 33$) after surgical revascularization using LSFG ((a) and (b)) and skin perfusion pressure (c). $^*P < 0.05$ compared to the preoperative value for each side.

compared to the preoperative value ($P < 0.01$) (Figure 4(a) and 4(b)). This improvement was correlated with a significant improvement in SPP after revascularization ($P < 0.01$ compared to preoperation) (Figure 4(c)). Thus, BSSP demonstrated the digitalized blood flow change due to revascularization immediately after surgery. Regarding the effect of core temperature changes after surgery on BSSP and SPP, the core temperature was significantly increased at day 3 compared to the preoperative temperature (36.7 ± 0.8°C on day 3 vs. 36.4 ± 0.6°C preoperation, $P < 0.01$), but the difference was not significant at day 7 (36.3 ± 0.3°C; P = 0.72), indicating that the effect appeared to be mild.

Discussion

This is the first study to evaluate foot blood flow changes with LSFG technology. The blood flow value that is assessed is BSSP, which represents the average amplitude of blood flow calculated from an individual pulse wave. Our results indicate that BSSP is suitable for assessing dynamic foot blood flow changes following surgical revascularization in the same individual, showing that BSSP remarkably and immediately increased after surgery and correlated with the improvement in SPP.

LSFG is a noninvasive technique that can cover a large field and measure the real-time, 2-D relative blood flow velocity of the foot via the laser speckle phenomenon. The amplitude of the pulse wave, specifically BSSP, is an important factor in this study as demonstrated by the result between PAD and non-PAD limbs. In comparison with other devices, LSFG exhibits superiority regarding blood flow dynamics compared with color thermography. LSFG is a noninvasive and contrast- and contact-free modality, and reduced patient stress to a single measurement. This device is easy to handle and can be used at the bedside. Use of SPP and $TcPO_2$ is typically limited due to extensive tissue loss and infective wounds given the need for direct contact and the length of time required to obtain accurate data. LSFG offers these advantages over thermography, positron emission tomography, and $TcPO_2$. Although this method produces a relative value of blood flow velocity, in ophthalmology, LSFG has emerged as a promising method for the measurement of ocular perfusion in humans and was recently granted clearance by the US Food and Drug Administration for the quantitative evaluation of blood flow in retinal vessels.[19] Thus, the flow data obtained from LSFG have been studied for more than 20 years, with accumulating evidence showing that correlations can be made with absolute blood flow from laser Doppler velocimetry.

BSSP is sensitive to improvements in foot blood flow immediately after surgical revascularization, and as a result, it can be used to judge the effect of revascularization during surgery. We propose using LSFG for a judgment of additional revascularization during operation as well as postoperatively, timing of reintervention for stenotic lesions through a detection of decreased blood flow as further clinical uses. In addition, LSFG can be used to analyze the relationship between BSSP and wound healing. LSFG offers the following advantages in wound healing prediction: (1) measurement areas include ulcers and surrounding skin, predicting focal wound healing ability; (2) this device can measure pulsation flow with heartbeats delivered to an ulcer through evaluation of dynamic changes of focal movement of blood cells not focal temperature. These are specific points of the LSFG device. Although ABI is a simple, noninvasive, widely used test that detects PAD, there are several limitations of ABI measurement in wound healing prediction: (1) ABI cannot predict wound healing of a foot ulcer in a patient with below-the-ankle arterial disease directly based on the ankle blood pressure measurement; (2) for evaluation of cutaneous blood flow of the ROI, focal measurement of BSSP by the LSFG device is more specific compared with ABI, which can predict blood flow of the entire foot; (3) ABI is typically inaccurate in cases with incompressible arteries due to severe calcifications.[20,21] We have started studying the usefulness of LSFG in foot blood flow evaluation for EVT, and wound healing is prospectively evaluated through the change in BSSP detected around wounds with time after revascularization, including EVT and bypass surgery.

The software used for LSFG provides an analysis of the MBR pulse waveform relative to the cardiac cycle. Various analytic parameters have been used to evaluate blood flow to the optic nerve with LSFG,[17,22–25] which can be used to assess the degree of arteriosclerosis and vascular resistivity. Although a future goal is to use LSFG technology for foot ischemia screening, especially the prevention of the onset and progression of CLI, further studies focusing on the development of LSFG technology for retinal blood flow evaluation and including a large number of PAD patients and non-PAD controls are essential. If this instrument can be improved so that anyone can use it, it may be applicable to a variety of clinical uses, such as a remote medical diagnosis system to close the urban/rural gap of the prevalence of CLI for patients who are unable to visit a vascular specialist.[26]

SPP is useful not only for assessing ischemia severity but also for predicting the self-healing capability of wounds without revascularization.[13,16,27] Moreover, SPP is described as an indicator of local perfusion in the 2016 American Heart Association PAD guidelines.[28] The correlation between SPP and BSSP with LSFG was significant ($P < 0.01$), although the correlation coefficient was moderate (approximately 0.6). The measurement depth for these two modalities (LSFG and SPP) appears to be similar, although the measurement methods are theoretically different. SPP is measured with the laser Doppler method and permits the absolute quantification of foot blood flow, while SPP is a microcirculatory perfusion measurement that is obtained during cuff deflation with a laser Doppler scanner and shows that skin microcirculatory perfusion begins to flow after foot compression.[29] In other words, SPP is a functional measurement of the microcirculatory perfusion of the skin regardless of the amount or velocity of blood flow in the foot, and LSFG is a measurement of the steady flow of blood in the foot without the skin interrupting the flow. The moderate correlation should be considered as a reference.

Regarding LSFG use for the dorsum of the foot, BSSP was lower on the dorsum compared with the plantar surface for PAD and non-PAD limbs (Supplemental Figure A). Although the increase in BSSP on the plantar surface was considerably increased compared with the dorsum after revascularization, SPP significantly improved revascularization on both sides (Supplemental Figure B and C). The following reasons potentially explain this finding: (1) The reflection of the laser to the camera could be reduced by laser scattering as a result of the curved and rugged surface due to flexor tendons of the dorsum of the foot, resulting in inaccurate measurement; (2) LSFG could reveal that the plantar aspect exhibits increased blood flow given its greater vascularity with thicker subcutaneous tissue compared with the dorsum. However, in this study, the difference in blood flow between the dorsum and the plantar surface remains inconclusive, and future studies should further investigate these differences. Regarding the aim of this study, measurement of the plantar surface of the foot using LSFG is more useful for the evaluation of foot blood flow compared with the dorsum.

One limitation of this study is the small number of patients included. However, the present results add to evidence supporting the usefulness of LSFG for evaluating blood flow changes after surgical reconstruction. Moreover, the results reported in this study are only from surgical revascularization, not EVT. Thus, an evaluation of the results of EVT is the next step in understanding the usefulness of LSFG.

Conclusions

LSFG is a new method for the rapid, contact-free evaluation of blood flow in the foot that also permits the visualization of blood flow in relation to the heartbeat. BSSP, which is the parameter assessed by LSFG, is useful for the evaluation of blood flow before and after surgical revascularization. Further analyses with a larger number of PAD patients and non-PAD controls are needed to assess the utility of LSFG and to establish LSFG as a new modality for further clinical use.

Declaration of conflicting interests

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