Circulation Reports
Circ Rep 2025; 7: 113–121
doi:10.1253/circrep.CR-24-0046

ORIGINAL ARTICLE
Medical Engineering

Usefulness of Blood Flow Measurement Device Using Bioelectrical Impedance Plethysmography in Lower-Extremity Artery Disease

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Background: Bioelectrical impedance plethysmography (IPG) for measuring human body fraction and disease has been progressing in the past half-century, and few studies have reported lower-extremity arterial disease (LEAD) in recent years.

Methods and Results: The present study enrolled patients who underwent examinations for LEAD. IPG with venous occlusion was performed, and flow volumes were compared with those measured using Doppler duplex ultrasonography, the ankle-brachial index (ABI), and assessments of arterial stenosis and collaterals using computed tomography and/or magnetic resonance angiographies. Fifty patients suspected of LEAD were enrolled; 15 had no arterial stenosis and 35 had LEAD. Arterial blood flow volume (BFV) was assessed. Although the area under the curve for IPG-BFV and Doppler-BFV in the popliteal artery with arterial stenosis were similar, IPG-BFV exhibited better diagnostic accuracy than Doppler-BFV (accuracy 0.765 and 0.694, respectively; McNemar's test $P<0.01$). In the analysis of covariance with IPG-BFV adjustment, Doppler-BFV was significantly lower in patients with LEAD (ABI<0.9), and morphological arterial stenosis, particularly in those with collaterals than in those without (F-test $P<0.05$, respectively).

Conclusions: IPG-BFV could have a better ability to discern the presence of arterial stenosis compared with Doppler-BFV and might not be confounded by the presence of collateral circulation when assessing blood flow in the entire lower extremity, which could be an advantage of IPG-BFV.

Key Words: Ankle-brachial index; Duplex Doppler ultrasonography; Impedance plethysmography; Lower-extremity arterial disease; Lower-extremity flow volume

Arteriosclerosis obliterans, an occlusive disease, primarily affects small to medium-sized arteries. If lower-extremity blood flow is impaired, the condition is referred to as lower-extremity arterial disease (LEAD).

Certain patients with LEAD are asymptomatic; however, they face a mortality risk comparable with those of patients with symptomatic LEAD.[1] The initial typical symptom is intermittent claudication. If untreated, this can progress to amputation or death.[2] In patients with intermittent claudication and a short aortoiliac occlusion, which causes severe hemodynamic impairment and limits daily activities, first-line treatments include endovascular therapy and exercise training.[3] Moreover, recurrent intermittent claudication was found to be closely related to the occlusion of the treated arteries after endovascular and surgical therapies.[4] However, current guidelines do not provide recommendations on disease management after endovascular therapy. Consequently, physicians rely on institutional policies and the availability of diagnostic tools. The resting ankle-brachial index (ABI), duplex Doppler ultrasonography, magnetic resonance angiography (MRA), and enhanced computed tomography angiography (CTA) are the most commonly used methods for assessing lower-extremity arterial blood flow. However, duplex Doppler ultrasonography results may depend on the skill of the operator. CTA requires a contrast medium, which should be avoided in patients with chronic kidney disease. MRA is time consuming and non-quantitative. Although the ABI is simple to measure, it can record artificially high

Received May 6, 2024; revised manuscript received October 20, 2024; accepted October 28, 2024; J-STAGE Advance Publication released online January 9, 2025 Time for primary review: 53 days
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Clinical Trial Registration: Japan Registry of Clinical Trials (registration no. jRCTs032200072; https://jrct.niph.go.jp/en-latest-detail/jRCTs032200072).
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ISSN-2434-0790

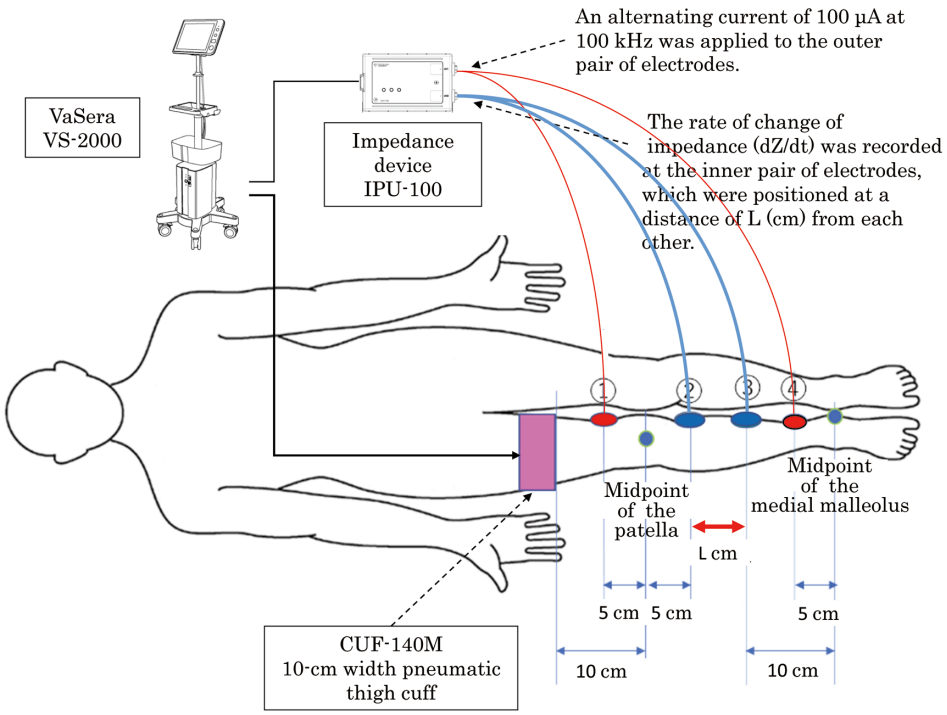

Figure 1. Diagram of the paired current and potential electrodes and the pneumatic thigh cuff connected to the monitor. Data are stored in VaSera VS-2000 through the impedance device (IPU-100).

ankle blood pressure if the artery is fibrotic or calcified and resists collapse, resulting in a persistent signal at high pressure.[5] Thus, approximately one-third of patients with critical limb ischemia and severe isolated infrapopliteal disease may have normal or incompressive ABIs.[6] Moreover, the collateral artery, which has a small diameter and low intraluminal pressure, can be compressed easily and is not included in the ABI. The ABI can only provide a semi-quantitative evaluation. Therefore, a quantitative evaluation of blood flow is still needed.

In several studies, venous occlusion in impedance plethysmography (IPG) is comparable with mercury strain gauges and has demonstrated a good correlation.[7–10] IPG is also convenient and non-invasive, not time consuming, and does not require a skilled operator. However, no commercially available device can evaluate lower-extremity blood flow using IPG. With advancements in technology, duplex Doppler ultrasonography can provide quantitative measurements of the regional arterial blood flow volume (BFV). To the best of our knowledge, no studies have compared lower-extremity arterial BFV between IPG with venous occlusion and duplex Doppler ultrasonography. This study aimed to evaluate whether IPG is a potentially useful clinical tool in monitoring whole lower-extremity blood flow status in patients with LEAD.

Methods

Inclusion and Exclusion Criteria and Data Collection

This single-center, non-blind, and non-control intervention study used an unapproved medical device for IPG with venous occlusion. Twenty consecutive patients suspected to have LEAD and 30 patients with confirmed LEAD (age 20–89 years) who underwent examination at Dokkyo Medical University Hospital, Tochigi Prefecture, Japan, between July 2020 and June 2021, were enrolled. Patients with a performance status of 4,[11] suspected pregnancy, leg wounds and/or inflammation near the electrode-attachment areas, pacemaker, and venous diseases (such as deep vein thrombosis, chronic venous insufficiency, or varicose veins) that could affect IPG measurements and patients unsuitable for duplex Doppler ultrasonography were excluded. Data regarding current medications and laboratory results were collected from the institutional database.

The study design and protocol were approved by the Saitama Medical University Ethics Committee (Certification no. CRB3180022). The study was conducted in accordance with the principles outlined in the Declaration of Helsinki and the guidelines set forth by the Japanese Ministry of Health, Labour and Welfare. All participants provided written informed consent.

Data Measurement and Analysis

IPG Measurement The bioelectrical impedance of a body segment is determined by the ratio of the applied current to the voltage drop across that segment. If the current remains constant, the voltage drop is directly proportional to the impedance of the body segment. Therefore, the expansion of capacitance vessels caused by blood accumulation after venous occlusion is believed to correspond to the change in impedance in lower-extremity segments. The theoretical equation of impedance in lower-extremity seg-

ments is provided in **Supplementary File**.

The participants were instructed to lie in a supine position for 10 min in a room maintained at 27°C. After cleansing the skin with ethyl alcohol, a pair of 10-mm-diameter disk silver chloride skin surface electrodes (Echorode III; Fukuda Denshi Co., Ltd, Tokyo, Japan) was affixed to the proximal inner side of the leg at the site 5 cm below the midpoint of the patella. Measurements taken at the distal inner side of the leg (10 cm above the midpoint of the medial malleolus) were denoted as L. Another pair of electrodes was attached on the inner side of the leg, positioned 10 cm proximally and 5 cm distally (**Figure 1**). The measurement site was not affected by the patella and malleolus that reflect the total blood flow of the gastrocnemius muscle, which accounted for most of the blood flow below the knee, as well as the anterior tibial artery (ATA), posterior tibial artery (PTA), and peroneal artery (PA), which perfuse the distal end of the foot. Moreover, the site where the proximal vein flow (femoral vein) could be occluded by the cuff was selected. An alternating current of 100 μV at 100 kHz, which is within the maximum allowable alternating current set by the Japanese Industrial Standard for medical electrical equipment and provides the optimal frequency for the signal-to-noise ratio of the waveform of each frequency (**Figure 2**), was applied to the outer pair of electrodes. The impedance-measuring device (IPU-100; Fukuda Denshi Co., Ltd, Tokyo, Japan) measured the impedance values (Z), ranging from 0 to 150 Ω, and a 15-bit analog-to-digital converter (least significant bit 0.00458 Ω) was connected to the inner electrodes.

Data collected were transferred to a vascular screening system (VaSera VS-2000, Fukuda Denshi Co., Ltd) for real-time monitoring and storage. Venous occlusion was induced using a 10-cm-wide pneumatic cuff (CUF-140M; Fukuda Denshi Co., Ltd)[12] wrapped around the thigh. To eliminate any cuff inflation artifacts, the cuff's lower border was positioned at least 3 cm away from the proximal current electrode. Once the impedance change stabilized and Z_0 was determined, the cuff pressure was increased to 50 mmHg for complete venous occlusion. The maximum occlusion pressure was reached within 5 s and maintained for 110 s. To avoid any confounding by cuff inflation noise, the $dZ/dt|_0$ calculation was based on IPG-BFV measurements obtained after 10–20 s of venous occlusion (**Figure 3**). The time required for IPG-BTF measurement, including 10 min of rest, was recorded.

Duplex Doppler Ultrasound Flow Measurement The BFV was measured 10 min after the impedance measurement using a high-resolution duplex ultrasound scanner (CUS-X200G; Canon Medical System Co., Otawara, Japan) equipped with an 8-MHz linear array transducer (PLV-1204BT; Canon Medical System Co.). A sonographer (C.H.), who had 10 years of experience in vascular sonography and was blinded to the patient's diagnosis, made the measurements. To measure the BFV, a longitudinal view of the straight arterial segment was used, and the sample volume was adjusted to fill the lumen. To ensure an accurate assessment of the time-averaged flow velocity, the ultrasonic wave beam angle was no more than 60°. To precisely measure the precise vascular cross-sectional area, color Doppler was used. The time-averaged flow velocity and arterial cross-sectional area were then used to compute the BFV (Doppler-BFV). Measurements were taken in the following arteries: common femoral artery (CFA), popliteal artery (POP), PTA, PA, ATA, and dorsalis pedis artery (DPA).[13] The time required for Doppler-BTF measurement was also recorded.

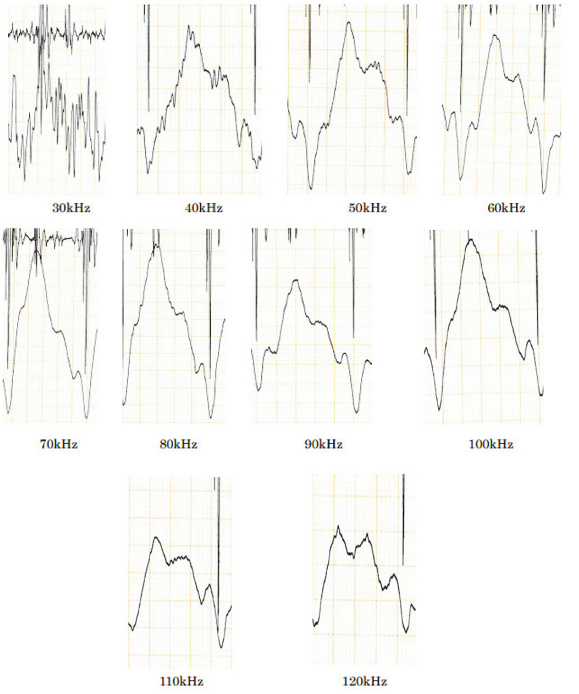

Figure 2. An alternating current of 100 μV at every 10 Hz, ranging from 30 to 120 Hz, is applied to the outer pair of electrodes. The impedance waveforms in the inner pair of electrodes are presented at each frequency. An upward deflection of the waveform represents decreased impedance caused by increased blood volume in 1 heartbeat.

ABI Measurement The ABI was computed by dividing the ankle systolic blood pressure by the arm systolic blood pressure using the VaSera VS-2000 oscillometric blood pressure device (Fukuda Denshi Co., Ltd).[14,15] ABI calculation data were obtained within 24 h of the impedance measurement. Abnormal values were defined as a resting ABI of <0.90 or >1.40.

Enhanced CTA or MRA Analysis To identify the anatomical location and degree of stenosis in the arteries of the lower extremities, lower-extremity CTA (Aquilion ONE, TSX-306A, Canon Medical System Co.) or MRA (Vantage Orian MRT-1550, Canon Medical System Co.) was performed within a few days of the impedance measurement. Significant LEAD was defined as arterial stenosis of at least 90% or complete occlusion above the ankle and/or the presence of collaterals. Collateral circulation was present when collateral vessels were visually identified on the scan.

Clinical Evaluation Items

The primary evaluation item was the lower-extremity BFV measured using the IPG device (IPG-BFV) compared with that measured using duplex Doppler ultrasonography (Doppler-BFV). The concordance of these 2 methods was assessed using receiver operating characteristic curve analysis to determine their accuracy in identifying significant lower-extremity stenosis or occlusion, as confirmed using CTA or MRA. The association between the IPG-BFV and Doppler-BFV in lumbar spinal canal stenosis (LSCS) and

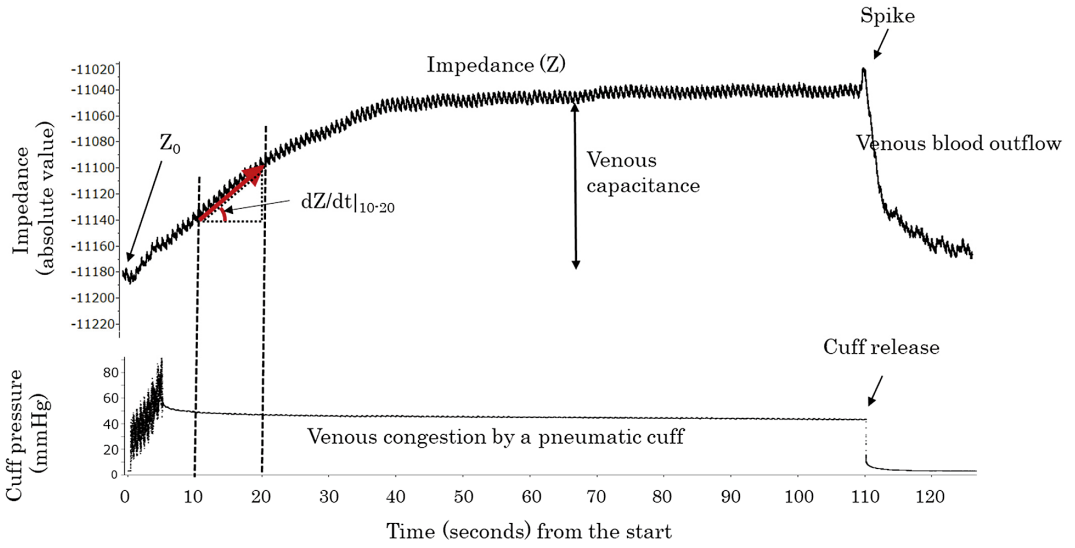

Figure 3. Typical time-cause impedance tracing during venous occlusion plethysmography. The upper tracing represents increased blood volume, which corresponds to decreased impedance. The lower tracing represents the pneumatic cuff pressure.

LEAD groups was also evaluated. The secondary evaluation item was the association between the IPG-BFV and Doppler-BFV in subgroups based on ABIs (ABI <0.9 vs. ≥0.9), as well as differentiating morphological arterial stenosis from non-arterial stenosis, and collateral flow from non-collateral flow, as observed on CTA or MRA. Furthermore, to compare reproducibility, we examined the correlation between IPG-BFV values of the right and left legs in patients having LSCS without stenosis in the lower limb arteries recorded at approximately the same time, and the safety profile of the IPG device was also assessed.

Statistical Analysis

To achieve a discriminatory power of 80%, the required sample size was estimated based on a correlation coefficient (r) of 0.5 and a type I error rate of 0.01; thus, the target sample size must be at least 44 legs. To account for a 10% attrition rate, a minimum of 50 legs must be assessed. Therefore, 50 patients (with a total of 100 legs) were enrolled. This number was chosen considering that the values would be lower than the measurement ranges in patients with LEAD.

Continuous data are presented as mean±standard deviation, whereas categorical data are presented as number and percentage. Student's t-test or analysis of variance was used to compare continuous variables, whereas the chi-squared (χ^2) test was used to compare categorical variables. For paired data, correlation coefficients were determined, and threshold-dependent sensitivity and specificity were determined using the area under the receiver operating characteristic curve (AUROC). The AUC and sensitivity and specificity were compared using the Delong's and McNemar's tests, respectively. The compatibility of different index measurement results was analyzed using Cohen's κ. The analysis of covariance (ANCOVA) was used to assess whether the mean of the dependent variable was equal across levels of 1 or more categorical independent variables. Given the small sample size, the bootstrap method with 1,000 samples was used. Statistical significance was determined by using a P value of <0.05. All statistical calculations were performed using IBM SPSS Statistics version 29.0.10 (IBM Corp., Armonk, NY, USA).

Results

Baseline Characteristics

Of the 50 patients, 15 did not have LEAD (due to LSCS, no arterial stenosis, or ABI≥0.9), whereas 35 had LEAD (10 had received endovascular and surgical therapies and 25 had not; **Table 1**). Of the total patients, 5 were women and 45 were men. The mean age, height, and body mass index were 74.2±7.2 years, 163±8.5 cm, and 24.3±3.3 kg/m^2, respectively. The baseline characteristics are summarized in **Table 1**. The LSCS and LEAD groups differed significantly in terms of sex, lower-extremity circumference, smoking status, fasting blood sugar, HbA1c, diabetes medications, serum creatinine, estimated glomerular filtration rate, and diastolic blood pressure. Thus, the LEAD group was more likely to have frail legs and a history of smoking, diabetes, and chronic kidney disease.

Thirteen legs in the LEAD group were not assessed because of POP occlusion identified in the duplex ultrasound scan (n=2, both legs in 1 patient), and baseline fluctuation in impedance readings caused by body movements (n=6), fine tremors (n=3), and external noise (n=2). Consequently, only data from 87 legs were analyzed. Values in all legs were within the IPG measurement range, including decreased impedance values after venous occlusion and beat-to-beat changes in the impedance level before the measurement.

Primary Evaluation Item

Initially, a sensitivity analysis was conducted on the distribution of the Doppler-BFV and IPG-BFV at each measur-

Table 1. Clinical Characteristics in Patients With LSCS and LEAD

	LSCS (n=15 patients)	LEAD (n=35 patients)
Age (years)	75.9±8.7	73.3±10.9
Male/female	15/0	30/5*
Height (cm)	165.5±7.9	161.8±21.7
Weight (kg)	66.9±12.1	63.2±14.2
Leg length (cm)	70.0±3.7	71.0±5.0
Body mass index (kg/m^2)	25.3±2.6	24.0±3.5
Thigh circumference (cm)	47.1±3.5	44.0±5.3*
Knee circumference (cm)	37.0±2.2	35.2±2.6†
Lower leg circumference (cm)	34.4±2.3	31.9±3.9†
Ankle circumference (cm)	21.4±1.4	20.4±1.9‡
Ever smokers	4 (27)	25 (72)†
Total cholesterol (mg/dL)	153.7±29.8	143.1±39.5
HDL-cholesterol (mg/dL)	50.5±15.8	44.2±13.7
LDL-cholesterol (mg/dL)	82.2±24.7	73.0±29.9
Triglycerides (mg/dL)	119.0±18.6	128.7±90.6
Lipid-lowering medications	10 (67)	28 (80)
Fasting blood sugar (mg/dL)	113.5±27.1	143.8±54.3‡
Hemoglobin A1c (%)	5.95±0.41	6.56±1.02†
Diabetes medications	2 (13)	16 (46)‡
Creatinine (mg/dL)	0.99±0.34	1.68±1.31‡
eGFR (mL/min/1.73 m^2)	60.3±16.2	45.1±13.3†
Systolic blood pressure (mmHg)	127.7±10.7	131.4±11.6
Diastolic blood pressure (mmHg)	78.9±8.8	73.2±8.9‡
Hypertension medications	10 (67)	27 (77)
Endovascular or surgical therapy	0	10 (28.6)*
Measurements	(n=30 legs)	(n=57 legs)
ABI	1.14±0.08	0.89±0.25*
ABI <0.9	0 (0)	25 (43.9)*
CTA or MRA		
Stenosis	0	34 (59.7)*
Collateral	0	20 (35.1)*

Data are presented as n (%), or mean±SD. *P<0.001. †P<0.01. ‡P<0.05. In LEAD, some legs were excluded because they could not be evaluated using electrical IPG. ABI, ankle-brachial index; CTA, computed tomography angiography; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IPG, impedance plethysmography; LDL, low-density lipoprotein; LEAD, lower-extremity arterial disease; LSCS, lumbar spinal canal stenosis without arterial stenosis; MRA, magnetic resonance angiography.

Table 2. BFV of the Bioelectrical Impedance Plethysmography in the Below-Knee Segment and Those of the Duplex Doppler Ultrasound in Each Segment

BFV (mL/min)	LSCS (n=30 legs)	ABI ≥0.9 (n=60 legs)	ABI <0.9 (n=25 legs)	Non-stenosis (n=51 legs)	Stenosis (n=34 legs)
IPG-BFV	15.12±5.84	15.19±6.93	9.28±3.88*	15.9±6.39	9.81±5.54*
Doppler-BFV					
CFA	244.9±58.6	227.6±64.3	164.7±76.1†	234.5±58.4	171.3±77.9*
POP	85.7±31.7	80.8±32.5	52.2±22.5†	84.0±31.5	54.9±25.8*
PTA	17.2±10.9	14.2±10.0	7.9±6.1†	14.7±10.2	8.5±6.3†
PA	37.8±28.9	27.3±25.1	11.1±14.9‡	30.1±25.7	10.6±13.3*
ATA	19.8±15.1	16.7±15.3	5.8±4.2*	18.3±15.8	6.4±5.1*
DPA	15.1±11.2	13.3±11.7	4.4±3.7*	14.6±12.1	4.7±3.8*

Data are presented as mean±SD. *P<0.0001 vs. ABI ≥0.9 or non-stenosis. †P<0.0005 vs. ABI ≥0.9 or non-stenosis. ‡P<0.001 vs. ABI ≥0.9 or non-stenosis (using analysis of variance). ATA, anterior tibial artery; BFV, blood flow volume; CFA, common femoral artery; DPA, dorsalis pedis artery; Non-stenosis, no morphological stenosis on CTA or MRA; PA, peroneal artery; POP, popliteal artery; PTA, posterior tibial artery; Stenosis, morphological stenosis on CTA or MRA. Other abbreviations as in Table 1.

Table 3. Correlation Coefficient Between the BFV of Bioelectrical Impedance Plethysmography in the Below-Knee Segment and Those of the Duplex Doppler Ultrasound in Each Segment

Correlation coefficient (r) between IPG-BFV and Doppler-BFV	LSCS (n=30 legs)	ABI ≥0.9 (n=60 legs)	ABI <0.9 (n=25 legs)	Non-stenosis (n=51 legs)	Stenosis (n=34 legs)
CFA	0.451†	0.446*	0.271	0.269	0.383‡
POP	0.743*	0.532*	0.486‡	0.507*	0.500†
PTA	0.590†	0.476†	0.151	0.464†	0.169
PA	0.349	0.227	0.031	0.172	0.016
ATA	0.260	0.348‡	0.567†	0.358‡	0.267
DPA	0.447‡	0.426†	0.070	0.447†	0.071

Data are presented as correlation coefficients (r). *P<0.0001. †P<0.005. ‡P<0.01. Abbreviations as in Tables 1,2.

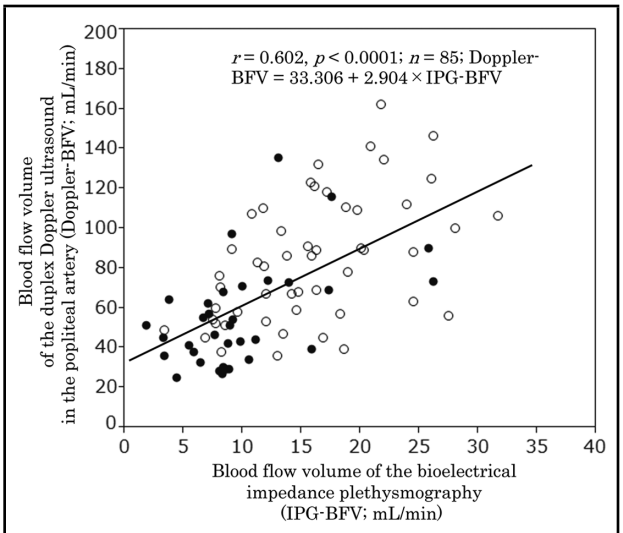

Figure 4. Correlation between the blood flow volume (BFV) measured using duplex Doppler ultrasonography in the popliteal artery and that measured using bioelectrical impedance plethysmography (IPG) for the below-knee segment. The open and closed circles indicate the values of the leg without (n=51) and with (n=34) arterial stenosis, respectively.

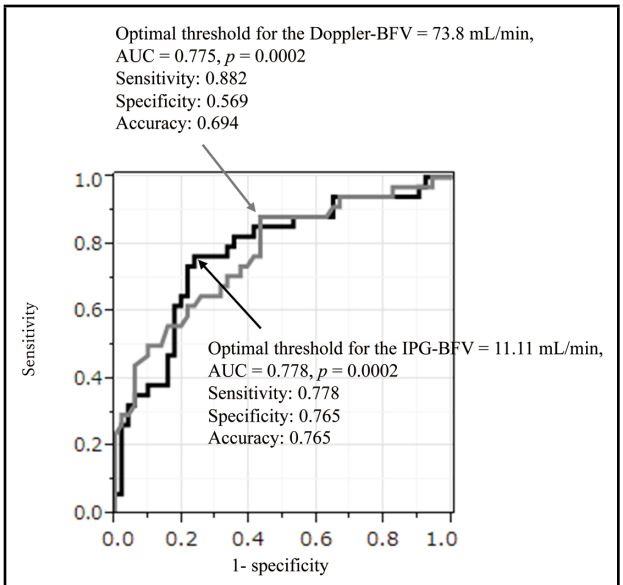

Figure 5. Per-patient receiver operating characteristic curves for the lower-extremity arterial blood flow volume (BFV) measured with impedance plethysmography (IPG) and duplex Doppler ultrasonography in the popliteal artery of patients with arterial stenosis on computed tomography angiography or magnetic resonance angiography. AUC, area under the curve.

ing point. The upper or lower limit of the whisker in the box plot was defined as the third quartile plus 1.5 times the interquartile range, and any data points outside the boundaries of the whiskers were considered outliers. Two obvious outliers in the same patients were identified, with Doppler-BFV values >200 mL/min and IPG-BFV values >35 mL/min in the POP. Therefore, these 2 values were excluded from the analysis because they could potentially inflate the Pearson correlation coefficients. Excluding 2 limbs, the final analysis included 85 limbs (LSCS legs n=30; non-LSCS legs n=55/57).

IPG-BFV measurements for the below-knee segment and Doppler-BFV measurements in the CFA, POP, PTA, PA, ATA, and DPA are provided in **Table 2**. In patients without LEAD, the IPG-BFV was found to correlate significantly with the Doppler-BFV in the POP, PTA, and DPA (**Table 3**). Among all patients, the strongest correlation between the IPG-BFV and Doppler-BFV was observed in the POP (r=0.602; P<0.0001; Doppler-BFV = 33.306 + 2.904 × IPG-BFV; **Figure 4**). However, the IPG-BFV and Doppler-BFV did not differ significantly between arteries in patients with LSCS, patients with ABI≥0.9, and patients without stenosis (**Table 2**).

The AUROCs for IPG-BFV and Doppler-BFV measurements in the POP of patients with arterial stenosis on CTA or MRA were significantly different (0.775 and 0.778; P<0.0001, respectively; **Figure 5**), and the AUROCs for these 2 measurement methods were not significantly different (Delong's test P=0.946). For the IPG-BFV, the optimal threshold was 11.11 mL/min in patients with arterial occlusion, yielding 0.778 sensitivity, 0.765 specificity and 0.765 accuracy. For the Doppler-BFV in the POP, the optimal threshold was 73.8 mL/min, with sensitivity, specificity and accuracy of 0.882, 0.569 and 0.694, respectively (**Figure 5**). The IPG-BFV was better at determining the presence of lower-extremity arterial stenosis than the Doppler-BFV in

the POP (McNemar's test P<0.01). When the optimal threshold levels of the IPG-BFV and Doppler-BFV for arterial stenosis were 11.11 and 73.8 mL/min, respectively, a significant moderate agreement was found between them (Cohen's κ coefficient [κ]=0.500; P<0.0001; **Supplementary Table**). Stents were inserted in 3 of the 4 patients with positive IPG-BFV and negative Doppler-BFV.

The ANCOVA test was used to examine the effect of the Doppler-BFV in the POP as the dependent variable, with the LSCS and LEAD groups as categorical independent variables and IPG-BFV as a covariate. The interaction between the IPG-BFV and group as predictors was significant (F=5.361; P=0.023). This indicates that the diagnosis of LEAD compared with LSCS would be a significant confounder in assessing Doppler-BFV; however, the IPG-BFV might not be confounded by the diagnosis of LEAD.

Secondary Evaluation Items

In the ANCOVA with IPG-BFV adjustment, Doppler-BFV was significantly lower in patients with ABI <0.9 than in those with ABI ≥0.9 and in patients with morphological arterial stenosis than in those without. The interactions between the IPG-BFV and each group as predictors were significant (F=4.206; P=0.049; F=5.009; P=0.027; respectively). Thus, presence of ABI <0.9 and morphological arterial stenosis would be significant confounders when assessing the Doppler-BFV but not the IPG-BFV.

This study also investigated the effect of collateral circulation on the IPG-BFV and Doppler-BFV in the POP in the morphological stenosis group. Using the ANCOVA after the bootstrap method with IPG-BFV adjustment, the Doppler-BFV was significantly lower in the collateral group than in the non-collateral group (95% confidence interval 39.44–53.81 vs. 51.87–82.97 mL/min; P=0.027). Thus, the presence of collateral circulation would be a significant confounder in assessing the Doppler-BFV but not the IPG-BFV, that is, some blood from the superficial femoral artery, located above the knee, flows into the lower-extremity arteries without passing through the POP. As shown in **Supplementary Table**, of the 18 patients with negative IPG-BFV (>11.11 mL/min) and positive Doppler-BFV (≤73.8 mL/min), collaterals were visually observed in 4 of 5 patients with arterial stenosis.

The reproducibility and safety profile of the IPG device were assessed. In the LSCS group, the IPG-BFV between both legs exhibited a highly significant correlation (r=0.884; P<0.001; n=15; right IPG-BFV = 0.870×left IPG-BFV + 7.583), indicating good reproducibility. Furthermore, no complaints or adverse effects were reported during or after the measurement using the impedance device and venous occlusion cuff.

Last, the average time required for IPG-BFV measurements (23±2 min) was significantly shorter than that for Doppler-BFV measurements (31±5 min; P<0.001).

Discussion

This study revealed that the AUROCs for the IPG-BFV and Doppler-BFV in the POP with arterial stenosis were not different; however, the IPG-BFV was better at determining the presence of lower-extremity arterial stenosis than the Doppler-BFV in the POP. In addition, the ANCOVA test revealed that the diagnosis of LEAD would be a significant confounder in assessing the Doppler-BFV but not the IPG-BFV. Although simple comparison between IPG-BFV and Doppler-BFV is difficult because the evaluation targets are different, the strongest correlation between the IPG-BFV and Doppler-BFV in POP was observed in all patients in this study. The IPG measurement segment spanned from 5 cm below the midpoint of the patella to 10 cm above the midpoint of the medial malleolus. This point was chosen considering the anatomical perfusion area of the leg arteries below the knee. Thus, it is a reasonable and expected result. The mean Doppler-BFV in the POP was 92.1 mL/min in 60 healthy individuals.[13] This value is similar to the Doppler-BFV observed in patients without arterial stenosis in the present study. Although anatomical variations in POP branches are common,[16] the perfusion area of each artery (i.e., ATA, PA, and PTA) varies. Most patients tend to have larger perfusion areas in the PTA. Therefore, the IPG-BFV was relatively highly correlated with the Doppler-BFV of the PTA compared with that of the ATA or PA in the LSCS or non-obstructive groups. However, this correlation was not observed in the LEAD group.

Notably, a significant correlation was found between the IPG-BFV and Doppler-BFV of the DPA, even though the DPA is outside the IPG measurement segment in the non-obstructive group. This can be explained by the principle of venous occlusion plethysmography, which includes temporary interruption in the venous drainage from the lower extremity, preventing blood flow from leaving the area while it enters through the arteries, leading to a linear increase in the BFV proportional to the arterial blood flow until the vascular capacity and maximum tissue compliance are reached. Strain gauge plethysmography has been used for over a century, and almost 40 years ago, an electrical impedance technique was developed and showed a good correlation with strain gauge plethysmography.[9,10,17] Electrical impedance tomography can produce 2-dimensional slice images that depict resistivity distribution changes within the tissue.[18,19] A study involving 14 healthy volunteers found decreased resistivity in 3 deep veins and some superficial veins in the calf during upper venous occlusion.[20] Thus, the rate at which the whole impedance decreased after upper cuff inflation was a measure of extremity arterial flow. The early slope, in terms of maximum flow, demonstrated a highly significant correlation with measurements obtained through strain gauge plethysmography at rest (r=0.87).[20] IPG with venous occlusion enables the assessment of lower-extremity arterial blood flow by reflecting the observed decrease in resistivity through electrical impedance tomography. This indicates that relatively large veins running parallel to the long axis of the lower extremity, and even the small veins, may have influenced impedance changes. In other words, the human extremities can be considered a parallel conductance model, as described by Nyboer.[21] Consequently, lower-extremity arterial blood flow can be measured even for collateral blood flow, such as in patients with LEAD. Indeed, analyzing the secondary evaluation items using the ANCOVA after bootstrapping with IPG-BFV adjustment revealed that the presence of collateral circulation would significantly confound the assessment of Doppler-BFV but not of IPG-BFV while assessing entire extremity blood flow, which could be an advantage of IPG-BFV. This is an important finding considering IPG and the lack of other methods to quantify blood flow in the entire extremity, including collateral blood flow. Thus, Doppler-BFV might

be relatively lower than IPG-BFV, particularly in patients with collateral circulation.

In this study, the Doppler-BFV in the POP significantly correlated with the IPG-BFV in all patients (r=0.602; P<0.0001; n=85; Doppler-BFV = 33.306 + 2.904×IPG-BFV). However, the absolute IPG-BFV value was lower than the Doppler-BFV in the POP (approximately one-third). This may be because measurements were not taken in certain areas, such as from the POP to 5 cm below the midpoint of the patella, from 10 cm above the midpoint of the medial malleolus to the foot, and from the heel to the toe (approximately 25 cm). In this study, the length of the IPG measurement segment in the lower legs was 19.1±2.2 cm. Although the cross-sectional area of each segment varied, the IPG measurement segment accounted for approximately one-third of the entire lower leg area (19.1 cm/[5 cm + 19.1 cm + 10 cm + 25 cm] = 0.32).

The analysis of the secondary evaluation items using ANCOVA with IPG-BFV adjustment revealed that the Doppler-BFV was significantly lower in the ABI <0.9 group than in the ABI ≥0.9 group and in the morphological stenosis group than in the non-morphological stenosis. Thus, the IPG-BFV might not be confounded by an ABI <0.9 and morphological arterial stenosis. In other words, the IPG-BFV appears to be less affected by ABI values or stenosis.

Duplex Doppler ultrasonography, CTA, and MRA are considered the gold standard for non-invasive diagnosis of LEAD. The ABI is also a non-invasive technique endorsed by guidelines for assessing LEAD.[22] In this study, ABI <0.9 had diagnostic sensitivity and specificity of 1.0 and 0.855, respectively, in patients with arterial stenosis on imaging. However, the specificity dropped to 0.688 in those with diabetes (data not shown), which was likely due to rigidity and atherosclerosis with calcifications of the arterial wall, which can lead to a false normal ABI.[23,24] Last, the results revealed that the ABI could not be used to quantify lower-extremity blood flow because the correlation between the IPG-BFV and ABI was weak (r=0.302; data not shown).

The reproducibility of IPG measurements in the LSCS group (r=0.884) and the safety profiles of the IPG with the venous occlusion device were considered good. In this study, the IPG-BFV and Doppler-BFV in the POP were slightly greater in the right leg than in the left leg, possibly due to a larger circumference of the right lower leg (328 vs. 326 mm).

This study might have important implications. Patients with negative IPG-BFV and positive Doppler-BFV may have collateral circulation and maintain a minimum level of lower limb blood flow below the knee compared with patients with positive indices. When further development of collateral circulation can be promoted by conservative therapy (pharmacotherapy and exercise therapy), the prognosis may improve. In addition, IPG-BFV may assess the effectiveness of increasing collateral blood flow. When there is little improvement, a treatment strategy such as intervention or another treatment would be considered. In the future, the formula $\Delta V = \rho(L/Z_0)^2 \Delta Z$ holds true, as shown in **Supplementary File**, when the electrode positions are the same in the same patient (according to the electrode position markings), which indicates that $\rho(L/Z_0)^2$ is constant, and ΔV and ΔZ show similar changes. Thus, real-time evaluation of blood flow changes from the height of the IPG waveform is possible without using a cuff. Therefore, limb blood flow can be continuously monitored with each heartbeat based on the height of the IPG, and new developments are expected in emergency, intraoperative, and postoperative monitoring settings.

Study Limitations

This study had several limitations. First, IPG-BFV measurements may have been influenced by the exclusion of deep vein thrombosis, chronic venous insufficiency, and varicose veins, as well as other factors affecting venous outflow, such as congestive heart failure.[25] However, these conditions would typically result in a slow decline in the IPG value 3 s after releasing the occlusive cuff (**Figure 3**). Second, although blood resistivity was assumed to be constant, it may vary with hematocrit values.[8] Third, patients with diabetes without LEAD may have had lower blood flow in lower-extremity arteries because of higher arterial stiffness and greater peripheral vascular resistance.[26] Fourth, 11 limbs were unable to undergo IPG measurements because of body movements (n=9) and external noise (n=2). Regarding body movements, the IPG can determine when the measurement date and time were changed, so the test was performed again. We cannot determine the cause of the external noise; however, recording without external noise was possible when the same patient was examined a few days later. Fifth, actual reproducibility requires repeated comparisons of measured values over different time points; however, blood flow, similar to blood pressure, also exhibits diurnal and daily variabilities, and requires further investigation. Last, it is necessary to confirm its clinical utility by measuring IPG-BFV before and after complete revascularization.

Conclusions

IPG-BFV with venous occlusion could have a higher ability to discern the presence of arterial stenosis than Doppler-BFV in the POP. IPG-BFV was less affected by the presence or absence of arterial occlusion and collateral circulation and yielded promising results when evaluating lower-extremity IPG-BFV, including collateral flow in patients with LEAD, which could be an advantage.

Acknowledgments

The authors thank Enago (https://www.enago.com) for English language editing.

Sources of Funding

Research funds and measuring instruments were provided by Fukuda Denshi Co., Ltd, Tokyo, Japan.

Disclosures

The authors declare that there are no conflicts of interest regarding the publication of this article.

Author Contributions

Conceptualization, methodology, and writing – original draft: S.H. Validation, formatting, and analysis: M.S. Resources and data curation: Y.Y. Investigation: M.W. Investigation and data curation: C.H. Supervision: S.T. Software, resources, funding acquisition, and project administration: T.Y.

IRB Information

The study design and protocol were approved by the Saitama Medical University Ethics Committee (Certification no. CRB3180022).

Data Availability

The individual deidentified participant data, demographics, laboratory duplex Doppler ultrasonography, CTA, MRA, and IPG findings will be shared. Additionally, the research proposal will be available. The data will become available immediately following publication, for up to 5 years after publication. Anyone wanting to access the raw data that support the findings of the present study will be able to do so immediately following publication; the data will be provided in formatted Excel files via email.

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Supplementary Files

Please find supplementary file(s);
https://doi.org/10.1253/circrep.CR-24-0046