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# Insights Into Microcirculation Underlying Critical Limb Ischemia by Single-Photon Emission Computed Tomography

*Jung-Tung Liu, MD, PhD, Cheng-Siu Chang, MD, Chen-Hsing Su, MD, and Cho-Shun Li, MD*

**Abstract:** Perfusion difference is used as a parameter to evaluate microcirculation. This study aims to differentiate lower-limb perfusion insufficiency from neuropathy to prevent possible occurrence of failed back surgery syndrome (FBSS).

Patients were retrospectively gathered from 134 FBSS cases diagnosed in the past 7 years. Up to 82 cases that were excluded from neuralgia by radiologic imaging, electrodiagnostic electromyography, and nerve conduction velocity were enrolled in this study. Perfusion difference was evaluated by single-photon emission computed tomography, and pain intensities were recorded via visual analog scale (VAS) score.

Lower perfusion at the left leg comprises 51.2% (42 of 82) of the patients. The mean perfusion difference of the 82 patients was $0.86 \pm 0.05$ (range: 0.75–0.93). Patients with systemic vascular diseases exhibited significantly higher perfusion difference than that of patients without these related diseases ($P < 0.05$), except for renal insufficiency ($P = 0.134$). Significant correlation was observed between perfusion difference and VAS score ($r = -0.78$; $P < 0.0001$; $n = 82$).

In this study, we presented perfusion difference as a parameter for evaluating microcirculation, which cannot be detected by ultrasonography or angiography.

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**Abbreviations**: ABPI = ankle-brachial pressure index, BMI = body mass index, CLI = critical limb ischemia, CT = computed tomography, DVT = deep vein thrombosis, EMG = electrodiagnostic electromyography, FBSS = failed back surgery syndrome, LSS = lumbar spinal stenosis, MRI = magnetic resonance image, NCV = nerve conduction velocity, NO = nitric oxide, PAOD = peripheral artery occlusive disease, SCS = spinal cord stimulation, SPECT = single-photon emission computed tomography, $TcPO_2$ = transcutaneous oxygen tension, VAS = visual analog scale.

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From Department of Neurosurgery, Chung Shan Medical University Hospital, School of Medicine, Chung Shan Medical University, Taichung City, Taiwan (J-TL, C-SC, C-HS, C-SL)
Correspondences: Jung-Tung Liu, Department of Neurosurgery, No. 110 Sec 1 Chien-Kuo N. Road, Taichung City 40201, Taiwan (e-mail: cshy654@csh.org.tw).
Cho-Shun Li, Department of Neurosurgery, No. 110 Sec 1 Chien-Kuo N. Road, Taichung City 40201, Taiwan (e-mail: cshy1350@csh.org.tw).
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## INTRODUCTION

Critical limb ischemia (CLI), a severe condition of perfusion insufficiency in the lower extremities, commonly leads to peripheral artery occlusive disease (PAOD). CLI is often caused by atherosclerosis related to hypertension, diabetes, or smoking; to date, no effective medical therapy is available for CLI.[1,2] The mean annual incidence of CLI is 340 to 1000 per million.[3] Up to 40% of CLI cases have lead to major amputation or even death exceeding 20% within 1 year.[2,4]

Failed back surgery syndrome (FBSS), also known as postlaminectomy syndrome, is characterized by recurrent and persistent chronic low back and/or leg pain, following anatomically successful spinal surgery.[5,6] Up to 19% of FBSS patients have received secondary spinal surgery for persistent pain or surgical complications in recent years.[7] The success rates of spinal surgery declined to 30% after second operation, 15% after third operation, and approximately 5% after fourth operation.[8] Multiple factors can lead to the development of FBSS. Surgery-related factors include wrong surgical technique, postoperative comorbidities, instability, recurrent disc herniation, and fibrosis-associated neuropathic pain. Age, lifestyle, and psychosocial factors (ie, depression, anxiety, and insomnia) may also negatively influence the outcomes of further operations.[9–14]

Recently, spinal cord stimulation (SCS) has become a regular treatment for both CLI and FBSS patients. The proposed pain relief mechanism in FBSS applies gate control theory and modulation of neurotransmitter release in the dorsal horn.[15–18] The vasodilatory mechanism in CLI patients may be ascribed to suppression of sympathetic vasoconstriction[19] and activation of vasodilatory molecules, thereby causing endothelial nitric oxide (NO) release and stimulating smooth muscle relaxation.[20–23] A dual effect occurs in facilitating vasodilation and microcirculation. Alleviation of ischemic pain is mediated by inhibition of nociceptive transmission[24] and release of opioid peptides, such as met-enkephalin.[25]

Measurement of transcutaneous oxygen tension ($TcPO_2$) has already been used as a predictive parameter to evaluate the efficacy of SCS in CLI patients.[26] To date, no effective parameter exists for diagnosis of CLI. Measurement of Doppler ankle-brachial pressure index (ABPI) is recommended for diagnosis of significant lower-limb arterial obstruction.[27] However, Doppler ABPI is unsuitable for detection of microcirculation.[28] Therefore, neuropathy is difficult to differentiate from atherosclerotic peripheral arterial disease in the lower limb because majority of individuals with PAOD do not experience recognizable ischemic symptoms. Although these conditions occur together in the lower limb, neuropathy may mask the symptoms and signs of CLI, thus confounding diagnosis.[29–31] The incorrect diagnostic information could be misguiding, leading to incorrect treatment of patients.[32] Thus, we hypothesize that some patients with perfusion problems may be included in FBSS patients. This

study aims to differentiate lower-limb perfusion insufficiency from neuropathy to prevent possible occurrence of FBSS.

## METHODS

### Patients

The study was performed at the Chung Shan Medical University Hospital and approved by the local Institutional Review Board. All patients signed an informed consent before participation. A total of 134 patients were diagnosed with FBSS within the past 7 years. Up to 52 cases, including 47 cases of recurrent neuropathic pain, were reoperated. Five other cases received arthroplasty. The other 82 cases excluded from neuralgia by radiologic imaging, electrodiagnostic electromyography (EMG), and nerve conduction velocity (NCV) were enrolled in this study. EMG detect the signal amplitude without any abnormal waves as well as NCV detect the latency, amplitude, and conduction velocity in motor, sensory, F-wave, and H-reflex in the range of normality. Computed tomography (CT) angiography ensures the limb arteries are intact. The mean age and body mass index (BMI) of the patients were $67.7 \pm 9.7$ (range: 41–84) years and $28.4 \pm 2.8$ (range: 23–39) kg/m$^2$, respectively. Males comprise 51.2% (42 of 82) of the patients. In this study, we used the 10-point visual analog scale (VAS) score with horizontal line anchored by "no pain" (score of 0) to the left and severity of pain to the right by "maximum pain" (score of 10).

### Lower-Limb Thallium-201 Scintigraphy

Previous studies have reported lower-limb thallium-201 scintigraphy as an efficient parameter for detection of lower-limb perfusion insufficiency undetected by ABPI measurement.[28,33] In this study, patients were instructed to remain in supine position for stress muscle imaging of lower extremities following intravenous injection of 2 mCi of thallium-201 chloride after intravenous infusion of 0.56 mg/kg dipyridamole (Persantin). Single-photon emission computed tomography (SPECT) was performed using a single-head, wide-angle-lens gamma camera and a low-energy, high-resolution collimator. Regions of interest, placed on thighs and calves, were automatically generated without any correction for background intensity. Perfusion difference represents low-to-high ratio of geometric mean between 2 legs. A ratio $<0.9$ defined an abnormal result of perfusion difference as previously described.[34] The mean perfusion difference of the patients was $0.86 \pm 0.05$ (range: 0.75–0.93).

### Statistical Analysis

Data plotting and statistics were processed using Prism (GraphPad software). Values represent mean $\pm$ SD. Comparisons among groups with different related diseases in perfusion difference were statistically assessed with Mann–Whitney $U$ test. Significance was set at $P < 0.05$. Correlation between perfusion difference and VAS score was statistically assessed with Spearman's correlation coefficient, ranging from 1 for perfect correlation to $-1$ for inverse correlation (0 value indicates no correlation between perfusion difference and VAS score).

## RESULTS

To verify whether the perfusion problem can be diagnosed, we retrospectively reviewed the records of 134 FBSS cases diagnosed in the past 7 years. Up to 52 cases were enrolled, including 47 cases that were reoperated because of typical neuropathic pain and 5 cases that received arthroplasty. The other 82 cases excluded from neuralgia by radiologic imaging, electrodiagnostic EMG, and NCV were enrolled in this study and received radionuclide treatment (thallium-201) of lower-limb muscle to evaluate microcirculation. Verifying the previous study, a patient with decreased perfusion at the left limb that cannot be identified by CT angiography was observed by lower-limb thallium-201 scintigraphy (Figure 1).

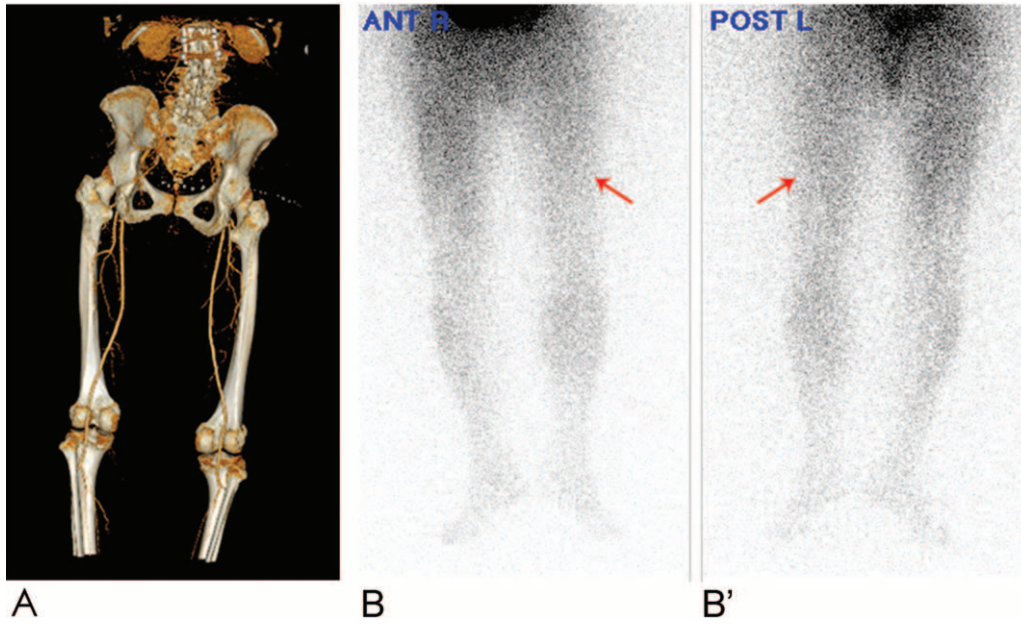


**FIGURE 1.** A 75-year-old female with left lower-limb pain. (A) Computed tomography angiographic examination manifests no definite deep vein thrombosis (DVT) or peripheral arterial occlusive disease (PAOD). (B and B') Compared with the right limb, decreased perfusion at the left limb (red arrowheads) was observed by lower-limb thallium-201 scintigraphy (perfusion difference: 0.87).

Lower perfusion at the left leg comprises 51.2% (42 of 82) of the patients. The mean perfusion difference of the 82 patients was $0.86 \pm 0.05$ (range: 0.75–0.93). Consistent with previous research, the ratio of perfusion difference manifests <0.9, suggesting possible perfusion problem in previously diagnosed FBSS patients. Systematic vascular diseases, such as diabetes mellitus (41 of 82), coronary arterial disease (38 of 82), hypertension (48 of 82), hyperlipidemia (25 of 82), and renal insufficiency (17 of 82), were also diagnosed in these patients. Only 4 patients were diagnosed without these related diseases.

The patients with systemic vascular diseases (DM; $85.2 \pm 4.3\%$, CAD; $85.3 \pm 4.3\%$, HT; $85.3 \pm 4.5\%$, HL; $84.9 \pm 4.4\%$; RI; $86.3 \pm 5.1\%$; $P < 0.05$) exhibited significantly higher perfusion difference than that of patients without these related diseases ($90.5 \pm 1.9\%$), except for renal insufficiency (RI; $86.3 \pm 5.1\%$; $P = 0.134$). This finding suggests that perfusion difference can indicate systematic vascular diseases in previously diagnosed FBSS patients (Figure 2). To test the correlation of perfusion difference with pain intensities, we assessed the correlation analysis between the perfusion difference and VAS score. We observed a significant correlation between perfusion difference and VAS score ($r = -0.78$; $P < 0.0001$; $n = 82$), demonstrating that a lower perfusion difference indicates higher pain intensities (Figure 3).

## DISCUSSION

Current noninvasive image technology can diagnose several symptoms. However, physicians must continue to rely on history and physical examination to guide their diagnosis because the presence of lumbar spinal stenosis (LSS) on magnetic resonance image (MRI) or CT scan is poorly correlated with lower-limb symptoms.[35,36] Similarity, most ultrasonography and angiography measurements during early stages of atherosclerotic disorders manifest normal blood circulation. Although neuropathy and atherosclerotic peripheral arterial diseases can coexist in the lower limb, neuropathy may mask the symptoms and signs of CLI, thus confounding diagnosis.[29–31] The incorrect diagnostic information could be misguiding, leading to incorrect treatment of patients.[32]

The symptoms of atherosclerotic peripheral arterial disease are difficult to distinguish spinal problems from

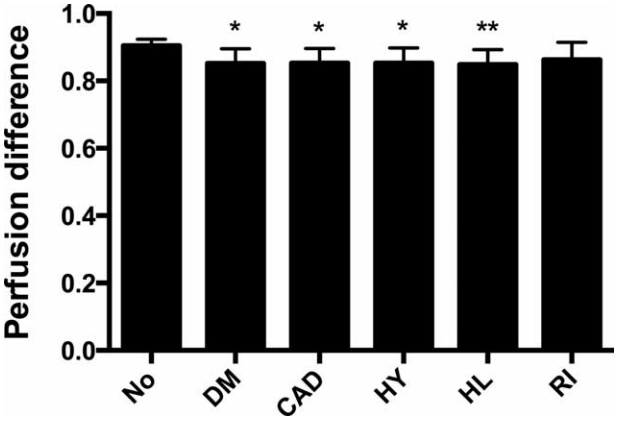


**FIGURE 2.** Perfusion difference between systematic and nonrelated diseases. Values represent mean ± SD. $*P < 0.05$; $**P < 0.01$ (Mann–Whitney *U* test). CAD = coronary arterial disease, DM = diabetes mellitus, HL = hyperlipidemia, HT = hypertension, NS = nonspecific, RI = renal insufficiency.

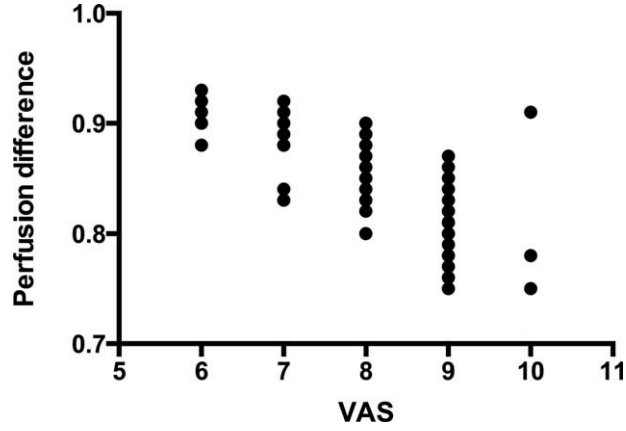


**FIGURE 3.** Correlation between perfusion difference and VAS pain score. Data were statistically assessed with Spearman's correlation coefficient, ranging from 1 for perfect correlation to −1 for inverse correlation (0 value indicates no correlation between perfusion difference and VAS score).

neuropathy. Many spinal surgeons emphasize the discrepancy between 2 categories. However, clear-cut separation is difficult to define. To assess lower-limb perfusion, previous studies have shown lower-limb thallium-201 scintigraphy as an efficient parameter for detection of lower-limb perfusion insufficiency undetected by ABPI measurement.[28,33] A ratio <0.9 defined an abnormal result of perfusion difference as previously described.[34] Table 1 shows the clinical feature difference between PAOD and perfusion insufficiency. Moreover, an article reported that 99mTc-MIBI also can indicate perfusion problem of lower limb muscles in patients without typical clinical symptoms.[37] Due to resolution limitation, traditional MR angiography is used to measure the perfusion of large arteries. Recently, the magnetic resonance angiography and perfusion (MRAP) is established for measurement of microvascular perfusion in PAOD patients.[38]

To differentiate lower-limb perfusion insufficiency from neuropathy, we assessed the lower-limb thallium-201 scintigraphy to evaluate microcirculation. In this study, 82 FBSS cases were excluded from neuralgia by radiologic imaging, electrodiagnostic EMG, and NCV. Consistent with previous research, the ratio of perfusion difference manifests <0.9, suggesting possible perfusion problem in previously diagnosed FBSS patients. These patients also manifest systematic vascular diseases, such as diabetes mellitus, coronary arterial disease, hypertension, hyperlipidemia, and renal insufficiency. Surprisingly, the patients with systematic vascular diseases exhibit significantly lower perfusion difference, except for renal insufficiency. Significant correlation between perfusion difference and VAS score was also observed. These results demonstrate that the symptoms of lower-limb perfusion insufficiency can be diagnosed in FBSS patients.

The current findings can explain the decline in success rates of operation times in patients with back pain. The source of pain cannot be solely attributed to neuropathy. Neuropathic pain can occur at any age but is not related to systemic disease. Aged patients may suffer from lower-limb disability, and no sufficient evidence can support the lesion originated from neural structure. Examination of microcirculation underlying CLI by using thallium-201 scintigraphy will discover symptoms for prevention of possible FBSS.

**TABLE 1.** Clinical Feature Difference Between PAOD and Perfusion Insufficiency

| Clinical Feature | PAOD | Perfusion Insufficiency |
|---|---|---|
| Pain type and location | Area below occlusive region | Calf tightness and cramping |
| Symptom migration | No migration | Distal to proximal |
| Exacerbation | Exercise | Exercise |
| Walking ability | Disable | Variable |
| Warm bathing | Symptom worse | Symptom release |
| Lower limb appearance | Skin color change, trophic ulcer, hair loss | Normal |
| Vascular pulse | Diminished | Normal |
| $TcPO_2$ | Decreased | Normal |
| Angiogram | Stenosis, occlusion | Patent |
| C-reactive protein (CRP) | Increased | Normal |
| Perfusion scan | Diminished | Diminished |
| Skin temperature | Variable | Normal |

PAOD = peripheral artery occlusive disease, $TcPO_2$ = transcutaneous oxygen tension.

## CONCLUSIONS

Perfusion difference can act as a parameter for diagnosis of perfusion insufficiency underlying CLI, which cannot be diagnosed by ultrasonography or angiography. The source of lower-limb pain may also not be solely attributed to neuropathy. Before decision of spinal surgery, physicians should consider the possible lower-limb pain resulting from perfusion insufficiency.

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