

## REVIEW ARTICLE

# Quantitative Assessment of Lower-limb Perfusion for Patients with Peripheral Artery Disease

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## Abstract

**Diagnostic procedures of noninvasive assessment for patients with peripheral artery disease (PAD) have been advancing for decades. Among diagnostic imaging modalities, lower-limb perfusion (LLP) planar scintigraphy and SPECT/CT are exclusively used for diagnosing lower-limb ischemia, therapeutic efficacies, and risk stratification in PAD patients. Of these modalities, LLP SPECT/CT particularly shows more accuracy in providing quantitative assessment of LLP using innovative imaging devices and dedicated software.**

**Keywords:** Lower-limb perfusion scintigraphy, Lower-limb perfusion SPECT/CT, Peripheral artery disease, Quantitative assessment for lower-limb perfusion

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**L**ower-limb atherosclerotic peripheral artery disease (PAD) is present in approximately 12% of the elderly population and is a leading cause of mortality. Patients suffering from PAD are currently on the rise (1–3). Defined as peripheral artery stenoses or occlusions by atherosclerotic plaques, this disease results in inadequate lower-limb perfusion (LLP) and consequent claudication and critical limb ischemia (CLI). CLI is the severest condition of PAD characterized by chronic ischemic pain at rest and the disintegration of skin tissue, including ulceration and gangrene. Patients with PAD are likely to have other comorbid conditions and those with CLI are especially at risk for cardiovascular events, cerebrovascular events, lower-limb amputations, and fatal events (4–6).

The noninvasive diagnostic modalities for patients with PAD include ankle brachial pressure index (ABI), ultrasonography (7), computed tomography angiography (CTA) (8, 9), and magnetic resonance angiography (MRA) (10, 11). Furthermore, LLP scintigraphy, which applies planar and single-photon emission computed tomography (SPECT) imaging, and SPECT-computed tomography (SPECT/CT) have been applied to diagnose lower-limb ischemia (12, 13).

The present review provides an overview of the most important clinical aspects of LLP quantification procedures

using various imaging modalities. Provided is an outline of relevant literature that discusses this issue, including analysis methods. As research is currently ongoing and the technique is being expanded into other applications, LLP imaging has a great potential for further clinical applications.

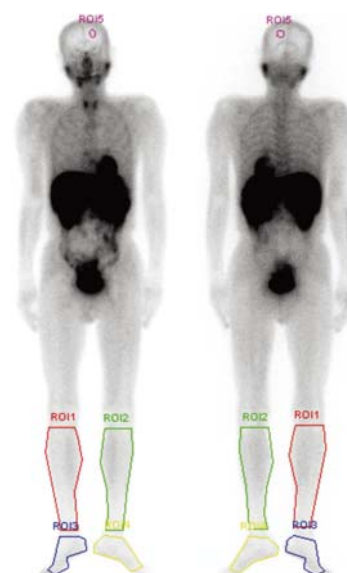
## Imaging modalities for diagnosing PAD

Over the past several decades, various methods for the noninvasive assessment of patients with suspected or confirmed PAD have been established. One widely used technique is the measurement of ABI using a transcutaneous blood velocity detector. Although this modality is an easily accessible routine screening test, the results can be misleading and are not always reproducible. Other assessment methods include noninvasive imaging modalities, such as ultrasonography, CTA, and MRA, that have been commonly used for the initial diagnosis of PAD. Whereas ultrasonography shows morphological findings and quantitative indices for blood flow in the major vessels, this modality is not reliable for the assessment of tissue perfusion (7). CTA and MRA are commonly used exclusively for the morphological assessment of the major vessels (8–11). Unlike these modalities, conventional LLP scintigraphy can evaluate lower-limb muscle perfusion and PAD-induced tissue ischemia. Furth-

ermore, for patients with PAD in small arteries due to causative diseases like diabetes mellitus (DM) or chronic kidney disease (CKD), whereas CTA and MRA will not be able to diagnose PAD, LLP scintigraphy can diagnose PAD by detecting the tissue ischemia. This scintigraphy has been reported to have high diagnostic accuracy, be a reliable determinant of therapeutic efficacies, and have a high prognostic value for PAD patients (14–16). SPECT/CT has also been applied to LLP imaging (13, 17). These modalities demonstrate different physiological findings, including muscle perfusion, as opposed to the aforementioned modalities.

### Lower-limb perfusion planar scintigraphy: procedures, visual and quantitative assessments

LLP scintigraphy, using  $^{201}\text{TlCl}$ ,  $^{99\text{m}}\text{Tc}$ -tetrofosmin, or  $^{99\text{m}}\text{Tc}$ -sestamibi, is the most common modality used to evaluate PAD-induced ischemia as well as therapeutic efficacies. In conventional planar imaging, anterior and posterior whole-body planar images show abnormalities in LLP in both rest and stress conditions (12). Both exercise stress (treadmill or ergometer exercise) and pharmacological stress (using adenosine, adenosine triphosphate, or dobutamine) can be used for the stress test. Furthermore, LLP scintigraphy can be performed simultaneously with myocardial perfusion imaging. In quantitative analyses, regional perfusions can be estimated by drawing regions of interests (ROI) on both thighs, calves, and feet and then comparing them with ROI on organs that have steady physiological uptake, such as the brain. Lower-limb-to-background ratio (LBR) can be calculated by dividing the target region mean count by background mean count, indicating the degree of regional perfusion (Figure 1) (14). With regard to the calculation method of lower-limb perfusion reserve, there are two suggested formula: 1) dividing stress regional total count by rest regional total count (15) and 2) dividing stress LBR by rest LBR (14). While quantitative analyses can stratify the severity of lower-limb ischemia in more detail, additional attention to the variation of calculated quantitative values is required, because the small count in the background with low accumulation and calculated LBR are susceptible to fluctuation. In Figure 2, showing a PAD patient, the right common iliac artery stenosis induced lower-limb ischemia can be recognized visually and quantitatively. Siegel et al. reported time-course changes of lower-limb accumulation between rest and stress conditions that were assessed by calculating regional gamma-ray counts in 10 PAD patients (12). More recently, Miyamoto et al. provided an index for LLP named “ $^{99\text{m}}\text{Tc}$ -tetrofosmin perfusion index” using planar scintigraphy. This index is identical to LBR (14). Kusmirek et al. observed the changes of regional perfusion in patients with early PAD by dividing lower-limb regional total count by whole body total count. The rest and stress regional perfusion



**Figure 1** Calculation procedure of lower-limb-to-background ratio (LBR) on conventional planar imaging.

Lower-limb regional counts and background count are estimated by drawing regions of interest (ROI) on both calves, feet, and brain (as background).

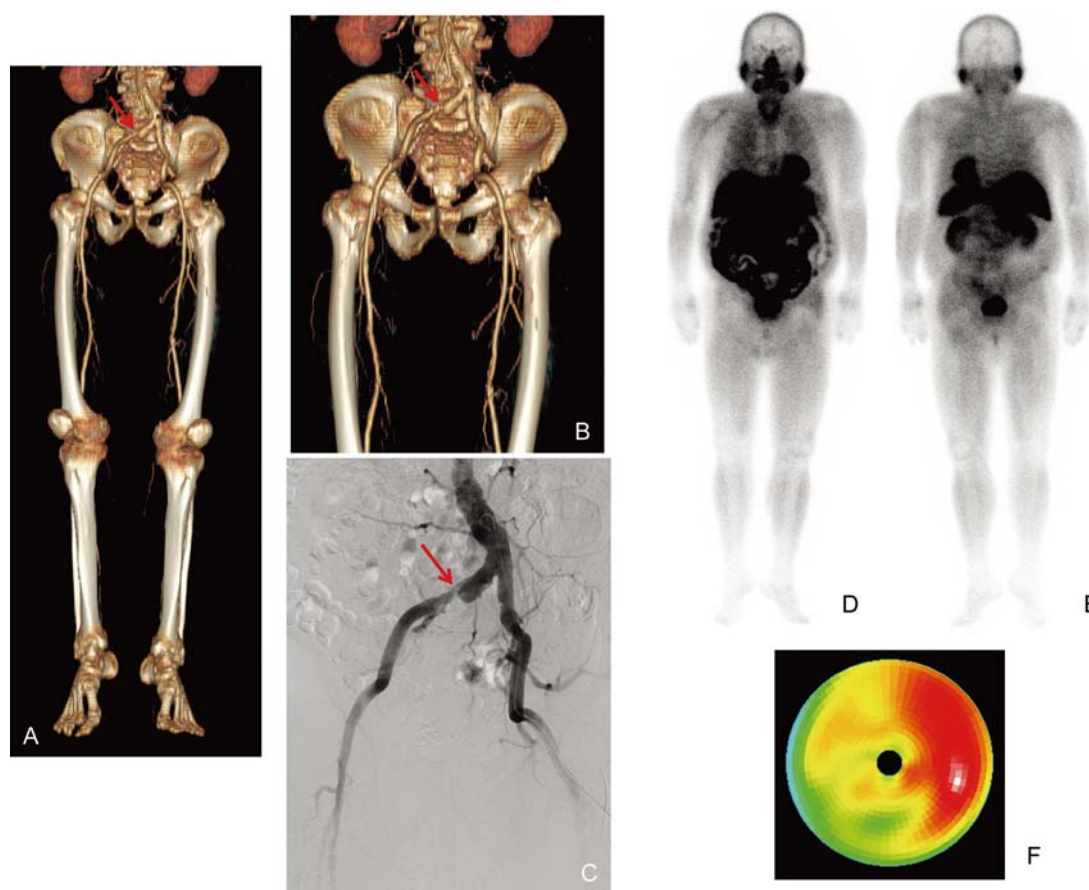
$$\text{LBR} = \frac{\text{Lower-limb regional mean count}}{\text{Brain mean count}}$$

indices in both the affected thigh and calf were lower in the early stage PAD group than in the non-PAD group. LLP planar scintigraphy could depict abnormal perfusion reserve even in patients with early-stage PAD (18). Based on these results, LLP planar scintigraphy can accurately evaluate LLP conditions using both visual and quantitative analyses.

LLP scintigraphy can assess therapeutic efficacies of various treatments. Miyamoto et al. reported that LLP scintigraphy using LBR clearly depicts improved muscle perfusion resulting from autologous bone marrow cell implantation and angiogenesis (pre-treatment LBR:  $1.32 \pm 0.10$ , post-treatment LBR:  $1.56 \pm 0.11$ ,  $p = 0.007$ ). However, ABI did not significantly increase ( $0.65 \pm 0.08$  vs.  $0.73 \pm 0.07$ ,  $p = 0.055$ ), showing that this modality is not a reliable indicator of therapeutic efficacies for patients with CLI (14). Another approach to diagnosing therapeutic efficacies was introduced by Takagi et al. Lower-limb vascular bed volume was quantified by lower-limb scintigraphy using  $^{99\text{m}}\text{Tc}$ -macroaggregated albumin (MAA). The degree of angiogenesis by bone-marrow mononuclear-cell implantation was quantified by calculating LBR (treated limb: [pre-treatment]  $1.03 \pm 0.27$  to [post-treatment]  $1.18 \pm 0.38$ ; untreated limb:  $1.01 \pm 0.28$  to  $1.16 \pm 0.34$ ,  $p < 0.01$ ) (19).

### Lower-limb perfusion SPECT/CT: procedures, visual and quantitative assessments

LLP SPECT/CT can be performed using a SPECT/CT combined system. Unlike conventional LLP scintigraphy,



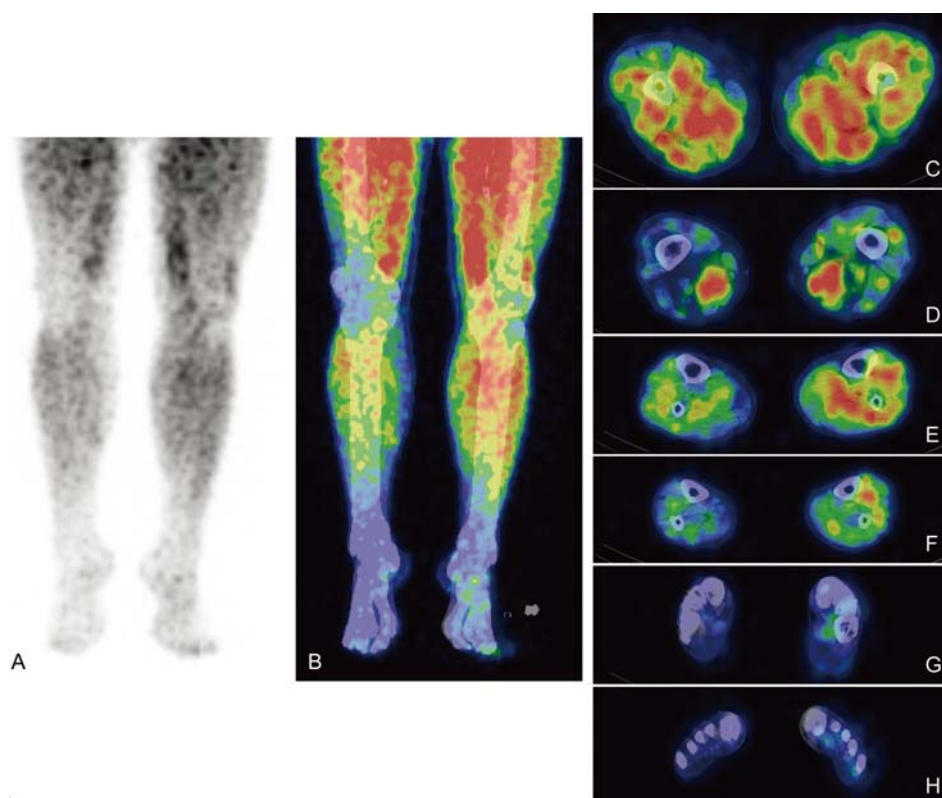
**Figure 2** Resulting images of conventional modalities of patient with peripheral artery disease.

CT angiography (A and B) and invasive angiography (C) images show saccular aneurysm and neighboring distal severe stenosis in the right common iliac artery. Lower-limb perfusion scintigraphy planar images using  $^{99m}\text{Tc}$ -tetrofosmin (D and E) show reduced perfusion in the entirety of the affected right lower-limb. Lower-limb-to-background ratios (LBR) were significantly lower in the right leg (right calf: 0.75, left calf: 1.09, right foot: 0.28, left foot: 0.46). Simultaneously acquired rest myocardial perfusion image (F) showed previous myocardial infarction in the left anterior descending artery and right coronary artery territories.

SPECT/CT can show both 3D perfusion distribution and morphological findings with clearer boundaries and higher contrast images, owing to CT attenuation correction (13). In the acquisition of SPECT images, the scan range is usually limited to 2–3 bed positions in order to minimize the acquisition time of SPECT and the radiation exposure during CT scanning. Since LLP SPECT/CT imaging does not include common body trunk, its image interpretation requires in-depth understanding as opposed to conventional planar images. Therefore, quantitative assessments are more viable when interpreting SPECT/CT images.

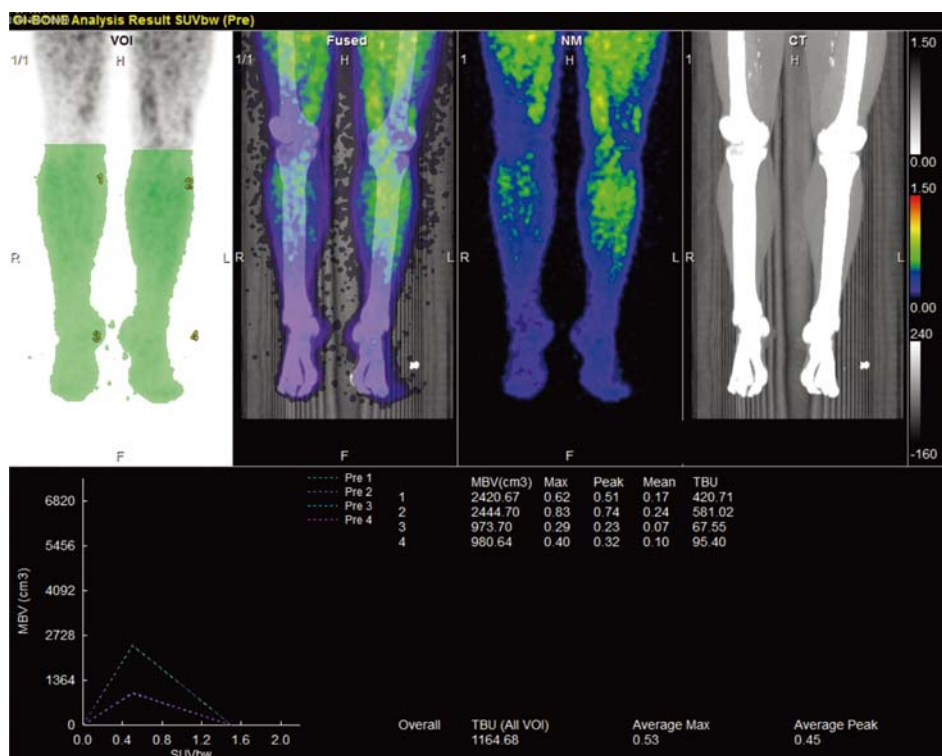
LLP SPECT/CT allows us to perform quantitative analysis more accurately than conventional planar imaging (13). Since conventional planar imaging lacks morphological information and overlooks low tracer accumulation components like fat tissues and bones, which need to be excluded, an underestimation of lower-limb muscle perfusion is therefore inevitable. Conversely, SPECT/CT imaging allows us to calculate 3D-based TBR and standardized uptake value (SUV). In Figure 3 and 4, showing a PAD patient, the right common iliac artery

stenosis induced lower-limb ischemia can be recognized visually and quantitatively. Dobrucki et al. reported 3D-based analyses of LLP in mice. Drawing volumes of interest (VOI) on the thighs and calves eliminating bones, the regional counts and ischemic-to-nons ischemic (I/NI) ratio was calculated. 3D-based I/NI ratio was better correlated with gamma-well counting I/NI ratio compared with 2D-based I/NI ratio (20). Hashimoto and Fukushima et al. applied another 3D-based quantitative analysis called lower-limb-muscle-to-background ratio (LMBR). LMBR can be calculated by dividing count per volume exclusively in the thigh, calf, and foot muscles on the affected side by mean count per volume in the bilateral distal-femur bone marrow as a background (Figure 5). This parameter reflects exclusively lower-limb muscle perfusion and can stratify PAD patients into the high and low LMBR groups. Lower-limb perfusion reserve can be calculated by dividing stress LMBR by rest LMBR. Although LMBR was significantly correlated with Fontaine classification, it was not correlated with Trans-Atlantic Inter-Society Consensus (TASC) classification diagnosed with morphological modali-



**Figure 3** Resulting images of lower-limb perfusion SPECT/CT using  $^{99m}\text{Tc}$ -tetrofosmin of patient in Figure 1.

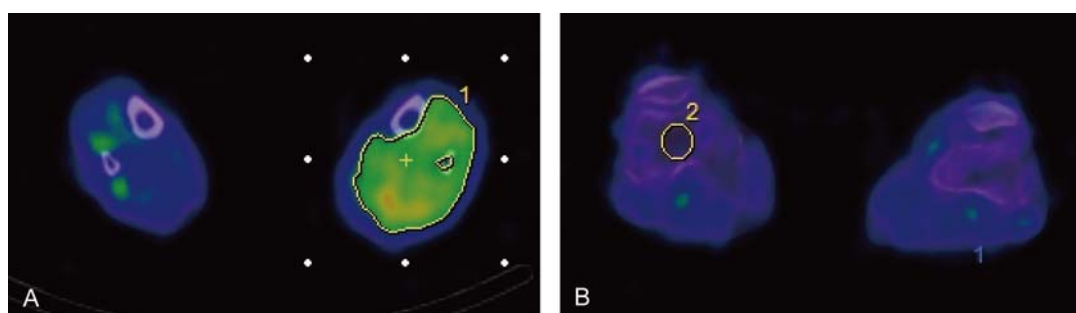
SPECT/CT images (A: SPECT MIP image, B: SPECT/CT fused MIP image, C-H: transaxial SPECT/CT fused image) show reduced perfusion in the entirety of the affected right lower-limb with clearer boundaries and higher contrast as opposed to planar imaging. Lower-limb-muscle-to-background ratios (LMBR) were significantly lower in the right leg (right calf: 1.95, left calf: 2.69, right foot: 0.76, left foot: 1.09).



**Figure 4** GI-BONE analysis results of lower-limb perfusion SPECT/CT using  $^{99m}\text{Tc}$ -tetrofosmin of patient in Figure 1 and 2.

Lower-limb perfusion is also assessed by calculating SUV using GI-BONE. Although SUV are shown to be significantly lower in the right leg (right calf: 0.17, left calf: 0.24, right foot: 0.07, left foot: 0.10), the range is not as far reaching as LMBR.





**Figure 5** Calculation procedure of lower-limb-muscle-to-background ratio (LMBR) on SPECT/CT.

Lower-limb muscle regional counts and background count are estimated by drawing volumes of interest (VOI) on regional muscles (A) and both distal femur bone marrow (as background) (B).

$$\text{LMBR} = \frac{\text{Lower-limb regional count/volume (cm}^3\text{)}}{\text{Mean count/volume (cm}^3\text{) of both distal femur bone marrow}}$$

ties like CTA. The discrepancies between the functional and morphological modality results indicate that morphological assessment for PAD cannot predict tissue ischemia due to the lack of information on the microcirculation, including collateral flow, which is prevalent in patients with DM or CKD (13). As indicated from these results, LLP SPECT/CT has greater diagnostic performance and quantitative ability when diagnosing LLP abnormality.

#### Prognostic value of lower-limb perfusion planar scintigraphy and SPECT/CT

For patients with PAD, LLP scintigraphy has a high prognostic performance along with the high diagnostic performance of LLP conditions. Patients with PAD, especially with CLI, have a poor prognosis, as they are at increased risk of CAD, CVD, lower-limb amputations, and death compared with healthy individuals (4–6). Tara et al. investigated the relationship between LBR in the affected lower-limb and the proportion of amputation in patients with CLI undergoing autologous bone marrow cell implantation. Patients in the low LBR group had a significantly higher incidence of amputation than patients in the high group (3 of 5 vs. 1 of 14,  $p = 0.008$ ) (16). Hashimoto and Fukushima et al. reported that the proportion of patients who experienced major adverse events was significantly higher in the low LMBR group than in the high group (7 of 12 vs. 1 of 26,  $p < 0.001$ ) (13). Based on these results, LLP planar scintigraphy and SPECT/CT can accurately stratify patient prognosis using quantitative analyses.

#### Conclusions

There have been notable advancements in noninvasive diagnostic procedures for patients with PAD. LLP SPECT/CT has proven effective and reliable thus far. Although this modality has some room for refinement and validation in a range of clinical applications, it is the foremost modality when

identifying lower-limb ischemia.

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#### Conflicts of interest

None.

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