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Intravenous Contrast-Free Standardized Exercise Perfusion Imaging in Diabetic Feet With Ulcers

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Abstract

Background: Impaired foot perfusion is a primary contributor to foot ulcer formation. There is no existing device nor method that can be used to measure local foot perfusion during standardized foot muscle exercise in an MRI environment.

Purpose: To develop a new MRI-compatible foot dynamometer and MRI methods to characterize local perfusion in diabetic feet with ulcers.

Study Type: Prospective.

Population/Subjects: Seven participants without diabetes and 10 participants with diabetic foot ulcers.

Field Strength/Sequence: 3.0T, arterial spin labeling (ASL).

Assessments: Using a new MRI-compatible foot dynamometer, all participants underwent MRI ASL perfusion assessment at rest and during a standardized toe-flexion exercise. The participants without diabetes were scanned twice to assess the reproducibility of perfusion measurements. The absolute perfusion and perfusion reserve values were compared between two groups and between regions near ulcers (peri-ulcer) and away from ulcers (away-ulcer).

Statistical Tests: Bland–Altman methods for the calculation of coefficient of repeatability (CR) and two-sided and unpaired Student's t-test to compare multiple differences.

Results: The perfusion reserves measured had the best reproducibility (CR in medial region: 1.6, lateral region: 0.9). The foot perfusion reserve was significantly lower in the participants with diabetes compared with the participants without diabetes (1.34 ± 0.32 , 95% confidence interval [CI]: 1.1, 1.58 vs. 1.76 ± 0.31 , 95% CI: 1.53, 1.98, $P = 0.02$). Both peri-ulcer exercise perfusion

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(8.7 ± 3.9 ml/min/100g) and perfusion reserve (1.07 ± 0.39 , 95% CI: 0.78, 1.35) were significantly lower than away-ulcer exercise perfusion (12.7 ± 3.8 ml/min/100g, $P = 0.02$) and perfusion reserve (1.39 ± 0.37 , 95% CI: 1.11, 1.66, $P = 0.03$), respectively.

Data Conclusion: This study demonstrates intravenous contrast-free methods for local perfusion in feet with ulcers by standardized exercise-based MRI. Ischemia regions around foot ulcers can be quantitatively distinguished from normal perfused muscle regions.

Level of Evidence: 2

Technical Efficacy: Stage: 2

FOOT ULCERS are the leading cause of hospitalization in patients with diabetes mellitus (DM).^{1,2} Approximately 85% of all diabetes-related lower-extremity amputations are preceded by foot ulcers.^{3,4} A foot ulcer is defined as a break-down in the foot skin that may extend to the subcutaneous tissue, bone, and muscle.⁵ The prime contributors to ulcer formation and impaired ulcer healing in the diabetic foot are neuropathy, biomechanical pressure, microtrauma, infection, immune cellular dysfunction, and impaired regional perfusion.⁶ Impaired regional perfusion results in decreased delivery of oxygen, nutrients, and cells (macrophages and other leukocytes) critical to healing of the wound bed and is a primary contributor to ulcer formation for up to 50% of the population with foot ulcers.^{7,8} More important, ulcers in DM are often associated with diffuse and/or distal capillary narrowing unsuitable for revascularization surgery. For these ulcers, patients receive prolonged medical treatment with no guarantee of ulcer-healing success. Delayed ulcer healing can become life-threatening as the risk for infection increases, and amputation is often inevitable. A local ulcer bed perfusion measurement tool would allow better determination of a critical factor in ulcer healing.

Current clinical evaluation of pedal perfusion, however, is indirect, at best. For instance, the most widely used ankle-brachial-index (ABI) test provides global macrocirculation information, but not direct and local tissue perfusion, and is a relatively poor predictor for ulcer healing in the diabetic foot.^{9,10} On the other hand, it would be necessary to induce some type of provocation, eg, exercise, to uncover the impaired exercise perfusion and measure perfusion reserve. Toe-flexion exercise at the meta-tarsal phalangeal joints has been shown to best activate the intrinsic foot muscles and has been demonstrated in several studies that investigated perfusion changes in feet.¹¹ Although there have been reports on the use of foot dynamometers to standardize foot exercise strength,^{12–14} there is no existing device nor method that can be used to measure local perfusion during toe-flexion exercise in an magnetic resonance imaging (MRI) environment. The purposes of this study were to develop a new MRI-compatible foot dynamometer and MRI methods for comprehensive evaluation of foot perfusion. The new approach was assessed in participants without diabetes and with diabetic foot ulcers.

Materials and Methods

Participants

This prospective study was approved by the local institutional Human Research Protection Office. Ten participants with diabetic foot ulcers (DM group) and seven age- and BMI (body mass index)-matched participants without DM and foot ulcers (non-DM group) were prospectively recruited. Written informed consent was obtained from each participant prior to the study. All seven non-DM participants (age: 62 years $\pm$ 11, BMI: 33.3 kg/m² $\pm$ 8.9, three female) were nonsmokers and free of diabetes, metabolic, and musculoskeletal diseases. There were nine type II DM and one type I DM. All DM participants (age: 58 years $\pm$ 8, BMI: 32.8 kg/m² $\pm$ 4.9, four female) had at least one current plantar ulcer. To ensure that participants did not have any peripheral arterial disease, inclusion criterion included: ABI >0.9 , toe brachial index (TBI) >0.6 , and no clinical history of peripheral arterial disease.¹⁵ We excluded participants who were hemodynamically unstable, pregnant, claustrophobic, or had rest pain or other contraindications to MR scanning.

Prior to MRI scanning, all participants had blood withdrawn to measure HbA1c, ABI test, and a TBI test. Both ABI and TBI tests were performed in the clinical vascular laboratory by trained vascular technicians at room temperature. The ABI was calculated as the ratio of systolic pressure of the anterior tibial artery to that of the brachial artery. The TBI was calculated by dividing the systolic pressure of the great toe by that of the brachial artery.

MRI-Compatible Foot Dynamometer

The foot dynamometer shown in Fig. 1 is the first one built for standardized foot exercise within an MRI scanner. During exercise, the participants used their toes to squeeze a pressurized air bulb that was connected through a polyethylene tube to a pressure regulator. The latter has one end connected to a custom-made pressure-voltage transducer that converts analog voltages to digits for real-time display. The front portion of the scanner bore was used as a screen for a projector so that the pressure data could be seen by the participants. Figure 1 also shows photos of the foot holder and two real-time displays of pressure digits. Toe-flexion maximal voluntary contraction (MVC) was determined for each participant. The 15% and 25% MVC were calculated and this range was projected onto the screen. The participant practiced maintaining the contraction within this range.

MRI

All participants underwent MRI perfusion assessment at rest and during a standardized toe-flexion exercise (~20% of MVC) using the MRI-compatible foot dynamometer. Each exercise lasted for ~4 minutes. The non-DM participants were scanned twice on two different days (at least 1 week apart) to assess the reproducibility of perfusion measurements. All patients with DM and foot ulcers were followed up at 3 months after the MRI measurements to determine the healing status of foot ulcers, ie, healed or nonhealed ulcers. Patients with foot ulcers were able to perform the 20% MVC exercise comfortably.

MRI PERFUSION MEASUREMENT.—The measurement of local perfusion, termed skeletal muscle blood flow (SMBF), was performed using an arterial spin labeling (ASL)

method that was validated previously in the heart muscle by a micro-sphere method.¹⁶ Briefly speaking, this ASL method is a pulsed FAIR approach in which spin tagging takes place within the imaging slice^{17,18}; thereby, the transit time effect is minimized at an expense of relatively lower flow sensitivity.

The details of ASL technique were reported previously.¹⁹ Briefly speaking, the ASL sequence acquires both slice-selective and volume-selective T_1 rapidly in a fashion similar to the Look–Locker sequence.²⁰ After an adiabatic hyperbolic secant 180° inversion pulse, a series of 2D gradient-echo images were acquired with an α train in a linear phase-encoding scheme during the inversion recovery time. The current ASL sequence parameters are: single-shot gradient-echo acquisition, repetition time / echo time (TR/TE) = 4.1 msec/1.3 msec; fat saturation; inversion time (TI) = 220, 720, 1220, ..., 3720 msec, flip angle = 5° ; field of view (FOV) = 320×240 mm²; matrix = 128×96 ; average number = 4; total acquisition = 60 seconds. Three 8-mm-thick slices, parallel to the plantar of the foot without gap, were prescribed to cover the majority of foot intrinsic muscles, including flexor digitorum brevis, lumbricals, quadratus plantae, abductor hallucis, and flexor digiti minimi brevis.

PERFUSION MAP PROCESSING.—SMBF maps were created using custom-made software for all three slices.¹⁹ All perfusion source images were reviewed frame-by-frame first. If there were apparent motion between frames, a custom-made software, written in MatLab (MathWorks, Natick, MA), was applied to correct in-plane translational and rotational motion. SMBF was calculated by measuring slice-selective $T_{1,ss}$ and volume-selective $T_{1,vs}$:

$$SMBF = \lambda \frac{T_{1,NS}}{T_{1,Blood}} \left(\frac{1}{T_{1,ss}} - \frac{1}{T_{1,vs}} \right)$$

where λ is the blood-tissue coefficient of water and was assumed to be 0.9 mL/g.²¹

The final SMBF maps were denoised using a blocking-matching and 3D filtering algorithm to reduce noise from the map creation.²² To facilitate the analysis of the ulcer location, a grids-eye display of SMBF distribution with six segments per slice was created in each foot. Figure 2 shows examples of SMBF maps of a healthy foot and corresponding grids-eye maps. It shows the overall increased SMBF during exercise, in comparison with the SMBF map at rest. With this display, a foot ulcer can be located in specific segments. The angiosome of a foot's medial or lateral region each has three segments. To simplify quantitative analysis for the reproducibility study, the global SMBF values within the M and L regions of the foot's angiosome were obtained by averaging SMBF values of the respective segments over three slices. For the feet with ulcers, the average SMBF value in segments immediately adjacent to a foot ulcer was measured as peri-ulcer SMBF. The average SMBF value in the rest of segments were measured as away-ulcer SMBF. If a foot ulcer was on the first toe, the peri-ulcer SMBF was calculated from the most adjacent segment in three slices, ie, segments 1, 7, and 13. It is noted that all regional SMBF values were obtained by averaging SMBF values of pixels with SMBF less than 200 ml/min/100g.

In a previous study,¹⁸ the averaged maximal SMBF during toe flexion at 100% MVC was $\sim 113 \pm 40$ ml/min/100g. Therefore, it is not expected that maximal SMBF during a 20% MVC contraction will exceed $113 + 2 \times 40 = 193$ or 200 (ml/min/100g). This thresholding helped to filter those sparsely distributed pixels with unrealistic high SMBF values on created SMBF maps. The SMBF reserve was calculated as the ratio of SMBF during flexion exercise to SMBF at rest from these regional measurements.

Statistical Analysis

Bland–Altman methods were first used to determine measurement reproducibility in the M and L regions for non-DM participants.²³ Arithmetic means and coefficients of repeatability (CRs) were calculated for absolute SMBFs and reserves in the two foot regions (M and L), at rest and during the toe-flexion exercise. The CR means that if any difference between two measurements is above this CR value, it is 95% confident the difference is real and not due to measurement errors. A lower CR indicates better reproducibility. A two-sided and unpaired Student's *t*-test was used to compare differences in absolute SMBF values and reserves between different foot regions or different groups. The level of statistical significance was set at $P < 0.05$. Statistical analyses were performed with JMP Pro Statistical Software Release 13.2.1 (SAS Institute, Cary, NC), SAS Statistica Release 13, and MedCalc Statistics for Biomedical Research Version 18 (MedCalc Software, Ostend, Belgium; <https://www.medcalc.org>; 2017).

Results

All participants successfully performed the study with no adverse incidents. HbA1c (%) in the DM group was significantly higher than that in non-DM group (8.1 ± 2.6 vs. 5.9 ± 0.4 , $P = 0.04$). There was no significant difference in ABI (DM, 1.32 ± 0.3 vs. non-DM, 1.14 ± 0.08 , $P = \text{NS}$) or TBI (DM, 0.75 ± 0.21 vs. non-DM, 0.76 ± 0.2 , $P = \text{NS}$) between the two groups. For the reproducibility study, the mean values of SMBF and related CR for global medial and lateral regions in feet are shown in Table 1. The CR for either rest or exercise SMBF was considerably lower in the lateral region than in the medial region. The SMBF reserves had the best reproducibility (Table 2).

In both groups, exercise SMBF values in both medial and lateral angiosomes were significantly higher than those at rest. However, these differences become smaller in the DM group. The resultant SMBF reserves in the DM group were significantly lower than those in the non-DM group (Fig. 3). When combining perfusion in both angiosomes, the foot perfusion reserve was significantly lower in the DM group compared with that in the non-DM group (1.34 ± 0.32 , 95% CI: 1.1, 1.58 vs. 1.76 ± 0.31 , 95% CI: 1.53, 1.98, $P = 0.02$).

In the DM group, the exercise SMBF and SMBF reserve adjacent to foot ulcers (peri-ulcer) were 8.7 ± 3.9 ml/min/100g and 1.07 ± 0.39 , respectively. These values were significantly lower than exercise SMBF (12.7 ± 3.8 ml/min/100g, $P = 0.02$) and SMBF reserve (1.39 ± 0.37 , 95% CI: 1.11, 1.66, $P = 0.03$), respectively, in other regions (away-ulcer) of the same foot (Fig. 3). If the DM group was further separated into healed ulcer ($n = 5$) and nonhealed ulcer ($n = 5$) subgroups, peri-ulcer exercise SMBF values were substantially lower in the nonhealed ulcer group (6.3 ± 3.1 ml/min/100g) than those in the healed ulcer group (11.1

± 3.2 ml/min/100g, $P < 0.05$). This is also true for exercise SMBF in the away-ulcer regions between healed and nonhealed subgroups (healed: exercise SMBF = 15.2 ± 2.8 ml/min/100g vs. nonhealed: exercise SMBF = 10.3 ± 3.3 ml/min/100g, $P < 0.05$). There was no significant difference in SMBF reserve between these regions (Fig. 3).

Figure 4 shows two cases of a healed foot ulcer and a nonhealed foot ulcer, 3 months after the respective MRI study. In the case of healed ulcer, the peri-ulcer SMBF increased from rest to exercise. The exercise SMBF was 11.8 ± 5.3 ml/min/100g and was larger than average peri-ulcer SMBF. In the case of the nonhealed ulcer, the peri-ulcer exercise SMBF was only 7.8 ± 1.7 ml/min/100g, despite a relatively high away-ulcer exercise SMBF of 11.2 ± 13.5 ml/min/100g.

Discussion

This pilot study demonstrated a new approach for exercise-based foot perfusion measurements with a dedicated foot dynamometer. Based on the mean and standard deviation of each SMBF and SMBF reserve, good to moderate reproducibility of perfusion measurement in the intrinsic foot muscles was achieved with 20% MVC. In participants with DM and foot ulcers, the regions adjacent to the ulcers showed significantly lower absolute exercise perfusion, in comparison with the perfusion in other muscle regions at a quantitative level by the assistance of grids-eye perfusion display. In addition, the overall perfusion reserve in these patients was significantly lower than that in the participants without DM and ulcers.

Although there was a report that a foot dynamometer has been used to measure the maximal toe-flexion strength, the MRI study was performed separately from the foot strength measurement.¹² Our foot dynamometer allows a participant to perform standardized foot isometric exercise in an MRI environment. This study demonstrates the feasibility of patients performing the tasks in a clinical setting. All participants appeared motivated to make the best effort to adjust the toe-flexion strength with the assistance of real-time video display during the exercise scan. In addition, the ASL method we employed is much less sensitive to the variation of tagging transit time. For example, mean blood flow velocity in dorsalis pedis artery is 3.4 ± 1.6 cm/sec.²⁴ For our imaging parameters in foot, the edge of the slice of the inversion recovery pulse to the edge of the imaging slice was 4 mm. Therefore, the transit time was estimated as 0.4 (cm)/ 3.4 (cm/sec) or 118 msec. Since all TIs we used were above 220 msec, the effect of transit time was minimized for this T₁-difference ASL approach.²⁵

The absolute SMBF values (~ 15 ml/min/100g in participants without DM) in this study were much lower than those (~ 97 ml/min/100g in healthy participants) reported in a previous study.¹⁸ There are four reasons for this: 1) in the previous study, participants were instructed to flex their toes as hard as possible (100% MVC), thus showing much higher exercise SMBF values, in comparison with exercise SMBFs in the current study with only 20% MVC; 2) in this study, regional SMBF values were obtained only in pixels with SMBF values less than 200 ml/100g/min on the SMBF maps. Those sparse pixels with unrealistic high SMBF values were thus filtered out; 3) the average number for a perfusion data

acquisition was 4 in this study and was 3 in the previous study. This may have resulted in improved accuracy for the perfusion measurement secondary to the increased signal-to-noise ratio (SNR); 4) careful image segmentation for identifying foot muscle was performed prior to perfusion map calculation, which may have reduced the variability of the perfusion calculation due to the presence of fat, tendon, and ligament.

Unlike the results presented previously,¹⁸ there was no significant difference in either rest or exercise SMBF on medial and lateral regions between participants without DM/ulcers and patients with DM and ulcers. Nevertheless, both studies demonstrated a significant difference in SMBF reserve for the medial region between the participants with and without DM. It appears that the SMBF reserve, rather than the absolute SMBF at rest or during exercise, is a useful biomarker to differentiate DM from non-DM. This finding will need a larger sample size to validate.

By using a 2D grids-eye display, the foot segments with ulcers and adjacent muscles can be easily identified for the entire foot muscle volume. Although the overall rest or exercise SMBF values were not significantly different between the participants with DM and without DM, the peri-ulcer exercise SMBF (8.7 ± 3.9 ml/min/100g) around ulcers was significantly below the away-ulcer exercise SMBF (12.7 ± 3.9 ml/min/100g, $P = 0.02$), per analysis of grids-eye segments in the same DM group. This observation is consistent with a “real angiosome assessment” in foot ulcers, in which foot ulcers were always located around an area with relatively lower tissue oxygen saturation (StO_2), compared with StO_2 in other normal foot areas.²⁶ The report explained the physiologic mechanism of the “real angiosome” associated with foot ulcers, but more experimental and clinical studies are needed for rigorous validation. Furthermore, both peri-ulcer and away-ulcer exercise SMBF values were significantly lower in DM patients who had nonhealed ulcers than those in DM who had healed ulcers. A large-scale study is therefore warranted to determine whether SMBF values and/or reserves can be sensitive predictors for foot healing.

There are several limitations in this study, in addition to the relatively small sample size. First, the participants might have had slight foot motion during the toe-flexion exercise. Despite motion correction in the image plane, the motion along the slice thickness direction cannot be corrected with current software and is acknowledged as a potential error for perfusion measurements. Second, the imaging volume covered only the intrinsic foot muscle within the surface coil, from level of transverse head of the adductor hallucis muscle to the level of calcaneus. There is no perfusion measurement in the soft tissue of toes. Third, there was no reproducibility measurement in patients with DM. Fourth, unlike the previous study,¹⁹ there was no MR angiography to verify the presence or absence of peripheral arterial disease, except relying on clinical assessment using ABI. Finally, there were no restrictions on the activity level and/or caffeine intake prior to MRI scans. This may have caused small variations in foot perfusion.

In conclusion, the new MRI-compatible foot dynamometer and standardized exercise foot perfusion measurement techniques allow simple, efficient, and intravenous contrast-free perfusion assessment of the diabetic feet in a clinical setting. While clinically established ABI method indicated no difference between DM and non-DM groups, our MRI method

demonstrated clearly the perfusion deficit in patients with DM and foot ulcers. The exercise perfusion and/or perfusion reserve adjacent to a foot ulcer was significantly lower than those in other foot regions at an exercise level of 20% MVC. This exercise-based perfusion thus may potentially allow the assessment of foot ulcer healing, although large clinical trials are needed to validate.

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FIGURE 1:

Schematic illustration of the new MRI-compatible foot dynamometer (a). The right dashed area indicates this portion is completely shielded from the magnetic field. Photos of the foot dynamometer device (b); screen shots of output display for the participant to view during a foot exercise scan (c,d). The blue curves are the dynamical display of flexion pressure so that the participant can control the flexion strength during the scan. The red dashed lines indicate the tolerance range of the strength (15–25% MVC). The rate of display was 5 Hz.

FIGURE 2: Grids eye display of SMBF. Angiosome of a right foot to show medial (blue) and lateral (yellow) regions that are segmented into six segments in one slice (a). Averaged SMBF maps over three slices of a foot in a non-DM participant at rest (b) and during the toe-flexion exercise (c). The color scale bar adjacent indicates 0–55 ml/min/100g. Illustration of a grids-eye display of a total 18 segments for three slices (d). The grids-eye maps of SMBF distribution from the same participant in (b,c), at rest (e) and during the exercise (f). Color scale of grids eye: 0–55 ml/min/100g.

FIGURE 3:

The comparisons of SMBF reserves in non-DM participants (for both repeated measurements #1 and #2) and patients with DM and foot ulcers (a). The foot area was separated to medial and lateral regions. The comparisons of exercise SMBF values in patients with DM and ulcers between peri-ulcer and away-ulcer regions (b). These patients were also separated into healed and nonhealed groups.

FIGURE 4:

A photo of a foot ulcer and averaged SMBF maps over three slices of a left foot in a patient with DM and a foot ulcer (a), at rest and during the toe-flexion exercise. The grids-eye maps of SMBF distribution from this patient during the exercise (b). The dashed yellow circles indicate surrounding segments adjacent to the ulcer with relatively low, but still elevated exercise SMBF. The ulcer was healed 3 months after this MRI. The photo of another foot ulcer and averaged SMBF maps in a patient (c). The grids-eye maps of SMBF distribution from this patient during the exercise (d). The dashed yellow circles indicate surrounding segments adjacent to the ulcer with very low exercise SMBF. The ulcer was not healed 3 months after this MRI. Color scale bars: 0–55 ml/min/100g.

TABLE 1.

Summary of Perfusion Values and Coefficient of Repeatability (CR)

	Rest			Exercise		
	Rest #1 (ml/min/100g)	Rest #2 (ml/min/100g)	CR	Exercise #1 (ml/min/100g)	Exercise #2 (ml/min/100g)	CR
Non-DM (M)	9.8 ± 3.9	9.6 ± 4.5	4.7 (3.1,9.6)	17.2 ± 7.2 *	16.3 ± 5.4 *	7.1 (4.7,14.4)
Non-DM (L)	7.0 ± 2.2	7.7 ± 3.7	2.9 (1.9,5.8)	12.6 ± 5.5 *	13.2 ± 6.1 **	2.7 (1.8,5.4)
DM (M)	11.1 ± 4.3			14.1 ± 3.8		
DM (L)	7.7 ± 3.2			10.2 ± 5.1		
Away-Ulcer	9.5 ± 3.3			12.7 ± 3.8 *		
Peri-Ulcer	8.6 ± 3.8			8.7 ± 3.9 †		

Data in the parenthesis in "CR" columns indicate the 95% confidence interval (CI). DM = diabetes mellitus, non-DM = without diabetes mellitus. M = medial foot region, L = lateral foot region.

* $P < 0.01$;

** $P < 0.05$. All P values were obtained by two-tailed paired t testing between SMBFs during exercise and respective SMBFs at rest.

† $P < 0.05$, vs. Away-Ulcer.

TABLE 2.

Summary of Perfusion Reserve Values and Coefficient of Repeatability (CR)

	Reserve #1	Reserve #2	CR
Non-DM (M)	1.76 ± .39 (1.47,2.05)	2.11 ± .53 (1.72,2.5)	1.6 (1.1,3.3)
Non-DM (L)	1.77 ± .36 (1.5,2.04)	1.82 ± .63 (1.36,2.29)	0.9 (0.6,1.8)
DM (M)	1.36 ± .36* (1.09,1.62)		
DM (L)	1.34 ± .38* (1.05,1.62)		
Away-Ulcer	1.39 ± .37* (1.11,1.66)		
Peri-Ulcer	1.07 ± .39* [†] (0.78,1.35)		

Data are expressed as mean ± standard deviation and data in parentheses indicates the 95% confidence interval (CI). DM = diabetes mellitus, non-DM = without diabetes mellitus. M = medial foot region, L = lateral foot region.

* $P < 0.05$, vs. Non-DM, Reserve #1.

[†] $P < 0.05$, vs. Away-Ulcer.