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Oximetric Angiosome Imaging in Diabetic Feet

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Abstract

Purpose—To develop a noncontrast oximetric angiosome imaging approach to assess skeletal muscle oxygenation in diabetic feet.

Materials and Methods—In four healthy and five subjects with diabetes, the feasibility of foot oximetry was examined using a 3T clinical magnetic resonance imaging (MRI) scanner. The subjects' feet were scanned at rest and during a toe-flexion isometric exercise. The oxygen extraction fraction of skeletal muscle was measured using a susceptibility-based MRI method. Our newly developed MR foot oximetric angiosome model was compared with the traditional angiosome model in the assessment of the distribution of oxygen extraction fraction.

Results—Using the traditional angiosome during the toe-flexion exercise, the oxygen extraction fraction in the medial foot of healthy subjects increased ($4.9 \pm 3\%$) and decreased ($-2.7 \pm 4.4\%$) in subjects with diabetes (difference = 7.6%; 95% confidence interval = -13.7 ± 1.4 ; $P = 0.02$). Using the oximetric angiosome, the percent difference in the areas of oxygen extraction fraction within the 0.7–1.0 range (expected oxygen extraction fraction during exercise) between rest and exercise was higher in healthy subjects ($8 \pm 4\%$) than in subjects with diabetes ($4 \pm 4\%$; $P = 0.02$).

Conclusion—This study demonstrates the feasibility of measuring skeletal muscle oxygen extraction fraction in the foot muscle during a toe-flexion isometric exercise. Instead of assessing oxygen extraction fraction in a foot muscle region linked to a supplying artery (traditional angiosome), the foot oximetric angiosome model assesses oxygen extraction fraction by its different levels in all foot muscle regions and thus may be more appropriate for assessing local ischemia in ulcerated diabetic feet.

Foot disorders (such as ulceration, infection, and gangrene) are the leading causes of hospitalization in patients with diabetes mellitus (DM).^{1,2} Foot ulcers are an important

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complication of DM and often precede lower-extremity amputation.^{3,4} Insufficient perfusion, due to peripheral vascular disease (PVD), ie, macrovascular disease, and/or DM, ie, microvascular disease, of the tissues may be the most important component contributing to ulcer formation and limiting healing.⁵ Percutaneous transluminal angioplasty is a commonly utilized revascularization option to increase downstream tissue perfusion. Despite successful revascularization, the rate of ulcer healing remains 40% or less in patients with foot ulcers and diabetes.⁶ One key prognostic factor that is currently lacking in diabetic foot care is an accurate indicator of the local microvascular bed basal flow (skeletal muscle perfusion) and responsiveness (skeletal muscle oxygenation) to help guide diagnosis and intervention.

The angiosome concept, defined by Taylor and Palmer in 1987,⁷ has been increasingly incorporated into endovascular procedures to treat patients with foot ulcers.^{8–10} This angiosome model (called traditional angiosome in this project) divides the foot into three angiosomes: medial plantar, lateral plantar, and calcaneal angiosomes. These angiosomes are supplied by blood flow from medial plantar, lateral plantar, and medial calcaneal arteries, respectively. After identifying the artery responsible for perfusing the angiosome in which the ulcer is located, directed revascularization of that end-artery is undertaken to optimize healing. However, this angiographic angiosome may not be appropriate to address the local tissue perfusion that cannot be visualized by angiography, especially in patients with DM.¹¹ Furthermore, assessment of the effectiveness of the vascular treatment still mostly relies primarily on the toe pressure or transcutaneous oxygen tension (TcPO₂), which may not be a sensitive indicator of the perfusion in the specific area where the wound is located.^{9,10} In addition to the observation that toe pressure often fails to assess the specific region at risk (ie, the wound), toe pressures cannot be obtained on patients with a toe amputation. TcPO₂ cannot assess perfusion beyond the skin, a critical limitation when the wound bed extends beyond the epidermis, into the dermis and muscles of the foot. The lack of specificity in blood perfusion assessment can result in unnecessary major arterial interventions, or patients may not undergo an intervention when one might be of value.

Recently, a study using a near-infrared tissue oximeter monitor provided tissue oxygen saturation (StO₂) foot-mapping as a modified angiosome assessment.¹² It was observed that this new “angiosome” is more appropriate for detecting the ischemic areas on skin associated with foot ulcers than is the traditional angiosome model. This modified angiosome model, however, still only evaluates skin oxygenation. Magnetic resonance imaging (MRI)-based microcirculation assessment approaches allow assessment of not only skeletal muscle blood flow (SMBF),¹³ but also skeletal muscle oxygenation extraction fraction. This project was thus performed with a twofold aim: to demonstrate the feasibility of an MRI-based microcirculation assessment method for measuring oxygen extraction fraction of foot skeletal muscle and to compare two types of angiosome models for evaluating oxygen distribution in both healthy and diabetic feet.

Materials and Methods

MRI Oximetry in Skeletal Muscle

The technical details of the MRI oximetry method were previously reported.¹⁴ Briefly, the method was derived from a model¹⁵ used to calculate tissue oxygen extraction fraction (OEF) with the magnetic susceptibility effect on deoxyhemoglobins.^{16,17} In this study, the OEF in foot muscle was termed skeletal muscle OEF (SMOEF). It is calculated as $([O_2]_{\text{artery}} - [O_2]_{\text{vein}})/[O_2]_{\text{artery}}$. A multislice 2D triple-echo asymmetric spin-echo sequence was implemented to acquire source images. The asymmetric spin-echo was formed when the 180° pulse has a time offset (τ) from $TE/2$. After the 180° pulse, triple-echo asymmetric spin echo images were acquired with $TE_1 = 44$ msec, $TE_2 = 76$ msec, and $TE_3 = 103$ msec. With varying τ , a total of 56 images were acquired. This acquisition scheme yielded a series of $TE(2\tau)$ ranging from $(-18$ msec, 27 msec), $(0, 45$ msec), and $(18, 63$ msec), respectively, for each echo. A special transverse relaxation rate $R_2' (=R_2 - R_2^*)$ with a decay time of 2τ was calculated.

According to a theoretical model,¹⁵ R_2' was written as:

$$R_2' = \lambda \frac{4}{3} \pi \gamma \cdot \Delta\chi_0 \cdot \text{Hct} \cdot \text{OEF} \cdot Y_a \cdot B_0. \quad (1)$$

where λ is the blood volume fraction containing deoxyhemoglobin, representing tissue venous blood volume; Hct is the fractional hematocrit; B_0 is the main magnetic field strength; and $\Delta\chi_0$ is the susceptibility difference between fully oxygenated and fully deoxygenated blood, which has been measured to be 0.27 ppm per unit Hct in centimeter-gram-second units.¹⁷ Both R_2' and λ were calculated by asymmetric spin echo signals as a function of τ .¹⁴

MRI Foot Oximetry Study Protocol

Four healthy volunteers (72 ± 3 years, four male) and five subjects with diabetes (Types I or II, 65 ± 4 years, four male, $\text{HbA1c} = 7.2 \pm 1.8\%$, diabetes duration = 1–10 years, three with neuropathy) without documented history of peripheral artery disease were scanned for the measurement of foot SMOEF. The exclusion criteria included participants who had contraindications to MRI (implantable cardiac defibrillator or pace makers, over 400 lbs, and pregnancy). This study was approved by our Institutional Review Board (IRB) and written consent was obtained from each participant prior to the study.

All imaging sessions were performed with a 3.0T Trio Siemens whole-body MR system (Siemens Healthcare, Malvern, PA). The subjects lay supine on the MRI table with one or two feet inside a head coil. A body coil served as the transmitter and the head coil was the receiver coil. The oximetry measurements were performed during a sustained “toe-flexion” exercise.¹³ Subjects were instructed to contract their intrinsic foot muscles to flex their toes at the metatarsal phalangeal joints and “shorten their feet,” which have been shown to best activate the intrinsic foot muscles.¹⁹ In these preliminary studies, this muscle contraction

could not be quantified as a percentage of maximum voluntary contraction and was merely used as a challenge to increase foot muscle activity and oxygen demand.

A scout image was first acquired to localize the foot in plantar and medial orientations, followed by a T_1 -weighted spin-echo imaging with three slices. This T_1 -weighted imaging was also performed during the toe-flexion exercise to ensure that the three slices covered the same muscle areas. The three-slice oximetry measurements were then performed at rest and during the toe-flexion exercise. Exercise lasted for 14 minutes and data acquisition started at 30 seconds after the start of toe-flexion. The imaging parameters for oximetry measurements were: TR = 4 sec; fat saturation; field of view (FOV) = $340 \times 255 \text{ mm}^2$; matrix size = 64×48 and interpolated to 128×96 ; slice thickness = 8 mm; total acquisition = 3 minutes 24 seconds.

Angiosome Models

In a similar fashion as reported previously,¹³ an SMOEF map of each slice was created using custom-made software written in Mat- Lab (MathWorks, Natick, MA). Because the foot consists of collagen, bone, tendon, ligaments, and muscle, the T_1 -weighted scout images were first used to select muscle regions; this was done based on the hypointensity of the muscle. These regions were then selected on the asymmetric spin-echo images for image processing to calculate SMOEF maps.

To create an angiosome map, a maximal intensity projection map was first obtained from the three slices of SMOEF maps. This projection image was further processed for two types of angiosomes. First, from the plantar view of the projected map the entire foot was separated into three regions: medial, lateral, and calcaneal. This is the traditional angiosome (Fig. 1a). Because the majority of the calcaneal region is composed of calcaneal bone, this region was excluded from further analysis. The mean SMOEF in medial and lateral regions were obtained using ImageJ software (National Institutes of Health, Bethesda, MD, v. 1.48v).

Second, from the same plantar view of the projection map the entire foot area (excluding the calcaneal region) was classified into regions based on four different SMOEF ranges: $0 \leq \text{SMOEF} < 0.3$; $0.3 < \text{SMOEF} < 0.5$; $0.5 < \text{SMOEF} < 0.7$; $0.7 < \text{SMOEF} < 1.0$ (Fig. 1b).¹¹ Generally speaking, normal resting SMOEF was in the 0.3 to 0.5 range, whereas exercise SMOEF should rise above 0.5. Areas of the four SMOEF regions were measured using ImageJ software, and each region's area was calculated as a percent of the total area. This angiosome model is called foot oximetric angiosome.

Statistical Analysis

The percent differences in a parameter between exercise and rest were calculated as follows: $(\text{Parameter_Exercise} - \text{Parameter_Rest}) / \text{Parameter_Rest} \times 100$. All data distributions were tested for normality with the Shapiro-Wilk W -test. Means, standard deviations, and 95% confidence intervals were used for descriptive statistics. Percent differences in SMOEF for the two groups of subjects (healthy vs. diabetes) were normally distributed (Shapiro-Wilk W -test, $P > 0.05$) and were assessed for differences with the t -test. Before performing the t -test, equality of variances was tested with the O'Brien, Brown-Forsythe, Levene, Bartlett,

and 2-sided F -tests, to determine if the t -test assuming equal or unequal variances would be used.

Results

All subjects were able to perform the instructed toe-flexion exercise during the 4-minute scans. Table 1 lists descriptive statistics for the two types of angiosomes (medial plantar and lateral plantar). SMOEF increased during the toe-flexion exercise in the medial region of healthy subjects (from 0.57 ± 0.06 to 0.60 ± 0.06), whereas SMOEF in this region decreased in diabetic subjects (from 0.69 ± 0.07 to 0.67 ± 0.07) with a significant difference between healthy and diabetic subjects ($P = 0.02$). No difference in SMOEF between rest and exercise was observed in the lateral region for healthy and diabetic subjects ($P = 0.15$). Boxplots for SMOEF in the medial plantar region for exercise and rest are presented in Fig. 2a. Figure 3 shows examples of the traditional angiosomes in a healthy subject and a subject with diabetes.

For the foot oximetric angiosome, Table 1 lists percent in areas of SMOEF in four different SMOEF ranges at rest and during the toe exercise. For the first three ranges in which SMOEF was less than 0.7, there was no difference between healthy subjects and subjects with diabetes. However, the difference between exercise and rest for the areas of SMOEF within the 0.7–1.0 range was significantly larger ($P = 0.02$) in healthy subjects ($8 \pm 4\%$) than in subjects with diabetes ($-4 \pm 4\%$). Boxplots for these percent differences in 0.7–1.0 range are presented in Fig. 2b. Figure 4 shows the foot oximetric angiosomes of the same subjects as in Fig. 3.

Discussion

Absolute tissue oxygen extraction fraction was measured in the foot at rest and during a toe-flexion exercise. Healthy subjects and subjects with diabetes were compared for the SMOEF values in their right feet. Two types of angiosomes were analyzed to describe the distribution of SMOEF in feet: 1) traditional medial and lateral angiosome, and 2) foot oximetric angiosome. The most clinically important finding is that increases in SMOEF from rest to toe exercise were significantly larger in healthy than diabetes subjects in the traditional medial plantar angiosome. This is also true of the 0.71–1.0 range in the foot oximetry. Due to the small sample size, a post-hoc power calculation indicated that in the 0.71–1.0 range the power was 97% with alpha set at 0.05. For the medial plantar region, the power was 71% with alpha set at 0.05. This post-hoc power calculation supports the feasibility of using oximetry-angiosome imaging in diabetic feet and indicates that further research of this approach with larger sample sizes is warranted.

Previous research found that angiosome-guided infrapopliteal revascularization resulted in a significantly improved ulcer healing rate in comparison with an indirect revascularization approach.^{20,21} Despite the initial success of this targeted revascularization, as many as 54% of foot ulcers cannot be simply categorized to a specific angiosome due to dual blood supplies.²² Furthermore, locally impaired tissue perfusion also affects ulcer healing and recurrence rates.²³ The foot oximetric angiosome allows for direct determination of the low-

or high-oxygenated regions that may be supplied by one or more pedal arteries. This angiosome distribution may be more appropriate for patients with diabetes because impaired local microcirculation is common and clinically important in subjects with diabetes, even without obstructive peripheral arterial stenosis.

The MRI technique to measure SMOEF in the foot muscle is the same one used in calf muscle¹³ and brain tissue.¹⁵ The former study revealed increased SMOEF during a 4-minute isometric ankle plantar flexion contraction in the calf muscles of healthy volunteers, but unchanged SMOEF in subjects with diabetes. This is consistent with results reported using near-infrared spectroscopy techniques to measure OEF in the skin and adipose tissue of lower extremities of healthy subjects, where increased muscle oxygen consumption during exercise was met with both increases in OEF and skin blood flow.^{24,25} However, there was no report of the same isometric toe-flexion exercise, as in this study, for the assessment of skin or skeletal muscle oxygenation. The relatively small increase in SMOEF during the toe-flexion exercise may be caused by the variations of toe-flexion strength controlled by the subjects. While the subjects were told to flex their toes and hold it there, current methods did not allow us to measure and monitor the force of the toe-flexion contraction. Despite the small changes in SMOEF, the exercise still can differentiate diabetic feet from healthy feet with both angiosome approaches.

The 0.71–1.0 range in oximetric angiosome represents the high end of these SMOEF values in the foot muscle. It appears that muscle with SMOEF in this high range at rest is capable of increasing oxygen extraction during exercise in healthy subjects. We do not see the same pattern in subjects with DM. This may be explained by a blunted oxygen increase to meet the demand of oxygen consumption in “activated” muscle area in the diabetic foot. For this reason, this range of SMOEF could be used as a potential biomarker to assess the impaired vasodilation. Nevertheless, this speculation needs a larger sample size to validate.

None of the subjects with DM had any clinical symptoms consistent with vascular disease, eg, rest pain, although 3/5 had neuropathy. It appears that the absolute mean SMOEF at rest in subjects with DM is higher than that in healthy subjects. This difference may be due to reduced tissue perfusion in these patients and oxygen demand in tissue has to be met with increased oxygen extraction, even at rest. No difference was observed in SMOEF values during exercise between healthy subjects and subjects with DM. While these observations may provide direct measures in the microcirculation in the neuropathic and/or diabetic foot, clinical guidance using this measurement remains unclear, until the results of this study are clarified and expanded with larger sample sizes.

There are several limitations in the current study. First, the sample size was small; therefore, limited statistical testing was performed and the results of statistical testing have to be interpreted carefully. Because six *t*-tests were performed, to protect against Type I error, a Bonferroni adjustment to an alpha of 0.05 could be used, which resulted in a Bonferroni adjusted alpha of 0.01. With this Bonferroni adjustment, none of significances in our results reach the threshold for statistical significance. However, there is a concern (particularly within epidemiology) that Bonferroni adjustment may be deleterious to statistical inference

and that by increasing the Type II error rate, its use may result in true biological differences being found to be nonsignificant.²⁶

Second, exercise strength was not normalized. This could result in relatively large variations in the measured SMOEF during the exercise. Nevertheless, the variation of measurements of SMOEF at rest was similar to that during the exercise, which indicated that this error would have been very small in this pilot study. Finally, foot motion during the 4-minute exercise period may affect the accuracy of the SMOEF calculation. Fortunately, this motion mostly affected the tissue around the toes, upon review of the individual source images from the SMOEF datasets. The intrinsic muscles (eg, flexor hallucis longus, flexor hallucis brevis, flexor digitorum longus, flexor digitorum brevis, etc.) involved in the toe-flexion demonstrated much less motion.

In summary, this study demonstrates the feasibility of measuring SMOEF in the foot muscle at rest and during toe-flexion isometric exercise. Two angiosome models are presented for the facilitation of assessment of SMOEF distribution in the foot. While the traditional foot angiosome is directly linked to individual end-artries, the foot oximetric angiosome reflects local SMOEF distribution, which may be more appropriate for assessing diabetic feet.

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FIGURE 1.

Schematic illustrations: (a) traditional angiosome and (b) perfusion oximetry. In (c), lateral view of a foot in a T_1 -weighted image at rest (top panel) and during toe-flexion exercise (bottom panel). For both angiosomes, the calcaneal region was excluded from data analysis.

FIGURE 2.

Boxplots for healthy subjects and subjects with diabetes. (a) For the traditional angiosome model, boxplots of percent differences between exercise and rest for medial-plantar SMOEF values. (b) For the foot oximetric angiosome model, boxplots of the percent differences between exercise and rest for the areas of SMOEF within the 0.7–1.0 range. The ends of the boxes are the 25th and 75th quantiles (quartiles). The lines across the middles of the boxes are the medians. The interquartile range is the difference between the quartiles. The lines (whiskers) extend from the boxes to the outermost points that fall within the distance computed as 1.5 (interquartile range).

FIGURE 3.

Comparison of SMOEF maps overlaid on anatomical images with the traditional model for a healthy subject (a) and a subject with controlled diabetes (b). The diabetic subject was a 72-year-old male without peripheral neuropathy and peripheral arterial disease. The calcaneal area outlined by the green line was excluded from data analysis. Note that during the toe-flexion exercise, the shape of foot was slightly different from that at rest. Distributions of SMOEF in feet are heterogeneous and exercise SMOEF appeared to redistribute blood flow. Such heterogeneity cannot be appreciated in the traditional angiosome model, although exercise SMOEF increased in the healthy foot and reduced in the diabetic foot in the medial angiosome. Also note that SMOEF at rest in the diabetic foot appeared higher than that in the healthy foot.

FIGURE 4.

Comparison of SMOEF distribution in the foot oximetric angiosome model for the same subjects as Fig. 3. In the healthy subject, toe exercise increased the “red” area, in a comparison with the map at rest. In the subject with diabetes, the “red” area in the exercise oximetry map appeared less than that in the corresponding map at rest. The overall SMOEF at rest in the diabetic foot also appeared higher than that in the healthy foot.

TABLE 1

Descriptive Statistics and Test Results for SMOEF in Healthy Subjects and Subjects With Diabetes, at Rest and During Toe-Flexion Exercise

Parameter	Healthy	Diabetes	Difference (95% CI)	P value ^d
Medial plantar	<i>n</i>	<i>n</i>		
SMOEF (Exercise)	4 0.60 (0.06)	5 0.67 (0.07)		
SMOEF (Rest)	4 0.57 (0.06)	5 0.69 (0.07)		
Difference, % ^a	4 4.87 (2.96)	5 -2.69 (4.43)	-7.56 (-13.69 to -1.43)	0.02 ^b
Lateral plantar				
SMOEF (Exercise)	4 0.59 (0.08)	5 0.61 (0.12)		
SMOEF (Rest)	4 0.58 (0.10)	5 0.70 (0.03)		
Difference, % ^a	4 2.08 (8.95)	5 -12.48 (15.72)	-14.56 (-35.57 to -6.46)	0.15 ^b
0 SMOEF 0.3				
Percent in Area (Exercise)	4 35 (19)	5 28 (14)		
Percent in Area (Rest)	4 43 (13)	5 26 (18)		
Difference	4 -8 (16)	5 2 (4)	35.76 (-22.69 to -94.21)	0.17 ^c
0.3 < SMOEF 0.5				
Percent in Area (Exercise)	4 19 (12)	5 24 (4)		
Percent in Area (Rest)	4 17 (9)	5 18 (6)		
Difference	4 3 (7)	5 6 (5)	30.58 (-39.07 to -100.24)	0.33 ^b
0.5 < SMOEF 0.7				
Percent in Area (Exercise)	4 13 (4)	5 15 (6)		
Percent in Area (Rest)	4 16 (5)	5 19 (7)		
Difference	4 -3 (9)	5 -4 (4)	-11.38 (-96.08 to -73.32)	0.73 ^c
0.7 < SMOEF 1.0				
Percent in Area (Exercise)	4 33 (6)	5 33 (10)		
Percent in Area (Rest)	4 25 (9)	5 37 (13)		
Difference	4 8 (4)	5 -4 (4)	-52.32 (-92.21 to -12.43)	0.02 ^b

Data are means (with standard deviations in parentheses) except where otherwise indicated.

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^a Difference, % are percent differences in SMOEF between rest and exercise.

^b *P* value for *t*-test assuming equal variances (O'Brien, Brown-Forsythe, Levene, Bartlett, and 2-sided *F*-test, $P = 0.05$) and normal distributions to assess the null hypothesis that there was no difference between the values for healthy and diabetes.

^c *P* value for *t*-test assuming unequal variances (O'Brien, Brown-Forsythe, Levene, Bartlett, or 2-sided *F*-test, $P < 0.05$) and normal distributions to assess the null hypothesis that there was no difference between the values for healthy and diabetes.

^d The Bonferroni adjustment was used to protect against Type I error. The Bonferroni adjusted alpha was 0.01, and none of the reported *P* values achieved this threshold for statistical significance.