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REVIEW

RECENT DEVELOPMENTS IN THE MANAGEMENT OF CRITICAL LIMB ISCHEMIA

Hyperspectral imaging for noninvasive tissue perfusion measurements of the lower leg: review of literature and introduction of a standardized measurement protocol with a portable system

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ABSTRACT

INTRODUCTION: Hyperspectral imaging (HSI) is a noninvasive technique for transcutaneous measurements of tissue perfusion. This study (1) provides a review of the current literature on HSI for tissue perfusion measurements of the lower leg and (2) introduces a standardized measurement protocol for HSI measurements with a portable system.

EVIDENCE ACQUISITION: A literature search was performed for studies on tissue perfusion measurements with HSI in the lower extremity. A standardized protocol was developed to perform HSI measurements in 43 healthy volunteers at the plantar side of the foot and at the lateral side of the calf, with 3 consecutive hyperspectral images at each location.

EVIDENCE SYNTHESIS: The literature review identified 9 studies, including 2 of healthy volunteers, 4 of patients with diabetes mellitus, and 3 of patients with peripheral arterial disease. In 5 of 7 patient studies, HSI values were associated with severity of disease or wound healing. In our study, the healthy volunteers' HSI values for oxyhemoglobin, deoxyhemoglobin, and oxygen saturation were (mean±SD) 82.8±24, 55.7±15.7, and 59.2±11.7, respectively, at the plantar surface of the foot, and 40.8±11, 38.0±7.8, and 51.7±10.5, respectively, at the lateral side of the calf. HSI values differed significantly between the calf and plantar locations. Intraoperator reliability between the 3 consecutive images ranged from 81% to 89%.

CONCLUSIONS: Limited evidence indicates that HSI is associated with severity of peripheral arterial disease and diabetes mellitus, and with wound healing. Hyperspectral images with a portable system can be taken with high precision when a standardized measurement protocol is used. However, differences exist at several locations at the lower extremity, so each measurement location should be used as its own reference when consecutive measurements are performed during follow-up. More studies with larger patient cohorts should be performed before HSI can be incorporated as standard tool in the diagnostic armamentarium of the vascular specialist.

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KEY WORDS: Peripheral arterial disease; Tissues; Perfusion; Wound healing.

Introduction

Hyperspectral imaging (HSI) is a perfusion imaging technique that uses visible light spectroscopy to determine concentration of oxyhemoglobin (oxyHb) and deoxyhemoglobin (deoxyHb) in the skin.[1] It has been used in different medical applications such as imaging-guided surgery and noninvasive diagnosis of cervical cancer.[1]

One of the emerging HSI applications is transcutaneous measurement of lower extremity tissue perfusion. The added value of HSI has been studied in patients with diabetes mellitus (DM), showing promising results.[2] Initial studies showed that HSI can determine a decreased tissue saturation caused by an impaired microcirculation.[3] In line with this, HSI could potentially be applied in patients with peripheral arterial disease (PAD) as well. Currently, the presence and severity of PAD is mainly determined by assessment of arterial inflow of blood in the legs with the focus on the macrovasculature. The diagnostic techniques used, including computed tomography scanning, magnetic resonance arteriography, and duplex ultrasound, determine stenosis or occlusion in large arteries but do not determine actual tissue perfusion. Assessment of tissue perfusion in patients with PAD is essential for diagnosis and quantifying disease progression and for guidance of treatment success, with focus on the microvasculature. Some studies have been performed with HSI in different patient groups, but studies on HSI in patients with PAD are scarce.

Several devices have been developed in recent years for measuring tissue perfusion with HSI. Most of the published studies have used the Oxy-Vu™-1 system (Hypermed Inc., Memphis, TN, USA). This device consists of a camera placed on a large workstation on wheels.[4-6] To enhance portability, a next-generation HSI device, named the HyperView™ system (Hypermed Inc.), has recently been introduced, which provides HSI incorporated in a hand-held camera. This hand-held camera has not been used in previous studies. Both image acquisition and assessment of the region of interest with this hand-held system are operator dependent, which is why standardization of the measurements is essential.

This report has two goals. First, a review is provided of current literature on tissue perfusion measurements with HSI in the lower extremity in healthy individuals and in patients with DM or PAD. Second, a standardized measurement protocol for portable HSI measurements is introduced to test the accuracy of HSI measurements in healthy subjects at different locations at the lower leg.

Evidence acquisition

Literature review

The literature search was performed in the electronic database PubMed for studies on tissue perfusion measurements with HSI. The search was performed with the help of Medical Subject Headings terms for "peripheral arterial disease," "diabetes mellitus," "hyperspectral," "HSI," "perfusion," and "lower extremity" for studies published in the last 20 years. Reference lists of included studies were screened for possible eligible articles. Articles were eligible if they used HSI to determine tissue perfusion of the lower extremity or feet in healthy subjects or in patients with DM or PAD. Exclusion criteria were case reports, reviews, case series (<10 patients), conference abstracts, letters to the editor, and commentaries. Studies using patient data from earlier published articles were also excluded.

Study details were extracted from the articles, and studies were categorized according to type of patient or subject. The following data were extracted: study design, number and type of patients, measurement location, measurement procedures, and HSI values. Literature search and data extraction was performed by 2 authors (S.K. and K.M.). In case of discrepancy between the 2 authors, a third author (J.P.V.) was consulted. Quality assessment of the studies was performed according to the Quality Assessment of Diagnostic Accuracy studies (QUADAS-2) method.[7]

Standardized measurement protocol for a portable hyperspectral imaging system

Hyperspectral imaging with the HyperView™ portable system

HSI uses wavelengths of visible light to illuminate and penetrate the upper 1 to 2 mm of the skin.[8] A spectrometer within the camera collects the light and measures the amount of light that is reflected, absorbed, and delivered by the skin. The multidimensional data are represented in hypercubes, and each pixel in the hypercube corresponds to the local reflectance spectrum of the tissue.[9] Knowledge of the absorption spectra of tissue chromophores is used to determine the amount of oxyHb and deoxyHb.[1] OxyHb has 2 absorption peaks at approximately 542 nm and 578 nm. DeoxyHb has a single absorption peak at approximately 554 nm. The measurements are presented as a 2-dimensional color-coded oxygenation map of the skin. Each pixel in the image represents the amount of oxyHb and deoxyHb. The HyperView™ portable camera is operated with 2 handlebars and a touch-screen for acquiring and analyzing images.

Healthy subjects

The study protocol was approved by the University Medical Center Groningen (UMCG) Central Ethics Review Board non-WMO studies (research register number #201900102). The study was conducted in the UMCG from June 2019 to August 2019. The inclusion criteria

Figure 1.—Positioning of the feet of a healthy subject and of the portable HyperView™ camera at a standardized distance of 15 inches and perpendicular to the plantar side of the feet.

were healthy volunteers, at least 18 years old, and who gave written informed consent. Exclusion criteria were the presence of PAD, DM, neurologic conditions, recent leg or ankle/foot fractures, lymphedema of the lower limbs, and other cardiovascular or pulmonary comorbidities. The study included 43 healthy volunteers. Participant characteristics were recorded, including sex, height, weight, and age. HSI was performed in 32 participants on the plantar side of the right and left foot and on the lateral side of the right and left calf muscle. Another 11 participants underwent HSI at the plantar side of the feet only.

Measurement protocol: preparation and positioning

The HyperView™ system user manual specifies a number of prerequisites for HSI. Taking into account these prerequisites, the following measurement protocol was developed. All participants underwent HSI in the same examination room in the UMCG outpatient clinic. This ensures that measurement conditions, such as light intensity and room temperature (20-23° C), were similar during every measurement session. Participants were placed on the examination table in a semi-Fowler's position with bare lower legs and feet (Figure 1). The legs were supported by a pillow and the feet positioned in a foot rest to minimize movement during the measurements. Attention was paid to a comfortable position of the legs and feet without any pressure points to the skin. Measurements were started after 5 minutes of rest.

Measurement protocol: imaging

HSI (3 consecutive images each time) with the HyperView™ portable system was performed at the plantar surface of both feet. The angle between the feet and examination table was determined, and the HyperView™ was placed on a tripod perpendicular to the surface of the forefoot at approximately 15 inches distance (Figure 1). The camera was focused on the plantar surface of the forefoot using the focusing lasers, just below and in between the head of the first and second metatarsal, ensuring that the complete foot was within the image. This plantar location was marked with a black marker (Figure 2A) to enable the same position of the camera for every image. Three hyperspectral images were taken subsequently of each location at the right and left foot. Local skin temperature of the marked locations was recorded in between the hyperspectral images with a FLIR 1020 infrared thermography camera (FLIR Systems, Wilsonville, OR, USA).

After imaging of the feet was completed, HSI was performed on the lateral side of the calf 6 cm distal from the fibular head. Hyperspectral images were taken 3 times at the right leg first. The local skin temperature was also determined with an infrared thermography camera. These measurements were repeated for the left calf.

Measurement protocol: imaging analyses

The hyperspectral images were analyzed with the use of commercially available software from HyperMed Inc. A region of interest (ROI) was manually selected at the same location for every image. The circle tool was selected, and a ROI with a diameter of 16 mm and an area of 215 mm^2 was drawn. The ROI in the images of the plantar side of the feet was selected around the head of the third metatarsal (Figure 2B). The ROI in the images of the lateral side of the calves was selected just distally from the marked location at the skin. The values for oxyHb, deoxyHb, and saturation at each location were recorded.

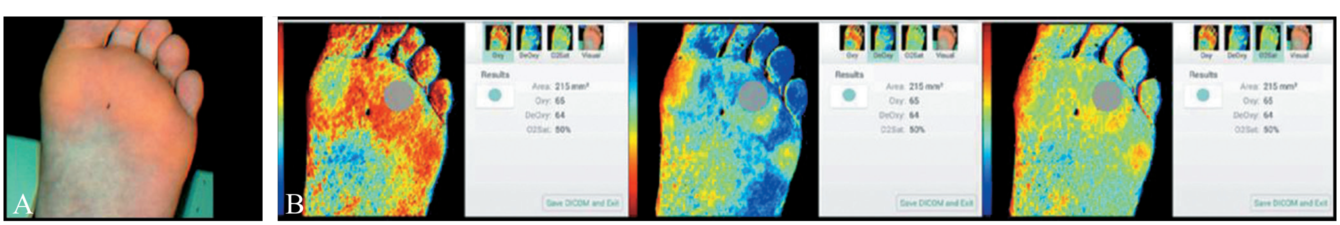

Figure 2.—A) Marked location (black spot) between the first and second metatarsal; B) example of hyperspectral imaging analyses with the HyperMed Inc. software. The region of interest was selected at the head of the third metatarsal (grey circle). From left to right, oxyhemoglobin, deoxyhemoglobin and oxygen saturation.

Statistical analysis

Data were collected in REDCap 7.3.2 (Vanderbilt University, Nashville, TN, USA). Statistical analyses were performed using SPSS 23 software (IBM Corp, Armonk, NY, USA). Descriptive statistics are described as mean and standard deviation or median and interquartile range according to the distribution of the data. Differences between the measurement location on the calf and the feet, and the differences between the right and the left leg were determined with a paired *t*-test. Intraclass correlation coefficient (ICC) estimates and their 95% confidence intervals (95% CIs) were used to evaluate intraobserver reliability. The calculations were based on a "single rater" type, absolute agreement, 2-way mixed-effects model. ICC values of less than 0.5 indicated poor reliability, values between 0.5 and 0.75 indicated moderate reliability, values between 0.75 and 0.9 were considered good reliability, and values greater than 0.9 reflected excellent reliability.[10]

Evidence synthesis

Literature review

Literature search

The literature search resulted in 9 articles investigating the use of HSI for tissue perfusion measurements in the lower extremity. There were 3 studies investigating HSI in patients with PAD, 4 studies in patients with DM, and 2 studies on healthy participants. The OxyVu-1 system was used in 6 of the 9 studies, 2 studies used another HSI device from HyperMed Inc., and in 1 study the device was not specified. Details of the studies are presented in Table I.[2, 4-6, 11-15] Bias and quality assessment with QUADAS-2 are shown in Figure 3, 4, respectively.[2, 4-6, 11-15]

Table I.—*Overview of studies on hyperspectral imaging in the lower extremity in patients with peripheral arterial disease, patients with diabetes mellitus and healthy subjects.*

Authors/year	Study design	N. patients	Measurement location	Measurement procedures	Main outcomes	HSI values
Studies on patients with PAD						
Jafari-Saraf 2010[11]	Prospective open comparator trial	Patients referred for ABI measurements. 53 ABI>0.9 22 ABI<0.9 and >0.45 10 ABI<0.45	Dorsum of the foot and ankle (3 locations) and volar side of forearm (1 location)	OxyVu system. Ambient room temperature 23-25° C.	There were no significant differences between the groups in HSI values. There was no significant correlation between ABI and HSI values.	OxyHb: ABI>0.9: 41.1±2.4, ABI>0.45 and <0.9: 38.5±3.9, ABI<0.45: 44.3±6.8. O_2 sat: ABI>0.9: 42.1±1.2%, ABI>0.45 and <0.9: 32.9±2.0%, ABI<0.45: 43.2±2.7%. (Mean with SEM)
Chin 2011[12]	Prospective cohort	65 PAD patients 46 healthy controls	9 locations: anterior calf, lateral calf, posteromedial calf, lateral ankle, medial ankle, dorsal metatarsal, plantar metatarsal, plantar arch, plantar heel angiosomes and at ulcer site when present.	Semi-Fowler's position. OxyVu system. Patients were divided in three groups for analysis according to triphasic, biphasic, and monophasic Doppler waveforms.	DeoxyHb values in the plantar angiosomes showed significant differences compared to healthy subjects. DeoxyHb values in the plantar angiosomes showed significant differences between the three groups. DeoxyHb correlated significantly with ABI for the plantar angiosomes.	Plantar metatarsal: OxyHb: PAD: 71.5±21.4, healthy: 73.3±21.0. DeoxyHb: PAD 49.7±12.9, healthy: 56.0±17.3*
Chiang 2017[5]	Prospective cohort	150 PAD patients 20 healthy controls	At the head of the first metatarsal on the plantar side	Supine. Room temperature: 20°-23° C. OxyVu system. HSI performed together with $TcPo_2$. Patients were divided in 2 groups for analysis according to Rutherford classification.	OxyHb and oxygen saturation correlated significantly with severity of PAD. Oxygen saturation correlated significantly with $TcPo_2$.	OxyHb: PAD: 76.4±24.4, healthy 100±31.3. DeoxyHb: PAD: 80.9±19.8, healthy: 71.2±13.2. O_2 sat: 47.8±10.6, healthy 56.9±8.4.

(To be continued)

TABLE I.—*Overview of studies on hyperspectral imaging in the lower extremity in patients with peripheral arterial disease, patients with diabetes mellitus and healthy subjects. (continues).*

Authors/year	Study design	N. patients	Measurement location	Measurement procedures	Main outcomes	HSI values
Studies on patients with DM						
Greenman 2005[2]	Prospective cohort	36 DM 51 DM with neuropathy 21 healthy controls	Forearm and foot	Sitting. HyperMed Visible MHSI system.	OxyHb and oxygen saturation in the foot of patients with diabetes was significantly lower compared to the control group.	OxyHb: DM + neuropathy: 19±9 DM: 24±9, controls: 25±13* DeoxyHb: DM + neuropathy: 45±13, DM: 41±11, controls: 44±8 O_2sat: DM + neuropathy 30±12, DM 37±12, controls 38±22.*
Khaodhiar 2007[13]	Prospective cohort	10 DM with ulcers 13 DM without ulcers 14 healthy controls	Plantar side feet, the palm of the hand, and at the ulcer site when present	Sitting. HyperMed CombiVu-R system. Healing index was calculated. Healing of ulcers was determined after 6 months.	HSI values were significantly lower at the site of non-healing ulcers than of healing ulcers.	OxyHb: healed 50±3, nonhealed 38±2* DeoxyHb: healed 49±2, nonhealed 26±3* (mean±SEM)
Nouvong 2009[4]	Prospective single-arm blinded	66 DM with ulcers	Dorsum of the foot and ulcer site when present.	Supine or sitting. OxyVu system. Healing of ulcers was determined at 24 weeks.	OxyHb and oxygen saturation was significantly higher in patients with healing ulcers.	OxyHb: healed 85±21; nonhealed 64±22 * DeoxyHb: healed 44±14; nonhealed 41±21 O_2sat: healed 66±9; nonhealed, 60±10*
Jeffcoate 2015[14]	Prospective clinical study	43 DM with ulcers	Dorsum of the foot between 1st and 2nd metatarsal and at the ulcer site	Device not mentioned. HSI expressed as one mean value in arbitrary units. Wound healing was determined at 12 and 24 weeks.	HSI value was significantly lower in patients with healed ulcers.	Healed ulcers: 47.9 (95% CI, 12.3-75.5) Nonhealed ulcers: 61.9 (95% CI 27.2-80.4)* (median and 95% CI)
Studies on healthy subjects						
Neville 2009[15]	Prospective cohort	194 healthy volunteers	11 regions; palm of hand, back of hand, anterior forearm, posterior forearm, lateral thigh, lateral leg above and below the knee, dorsal metatarsal, plantar metatarsal, heel, and plantar arch.	Supine or sitting. OxyVu system. HSI was repeated after 8 hours in 74 subjects.	Normal HSI values for population ranging from 18-80 years. Higher HSI values at the plantar side of the foot. There were no differences when repeating HSI after 8 hours.	Plantar forefoot (male): OxyHb 79±17, DeoxyHb 51±12 O_2 sat 61±8 Lateral calf (male): OxyHb 36±9, DeoxyHb 40±13, O_2 sat 48±7
Jafari-Saraf 2012[6]	Prospective study	4 healthy volunteers	23 sections of foot or wrist	OxyVu system. HSI performed 2 min after $TcPO_2$ at 37°, 41°, and 45° C.	HSI values correlate significantly with $TcPO_2$ measurements at 37°C. OxyHb and oxygen saturation increased with an increase of temperature.	Baseline: OxyHb: 49.6±30.6 DeoxyHb: 53.2±14.2 O_2 sat: 44.5±13.0%

HSI values are expressed as mean±standard deviation, unless otherwise described.
CI: confidence interval; deoxyHb: concentration deoxyhemoglobin; DM: diabetes mellitus; HSI: hyperspectral imaging; OxyHb: concentration oxyhemoglobin; PAD: peripheral arterial disease; $TcPO_2$: transcutaneous oxygen pressure.
*Indicates the statistically significant different HSI values between patient groups.

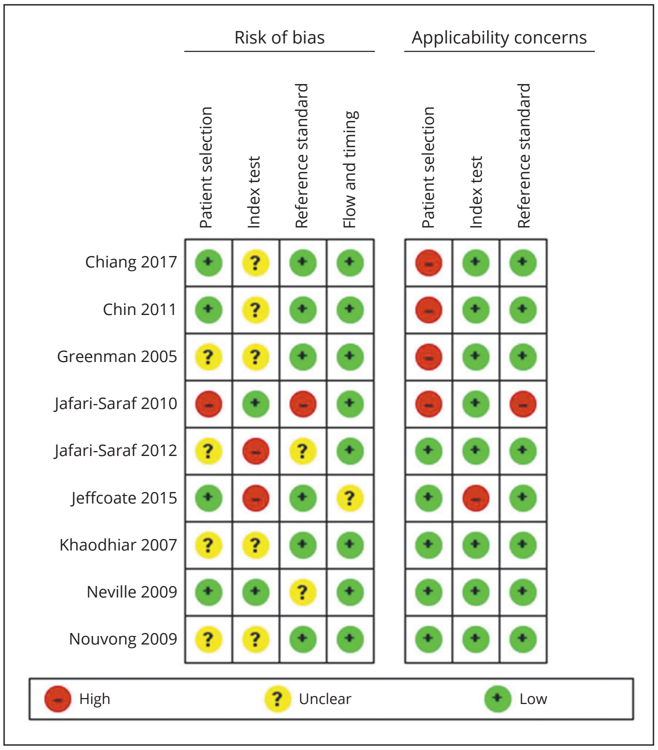

Figure 3.—Bias and quality assessment of the included studies according to QUADAS-2.[2, 4-6, 11-15]

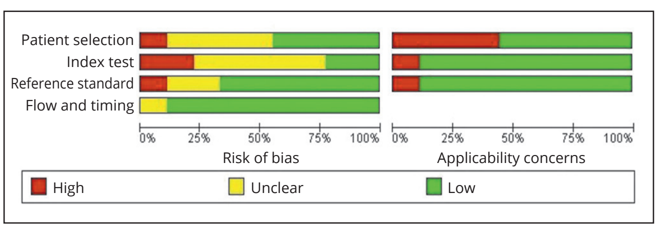

Figure 4.—Graphical display of the bias and quality assessment according to QUADAS-2.

Studies in patients with peripheral arterial disease

Three prospective studies investigated the use of HSI in the lower extremity of patients with PAD. Jafari-Saraf *et al.* investigated the correlation between the Ankle-Brachial Index (ABI) and HSI in reference to PAD.[11] All included patients were referred for routine vascular laboratory studies including ABI and were divided into 3 groups: ABI >0.9, ABI >0.45 and <0.9, and ABI <0.45. There were no significant differences in oxyHb and oxygen saturation between the 3 groups, and there was no significant correlation between ABI and HSI values. Chin *et al.* determined whether HSI can assess presence or absence of PAD and determine PAD severity.[12] Patients with an ABI<0.9 or a non-triphasic Doppler waveform were classified as having PAD. Patients were categorized according to monophasic, biphasic, and triphasic Doppler waveform analyses. DeoxyHb was significantly lower in patients with PAD and significantly different between the 3 subgroups at the plantar angiosomes, which is an anatomic unit of tissue vascularized by a feeding artery and drained by specific veins. DeoxyHb correlated significantly with ABI for the plantar angiosomes. Chiang *et al.* performed a study to correlate HSI to transcutaneous oxygen pressure ($TcPO_2$) measurements, ABI, and severity of PAD.[5] Patients were categorized according to the Rutherford classification. OxyHb and oxygen saturation correlated significantly with the severity of disease, and oxygen saturation correlated significantly with $TcPO_2$ values.

Studies in patients with diabetes mellitus

Four prospective studies investigated the use of HSI in the lower extremity of patients with DM. One study investigated DM patients with and without neuropathy and 3 studies included DM patients with or without ulceration. Greenman *et al.* performed a study to determine HSI values in DM patients with or without neuropathy and healthy controls.[2] Oxygen saturation was significantly lower in patients with DM compared to the control group. The difference in oxygen saturation was found to be greater in patients with DM suffering neuropathy than in the control group. Khaodhiar *et al.* evaluated whether HSI can predict healing of diabetic foot ulcers.[13] Diabetic patients with and without ulcers and healthy controls were compared. The results showed significantly lower HSI values surrounding non-healing ulcers compared to diabetic patients with healing ulcers. A healing index was introduced, with a sensitivity of 93%, a specificity of 86%, positive predictive value of 93%, and negative predictive value of 86%. Nouvong *et al.* also studied whether HSI can assess the healing potential of diabetic foot ulcers.[4] A significantly higher oxyHb and oxygen saturation in patients with healing ulcers was found. The same healing index was introduced with a sensitivity of 80%, a specificity of 74%, and a positive predictive value of 90%. Jeffcoate *et al.* also investigated the use of HSI to predict healing of ulcers in patients with DM.[14] The device used to perform HSI was not reported. Data were expressed as one HSI value in arbitrary units. In contrast to the other studies, the results showed significantly lower HSI value in patients with healed ulcers.

Table II.—*Hyperspectral imaging values and skin temperature from healthy subjects at the different measurement locations.*

Location	No.	Oxyhemoglobin (a.u.)	Deoxyhemoglobin (a.u.)	Oxygen saturation (%)	Skin temperature (°C)	P
Right leg						
Plantar side foot	43	85.2±24.9 (2.2)*	54.1±15.4 (1.4)*	60.5±11.7 (1.0)*	28.9±3.8 (0.3)*	P<0.001
Lateral side calf	32	41.9±11.4 (1.2)	37.8±9.9 (1.0)	52.4±10.6 (1.1)	33.4±0.8 (0.1)*	
Left leg						
Plantar side foot	43	80.4±23.1 (2.0)*	57.3±15.9 (1.4)*	57.9±11.7 (1.0)*	28.7±3.7 (0.3)*	P<0.001
Lateral side calf	32	39.8±10.5 (1.1)	38.3±9.8 (1.0)	50.9±10.3 (1.1)	33.2±0.8 (0.1)*	

Values expressed as mean±SD. P value represents comparison between the different measurement locations for the HSI values and skin temperature.
a.u.: arbitrary units.
*Significant difference (P<0.05) for the values between the right and left leg.

Studies in healthy individuals

Two studies investigated the use of HSI in healthy volunteers. Neville *et al.* performed a study to establish normative values of HSI in 194 healthy subjects.[15] A subgroup of 74 subjects underwent a repeated HSI measurement after 8 hours. Significantly higher HSI values at the plantar side of the foot were found in comparison with the lateral side of the calf and also the lateral sides of the ankle and thigh. There were no significant differences in HSI values between the repeated measurements. Jafari-Saraf *et al.* investigated the correlation between HSI with $TcPo_2$ measurements in healthy subjects.[6] HSI and $TcPo_2$ were performed subsequently in only 4 healthy volunteers at the foot and wrist, at varying temperatures of the $TcPo_2$ probe. Results showed a significant correlation between oxyHb, deoxyHb, and $TcPo_2$ values. HSI values increased with higher $TcPo_2$ temperature, but the correlation became weaker. These correlations, however, were assessed with a low number of subjects.

Standardized measurement protocol with a portable system

HyperView™ measurements

In the current study we recruited 43 healthy subjects (26 men), with a mean age of 27±2.2 years, and median body mass index of 22 kg/m² (interquartile range, 3 kg/m²). The mean HSI values and skin temperatures of the participants are reported in Table II. HSI values and skin temperature were significantly lower at the calf compared to the feet for both legs (P<0.001). The mean HSI values and skin temperature were significantly different between the right and left foot (oxyHb, P=0.007; deoxyHb, P=0.01; oxygen saturation, P=0.003; and skin temperature, P=0.045). At the calf, only skin temperature was significantly different between the right and left side (P=0.017).

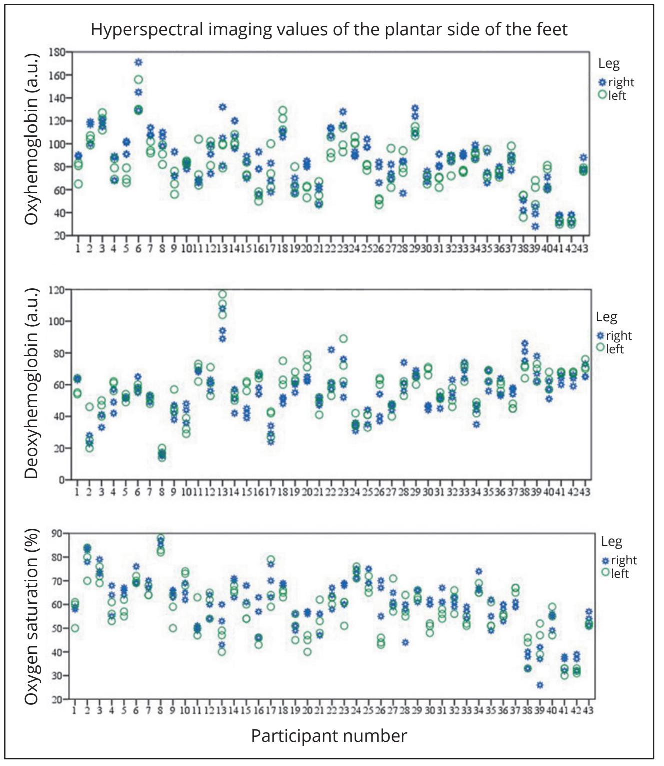

Figure 5.—Hyperspectral imaging (3 consecutive images per location) values for every healthy subject at the plantar side of the feet.

The 3 consecutive hyperspectral images taken at all 4 locations are shown in Figure 5 for the feet and Figure 6 for the legs. The mean ICCs (95% CIs) for the right foot were oxyHb, 0.86 (0.78-0.92); deoxyHb, 0.87 (0.79-0.92); and oxygen saturation, 0.86 (0.78-0.92) and for the left foot were oxyHb, 0.84 (0.76-0.91); deoxyHb, 0.89 (0.83-0.93); and oxygen saturation, 0.85 (0.77-0.91). The ICCs for the right calf were oxyHb, 0.83 (0.70-0.91); deoxyHb, 0.87 (0.78-0.93); and oxygen saturation, 0.81 (0.69-0.89) and for the left calf were oxyHb, 0.87 (0.79-0.93); deoxyHb, 0.89 (0.82-0.94); and oxygen saturation, 0.82 (0.71-0.90).

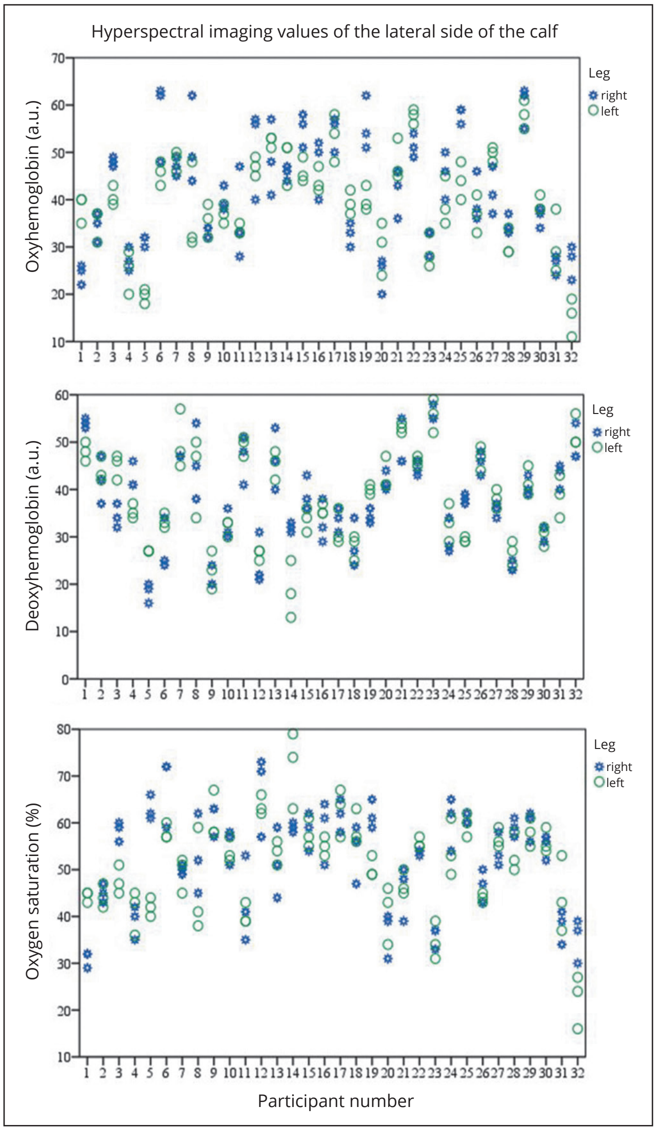

Figure 6.—Hyperspectral imaging (3 consecutive images per location) values for 32 healthy subjects at the lateral side of the calves.

Discussion

Most diagnostic techniques currently used in patients with DM or PAD focus on macrovasculature and are used to detect steno-occlusive lesions in the feeding arteries. However, tissue loss and ischemic pain depend not only on macrovascular deficits but also on impairment of the microvasculature in peripheral tissue and skin. Assessment of tissue perfusion is therefore essential for detection of disease extent and to monitor progression of ischemia and results of revascularization procedures. The preferred method to determine tissue perfusion would be quick, nonexpensive, accurate, and noninvasive.[16]

Literature on HSI for tissue perfusion measurements of the lower extremity in DM and PAD patients is scarce. Moreover, a substantial number of the studies in the current review were at risk of bias and included heterogeneous groups of patients.

The studies on HSI measurement in PAD patients show that HSI values might indicate the severity of disease, especially when measurements are performed at the plantar side of the foot. Only Jafar-Saraf *et al.*[11] was not able to confirm this concept, which may be explained by the low number of patients with low ABIs and the lack of clinical information about the included patients. This is also reflected in the risk of bias and quality assessment, scoring high risk at 4 of the domains. An important consideration is that ABI is mainly a representative of the patency of the large arteries in the lower extremity and does not adequately represent the microvasculature and thus tissue perfusion.[17] A more accurate technique to determine tissue perfusion is $TcPO_2$, although these measurements are labor intensive and operator dependent.[5, 18]

The use of HSI in patients with DM can detect the presence of disease and predict healing of ulcers.[2, 4, 13] HSI could potentially also be used to predict wound healing in patients with ischemic ulcers and could be of help in determining whether revascularization procedures sufficiently increase tissue perfusion around ulcers by comparing post- and preprocedural measurements. This concept has to be proven in future prospective trials.

Here we report the first results of our study of HSI measurements with the portable HyperView™ system. The mean values at the calf and feet in the current study are similar to those from Neville *et al.*[15] The ICCs of the consecutive hyperspectral images at each location in this study were high, which indicates that these measurements at one location are accurate. However, the measurements are significantly different between the right and left foot and in-between the foot and calf in one leg. Therefore, every location within a patient should be used as its own reference when HSI follow-up measurements are performed. A possible explanation of the higher HSI values at the feet might be that this location is more susceptible to vasodilatation of the dense capillary bed.[19] Moreover, these arteriovenous anastomoses may result in higher oxygenation levels.[13]

In addition, the structure of skin on the plantar side of the feet is different compared to the lateral side of the calf.

In general, the skin of the feet is glabrous and has generally high levels of oxygenation and greater reactivity than skin from other parts of the body.[13] The plantar side of the foot might be the most optimal location to perform HSI measurements in future studies. It should be determined in large clinical trials whether HSI measurements can be reliably performed at the different angiosomes of the foot. To date, this is only supported by the findings from Chin *et al.*,[12] who found an association between HSI values and severity of disease at the plantar angiosomes.

The portable HyperView™ system has several advantages that enable monitoring of patients with ulceration or PAD. First, it is a noninvasive device that measures tissue perfusion transcutaneously, without the use of contrast agents or direct contact with the patient. The camera is easy to use, and enables assessment of tissue perfusion of any preferred region of the skin and at any moment in the patient's clinical trajectory.

A possible disadvantage of a hand-held HSI device is the risk of introducing operator-dependent variables that may influence the images and HSI values. When performing tissue perfusion measurements with the portable HSI system at different locations, for example, at the area around an ulcer, standardization must be taken into account. Another current limitation is that analysis of the data is manually done on the system itself with a touchscreen. This may lead to imprecise selection of ROIs. Ideally, analyses should be performed automatically, with the possibility to align images in case of repeated measurements during follow-up of a patient. Moreover, determining interoperator reliability for this device in a large cohort is necessary together with intraoperator reliability for different measurement moments.

Limitations of the study

One of study limitations is the small number of healthy volunteers included to test the standardized HSI measurements with the portable HyperView™ system and the lack of inclusion of DM or PAD patients. This will be the topic for future HSI studies. In these studies the HSI measurements will also be compared to $TcPO_2$ measurements which is still considered as gold standard.

Conclusions

We can conclude that there is need for accurate and noninvasive determination of tissue perfusion, especially in patients with DM and PAD with impaired microvasculature and ulcers. Preferred methods should be quick, nonexpensive, accurate, and noninvasive. HSI with use of a portable system might be one of these. So far, limited evidence indicates that HSI values are associated with severity of DM and PAD and wound healing.

With the use of a standardized measurement protocol, hyperspectral images can be taken with high precision with a portable system. However, differences exist at several locations at the lower extremity, so each measurement location should be used as its own reference when consecutive measurements are taken during a patient's follow-up. More studies with larger patient cohorts should be performed before HSI can be incorporated as standard tool in the diagnostic armamentarium of the vascular specialist.

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