Detection of diabetic peripheral neuropathy using spatial-temporal analysis in infrared videos

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***Abstract*—Limitations of previous thermographic studies to detect diabetic peripheral neuropathy (DPN) are addressed in this combined analysis using spatial and temporal features. In our approach, we extract information of temperature patterns before cooling and during recovery after cooling. Temporal features are extracted from, angiosome patterns, principal component analysis (PCA) and independent component analysis (ICA) from the recovery stage after applying a cold stimulus to the plantar foot. The features are processed by a linear support vector machine (SVM) classifier achieving area under the ROC curve (AUC) of 0.95 and 0.83 for the detection of DPN in females and males respectively.**

Keywords—Thermal, Imaging, Diabetes, Peripheral, Neuropathy, Screening

I. INTRODUCTION

Foot pathology accounts for 25% of all hospital stays among DPN patients resulting in an economic impact to the U.S. estimated at $13.7 billion annually. The standards for identifying distal symmetric diabetic neuropathy are electrodiagnostic techniques and qualitative sensory testing, such as monofilament and tuning fork tests. To address the lack of tests for early detection, we have created a methodology based on thermal imaging and advanced image processing techniques for preclinical detection of DPN. This study shows the potential of this method for use in primary clinics where early detection of DPN is critical and when intervention is most cost effective.

II. BACKGROUND

There are several tests to assess DPN, but none provide a repeatable, non-invasive means for monitoring DPN in the preclinical stage. Nerve biopsies [1] can reveal evidence of DPN, but are invasive and not appropriate for repeated clinical use. Nerve conduction velocity (NCV) tests [2] [3] have been used as alternative, but such tests are not available in most primary care clinics and can be confounded by significant variability when not performed by a trained specialist [4]. Sensation tests for DPN have been shown to lack sensitivity in the early stages of DPN [5] [6] [7]. The vibration perception threshold (VPT) test with a tuning fork, the Semmes-Weinstein nylon 10 gm monofilament touch, and the thermal discrimination threshold (TDT) require cooperation of the patient [7]. Ankle Brachial Index (ABI) [8] is also used by some physicians; however, ABI in the diabetic foot may be subject to errors due to stiffening of the intimal layer of the arteries as a result of arterial calcification [9] [10]. An alternate approach to identifying preclinical DPN is based on the characterization of thermoregulation as expressed by changes in blood flow in the plantar foot. The mechanistic process, which has been described by Brodal [11] and others [12] [13] [14], is thermoregulation of homeostasis. Exposure to cold causes the skin blood flow to decrease via cutaneous vasoconstriction.

Thermal imaging of a plantar foot after a cold provocation has been studied by investigators as a means of evaluating impaired thermoregulation in the neuropathic foot [15] [16] [17]. Variations of plantar foot thermographic patterns in controls and diabetic patients have been used to assess risks of DPN in diabetic patients [18] [19] [20] [21]. The diagnostic accuracy reported in these studies was 40% to 60% for pre-ulceration DPN. The individual variations in plantar thermographic patterns showing different trends between healthy controls and diabetic subjects have not been fully elucidated. Based on thermal patterns (e.g.- a "butterfly pattern"), one study obtained a specificity of 65% (i.e.- healthy controls correctly identified as true negatives).

Though some investigators have attempted to develop a classifier based on asymmetric patterns of plantar temperature [22] [23] [24] these simple approaches, such as using bilateral temperature differences or single points in time after a cold provocation, have met with only limited success. DPN sometimes results in elevated microcirculation in the foot and hence, raised foot temperature compared to non-diabetic patients. Studies have reported asymmetry in temperature of more than 2.2 C° for the same region of the right versus the left plantar foot, indicating possible DPN. There remains uncertainty with these results because of large variations in the reported findings.

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III. Thermal Imaging Protocol

The device consisted of a cold provocation procedure administered with a cold gel pad and a thermal imaging camera. The cold pad was kept in a freezer at -4ºC but remained in a flexible gel state to conform to the contours of the plantar foot. The thermal imaging device used was a high-end, low noise 7.5-13 µm infrared camera (FLIR Model SC 305, Boston, MA) that was calibrated to give a thermal sensitivity of <0.05°C. Measured temperature changes were of the order of 5-10°C; thus measurement errors were of the order of 0.1%. The camera was placed at a distance of one meter from the subject to capture the full extent of both feet in the field of view. The data acquisition was at 8.6 frames per second at 320X240 pixels. Figure 1 shows the experimental setup with the FLIR and the leg rest during the imaging session.

All subjects rendered written informed consent as approved by the University of New Mexico Human research Review Committee (Study # 15-494) and/or the Ethical and Independent Review Services Institutional Review Board (Study # 15085-01A). Table I shows the enrollment of subjects for each category. Of the one hundred twenty-seven subjects who were enrolled, 27% (n=32) had diabetes with previously diagnosed DPN, 39% (n=46) were healthy controls, and 34% (n=49) had diabetes without DPN.

TABLE I. Subjects in Phase I study

	♂	♀	%	Avg. Age
DMs	17	32	34%	60
DPNs	15	17	27%	61
Control	21	25	39%	60
Total	**53**	**74**		

IV. Analysis

A. Temperate Features

Previous studies have mostly relied on qualitative approaches to assess the differences in features between the controls and DPNs. In this study, all features were analyzed quantitatively. Further, these features were combined with newly developed markers, such as those associated with spatial-temporal analysis of features using PCA. Initial temperature and cooling temperature after cold provocation were recorded from the thermal images.

B. Principal Component Analysis

A time-tested methodology that previously had not been applied to thermal videos of the plantar foot. PCA is a well-known statistical technique that uses orthogonal transformation to convert observations of possibly correlated variables into a set of uncorrelated variables called principal components (PC). Each PC accounts for a part of the variability of the data. The first component (PC1) will account for the largest possible variance, while the second PC (PC2) explains the second largest variance and so on. In the case of a video, where spatial-temporal change is very smooth, the pixel values will be highly correlated and the PC1 on average accounts for the majority of the variance. On the other hand, if the spatial-temporal difference between frames is high (DPN subject in the bottom row of Figure 2), more than one PC will be necessary to account for the variability of the video frames.

C. Independent Component Analysis

ICA is a statistical methodology that decomposes a multivariate signal into statistically independent signals, called independent components (ICs). Thermal videos for all the subjects were decomposed into spatial components modulated by their temporal dynamics.

D. Angiosome Based Features

Morphological pattern analysis of plantar foot's natural temperature was studied by Mori et al. [20] and others [19]. Their hypothesis was that the thermographic patterns in controls differ from those of diabetics. This study adopted Mori's methodology for segmenting thermally similar regions, which he called angiosomes.

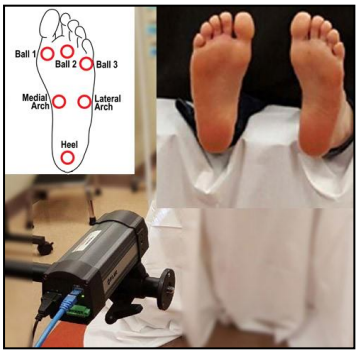

Fig. 1. Photo of FLIR and foot set-up. Regions of Interest in upper left corner

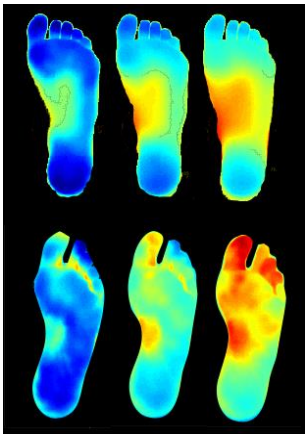

Fig. 2. Thermal patterns for a control (top) and a DPN (bottom) for three recovery phase points in time.

V. Results

A. Temperature Features

Initial temperature (Table II) and cooling temperature (Table III) after cold provocation were tabulated. Controls had higher average plantar foot temperature than DPNs by 2.2 ℃ for female subjects and 1.9 ℃ for male subjects. Average temperature decrease due to application of the cold provocation was 1.4 ℃ for female controls and 0.5 ℃ for male controls. The temperature recovery after removal of the cold pressor (Table IV) at 1, 5, and 10 minutes for healthy controls and DPN subjects was greatest in the first minute.

TABLE II. Precooling temperature of plantar foot and p-value for difference between controls and DPNs.

Control (F)	DPN (F)	p-value	Control (M)	DPN (M)	p-value
27.1 ℃	24.9 ℃	0.17	28.7 ℃	26.8 ℃	0.06

TABLE III. Average temperature drop at the end of cooling of plantar foot and p-value for statistical difference between controls and DPNs.

Control (F)	DPN (F)	p-value	Control (M)	DPN (M)	p-value
-9.8Δ ℃	-8.4Δ ℃	0.012	-9.3Δ ℃	-8.8Δ ℃	0.259

TABLE IV. Percentage recovery temperature at 1, 5 and 10 min of plantar foot and p-value for the difference between controls and DPNs.

	Control (F)	DPN (F)	p-value	Control (M)	DPN (M)	p-value
1 min	21.0%	24.8%	0.0028	21.9%	22.8%	0.2143
5 min	46.6%	53.4%	0.0065	49.1%	48.7%	0.8388
10 min	58.8%	67.5%	0.0053	62.2%	62.1%	0.9605

B. Principal Component Analysis

For a DPN subject more than one principal component (PC) will be necessary to account for the variability of the video frames. In the case of a control subject, where spatial-temporal change is smooth (Figure 2), the pixel values are highly correlated so PC1 on average accounts for > 96% of the variance (Table V). Table V confirms that PC1 on average only accounts for 88% of the variance for a DPN. The difference in average of the PC1 between the two classes is significant for both with p=0.047 for females.

C. Independent Component Analysis

Figure 3 shows four independent spatial-temporal ICs calculated for the male and female DPNs and controls. A two-sample t-test between the temporal responses of the control and DPN groups was applied. For the females, IC2 and IC4 show the best p-value for discrimination of DPN patients. The lowest p-value for discrimination of controls and DPNs are the heel and medial arch. In the case of males, the significant components are IC1 and IC2. Besides the heel, the right part of the ball presents higher variation in the thermal response among DPN subjects.

TABLE V. PCA 1 vs PCA 2 by gender

Category		Average PC1 %	Average PC2 %	p-value
Females	***Controls***	96.28%	3.71%	0.047
	DPNs	88.07%	11.93%	
Males	***Controls***	96.93%	3.07%	0.076
	DPNs	89.03%	10.94%	

D. Angiosome Based Features

One of the common patterns is the butterfly pattern (see top row of Figure 4) which is present in 21% of subjects from all three groups (normal controls, DPNs, and DMs). The analysis found that uniformly cold feet (last row in Figure 4) are only present in DPN subjects, with 40% of females and 17% of males presenting this pattern. We calculated the ratio of the pre-cooling "hot" and "cold" areas of the plantar foot for creating a classifier based on angiosomes. This feature alone provided classification AUC of 0.67 for males and 0.82 for females.

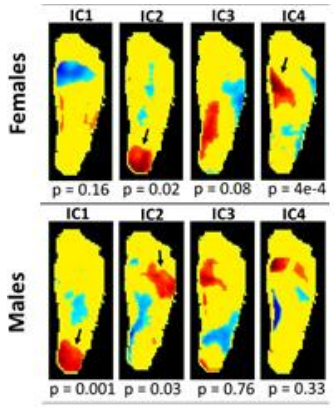

Fig. 3. ICA components/p-values for discrimination of controls vs. DPNs. DPN discriminating areas are highlighted with the arrows.

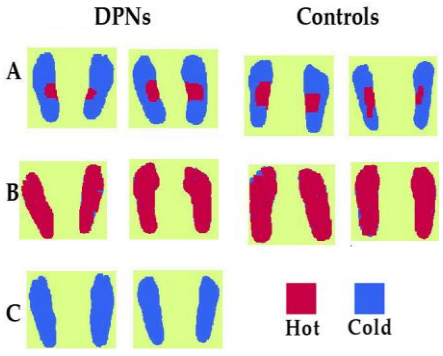

Fig. 4. Thermographic patterns of the plantar foot for the analyzed subjects.

E. Classification Results

In order to classify the controls vs. DPNs, a total of 35 features from the methods presented in the sections above were extracted. A linear support vector machine (SVM) classifier was used to classify control and DPN subjects. Table VI shows the individual performance for each type of features and the overall classification performance. A very high sensitivity (97%) and specificity (95%) was found for the classification of DPNs and controls in females when combining all features, and the AUC of the receiver-operator curve was 0.95. The sensitivity and specificity for males was 92% and 63%, respectively, and the AUC of the receiver-operator curve was 0.83. The lower number of male controls subjects affected the classification accuracy. The best individual features for classification were measured by AUC and were different for males and females. For females, the best AUCs are given by a) change in temperature from the application of the cold provocation, b) angiosomes and c) PCAs. The features with the best AUC for the males are: a) recovery temperature, b) PCAs and c) ICAs.

TABLE VI. PERFORMANCE OF SVM CLASSIFIER FOR EACH TYPE OF FEATURES AND THE COMBINATION

Method	Male AUC (sens/spec)		Female AUC (sens/spec)	
Changes of temperature	0.68	83%/63%	0.92	90%/85%
Recovery of temperature	0.81	83%/75%	0.61	80%/69%
Angiosome	0.67	83%/50%	0.82	100%/69%
PCA	0.79	75%/100%	0.80	60%/92%
ICA	0.76	75%/100%	0.72	70%/69%
Combination	0.83	92%/63%	0.95	97%/95%

VI. DISCUSSION

As seen in Table II, the difference in the natural plantar foot temperature before cold provocation between female controls and female DPN patients was not significantly different. Though not statistically significant at p-value = 0.06, the difference was greater between male controls and male DPN subjects. Neither difference was found to be statistically significant, i.e. p-value $\leq$ 0.05. The lack of significant differences in the two classes of subjects is supported by some studies [25] that found warmer temperatures for DPN subjects, while other studies agree with our findings [26]. This suggests that precooling temperature by itself is not a robust indicator of DPN and measurements must be better controlled or must be rejected entirely as useful in detecting early DPN.

Table III showed the average decrease in temperature of the plantar foot after exposure to the cold provocation. The mean difference in temperature drop between controls and DPNs was statistically significantly for females. Less effect of the cold provocation in the DPNs' plantar foot is likely due to the reduced functionality of the vasoconstriction in DPN subjects. In the controls, vasoconstriction occurs rapidly in response to the cold provocation, a natural response for maintaining core temperature by reducing blood flow to the plantar foot. Future experiments may help explain these differences between the male and female subjects.

VII. CONCLUSION

Thermal videos provide a potential means for detecting signs of DPN in DM patients that were not otherwise clinically diagnosed with DPN. This study shows that any single feature as previously reported in the literature is insufficient to classify patients as having DPN. The combination of features reported here is needed for high sensitivity and specificity.

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