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A Device for Noninvasive Assessment of Vascular Impairment Risk in the Lower Extremity

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Abstract:

The repeatability and resolution of the clinical gold standard of vascular assessment, the ankle-brachial index (ABI), was compared to that of a new device that dynamically assesses tissue perfusion during external loading utilizing laser Doppler flowmetry. Eight subjects of varying levels of vascular impairment were tested in

successive weeks using two different sites on the subject's posterior calf. These new measures included the perfusion decrease as well as the unloading delay during cyclic loading. Some new dynamic tissue perfusion measures demonstrated comparable levels of reproducibility with the ABI (e.g., 10%-20%). Only the unloading delay showed potentially enhanced resolution over ABI measures. The perfusion decrease showed little resolution, and the remaining parameters exhibited too great variability (25%-90%). The unloading delay associated with the reperfusion response during cyclic loading displayed the greatest combination of reproducibility and differentiation between subject groups of varying levels of vascular impairment. The preliminary results of this pilot study were also used to estimate sample sizes necessary to detect possible significant ($P < 0.05$) differences between subject groups for all measured perfusion parameters. From these calculations, at least 30 subjects are needed for future study in each of the five subject groups.

SECTION I. Introduction

Ninety-Five percent of the 400 000 individuals in the U.S. with amputations have amputations of the lower limb [1]. About 75% of these amputations result from vascular complications [1]. In many of these cases, the vascular complications result from both poor vessel integrity and poor blood distribution. This vascular complication, peripheral vascular disease (PVD), has both macrovascular and microvascular components. The macrovascular symptoms include arterial lesions, while the microvascular symptoms involve shunting of blood away from nutritional pathways of the cutaneous tissue [2], [3].

THE current gold standard for assessing vascular impairment, the ankle-brachial index (ABI), is a static measure and defined as the ratio of the highest ankle (or toe) systolic pressure to the highest brachial systolic pressure. This static measurement provides an assessment of the macrovascular deficiency, but does not reflect any microvascular deficiency. Although the reliability and repeatability of the ABI are quite good (interrater variability of 10%–20%, mean variability of approximately 16% [4]), the resolution of the ABI is relatively poor. Normal healthy ABI values range between 0.9 and 1; values of 0.5–0.9 indicate vascular impairment and poor circulation; values below 0.5 indicate critical ischemia [5]. In particular, greater resolution within the 0.5–0.9 range is needed to better assess risk of vascular impairment. By the time the ABI for a given individual changes, the changes in the vasculature are often irreversible. Increased resolution is needed to facilitate earlier detection of vascular impairment, and support earlier intervention and treatment. One means of early detection is through noninvasive measurement of local blood flow through laser Doppler flowmetry (LDF).

LDF involves emission of a laser wavelength through a fiber optic cable onto tissue. The light scatters in different directions due to contact with the red blood cells (RBCs). This light is reflected from the moving fluid (plasma, blood) in the tissue to a second fiber-optic cable, with decreased amplitude and a change in frequency or Doppler shift, which is analyzed and used to calculate the local flow or perfusion measurement [6]. Commercial LDF systems display the resultant perfusion in arbitrary units, relative to the product of the mean velocity of the RBCs and the total number of RBCs in the local tissue. Since the average number of RBCs is changing and unknown, the measure is relative [6].

There are some limitations to the LDF measurements. If there is a change in background light for the LDF probe, the perfusion measurement may not be reliable. This can be caused by movement of the probe with respect to the skin, or if the probe breaks contact with the skin. Discerning ordered motion is also difficult with LDF. The LDF system detects all motion of RBCs. The signal reflects the total flux in the volume of tissue (1–1.5 mm deep and 1 mm² area), but the signal can vary greatly based on probe placement if there are underlying nonhomogeneities in the microvasculature [7].

As LDF has not been used previously to assess tissue vascular health, the reproducibility of the LDF measurements for the lower extremity during external loading must be examined. The purpose of this study was

to investigate the ability of a new device to reliably assess vascular health by taking measures of tissue perfusion and load, which may then be used as a potential measure of risk for lower extremity amputation. By establishing a database of perfusion characteristics, as well as clinical measures of vascular health as assessed by ABI, this study investigates whether these new perfusion characteristics correlate with clinical measures of vascular health (e.g., ABI).

SECTION II. Methods

The specific aims of this study were: 1) to evaluate the intertrial repeatability of these new perfusion measures during external loading with a rate-controlled soft tissue indenter and 2) to compare the intertrial reproducibility and resolution of these measures to that of the ABI. To evaluate the reproducibility of the new measures, subjects were tested on four separate occasions. To compare the new perfusion measures of this study to that of the ABI, subjects were selected from five different populations of varying levels of vascular impairment. The first group [healthy elderly (HE)] included HE subjects, 55–75 years old with no medical history of high blood pressure, diabetes, smoking, or vascular impairment. The second and third groups were composed of individuals with diabetes mellitus (type 1 or 2) between 55 and 75 years of age. These subjects were further divided into two groups: one group [low-risk diabetic (LRD)] had a perceived low risk of vascular impairment and potential lower extremity amputation, and the other group [high-risk diabetic (HRD)] had a perceived high risk of PVD and potential lower extremity amputation. The level of risk was assessed using the criterion specified in Table I. To be classified as low risk, a diabetic subject's health information must fall in the low-risk category for all parameters. If any parameters were categorized as high risk, the subject was classified as high risk. Finally, the fourth and fifth subject population groups included individuals with unilateral transtibial amputation, who demonstrated a stable limb volume and were comfortable with their prosthesis. These amputee subjects were classified based on their cause of amputation, traumatic, or vascular. The traumatic amputees [traumatic transtibial amputees (TTA)] included individuals with transtibial amputation from traumatic causes, healthy ABI measures (>0.95), nonsmoker, normal cholesterol, and normal blood pressure ($<120/<85$); note that the subject age criterion was relaxed for these subjects. The vascular transtibial amputees (VTA) included individuals with unilateral transtibial amputation due to vascular complications; all subjects were between 55 and 75 years of age.

Table I High Versus Low-Risk Factors for Diabetic Subjects

Parameter	Normal Level	"Low" Risk 181,191	"High" Risk 181,191
Hemoglobin A (Hb Ale)	3.9-6.1%	$<7\%$	$>8.5\%$
Blood Pressure (mmHg)	$<130/<85$	$<139/<89$	$>140/>90$
Cholesterol			
HDL(mg/dL)	40-60	40-60	<45
LDL(mg/dL)	<100	<129	>130
triglycerides (mg/dL)	<150	<199	>200
ABI	0.95-1.2	>0.9	<0.9
Smoking History	non-smoker	Non- smoker or quit 10 yrs ago	Current smoker or recently quit(< 5 yrs)

Subjects were recruited from Froedtert Memorial Lutheran Hospital (FMLH) and General Medicine and Amputee clinics. Institutional Review Board (IRB) approval was obtained at both Marquette University and the Medical

College of Wisconsin. Informed consent was obtained from each subject prior to testing. All subjects were tested weekly for four weeks. While tests were to be conducted during successive weeks, most subject trials were conducted over a five-week period; one subject was tested over a seven-week period. All tests were performed at FMLH.

Two different tests were conducted: 1) tissue loading–perfusion tests incorporating cyclic loading at three different rates and 2) ABI studies. For the tissue tests, two sites were evaluated on the posterior calf for each subject. The test sites were identified as 2 cm proximal and distal to the region of largest circumference of the calf. These sites were selected as they may demonstrate vascular change due to PVD as these sites encompass the infrapopliteal artery, a region often affected by PVD [10].

A. Tissue Loading–Perfusion Tests

A rate-controlled tissue indenter [11] was used to apply the aforementioned loading protocols. This indenter was modified so as to incorporate a commercial LDF system [Periflux System 5000 including a signal conditioning unit (PF 5010 LDFM) and probe (#409), Perimed AB: Järfälla, Sweden] [1]. As tissue perfusion is temperature-dependent, both skin and ambient temperatures were also monitored. A laptop (Compaq nc 8000) was used to control the tissue indenter, as well as acquire the load, perfusion, temperature, and indentation data through LabVIEW software (National Instruments, Austin, TX).

Subjects were asked to expose their dominant lower leg (residual limb for amputee subjects) and stand for 10 min prior to testing. Each site was marked with a permanent marker to help identify the test site for successive trials.

Starting randomly with one of the sites, the maximum tolerable indentation was determined manually, and 85% of this value was used as input for testing. Temperature sensors acquired skin temperature at the test site as well as ambient temperature for 10 min, prior to testing, to establish baseline temperatures. Ten loading/unloading cycles were then applied at each of three different speeds (1, 5, and 10 mm/s), tested in random order.

B. ABI Studies

The ABI procedures were conducted at the Vascular Laboratory, FMLH. The subject rested on an examination table in the supine position for 10 min prior to testing. Manual pneumatic cuffs were positioned on the proximal arms and proximal to the ankles by the vascular technician. The subject's pulse was monitored by the vascular technician with a stethoscope to obtain the systolic pressures at the distal arm and ankle. With the exception of the amputee subjects for whom only the residual limb side was examined, the ABI for both left and right legs was calculated as the ratio of the highest ankle to the highest arm systolic pressure.

C. Postprocessing

Prior to parameter estimation, the perfusion data were filtered using a simple fifth-order low-pass Butterworth filter with cutoff of 1.25 Hz. The force data were filtered at 3 Hz. These cutoffs were based on the power spectra of the perfusion and force data at the various indentation speeds during the cyclic loading trials. Additional signal processing was conducted to assess the integrity of the perfusion data during all loading protocols. A feedback signal from the LDF system, total backscatter, measures the total available light measured by the laser. If the total backscatter changes were erratic or discontinuous, the perfusion data may not be valid. Based on thresholding the derivative of the total backscatter, valid perfusion data were retained and questionable perfusion data were removed prior to further analysis [12].

Several new perfusion parameters were evaluated based on the acquired perfusion and force time series during the various loading protocols. The magnitude of the perfusion decrease during each loading cycle was assessed

(see Fig. 1). The unloading delay, that between the onset of tissue unloading and the corresponding increase in perfusion, was also evaluated.

Fig. 1. Key extracted features from the force (thin) and perfusion (thick) data. (Star) initial force application; (open circle) peak force; (filled circle) initial perfusion decrease, square—initial perfusion increase, triangle—perfusion recovery point to preloading level. The corresponding unloading delays are also shown.

These perfusion parameters were evaluated for each of the four trials at a given site for each subject. To exclude possible preconditioning effects [1] at each of the three indentation rates, parameters were assessed during the latter five of the ten loading cycles. Each parameter was also expressed in terms of the mean intertrial value and standard deviation—thereby quantifying the respective parameter repeatability.

SECTION III. Results

The medical profile (e.g., subject group, age, blood pressure, ABI, lipid profile, cholesterol, and HbA1c) of each subject tested is summarized in Table II. Full medical profiles were not available for all subjects; neither the control subjects nor the amputee subjects had HbA1c and lipid profile test results in their medical file. Values that are indicative of high risk of vascular disease for the diabetic and amputee subjects are in bold.

Table II Medical Profile Data for Tested Subjects

				Lipid Profile (mg/dL)						
ID	Age (yrs)	Diab Type	BP (mmHg)	HDL	LDL	TRI	Chol (mg/dL)	Smoking History	HbA1c (%)	ABI
High risk threshold			> 140/90	<45	> 130	>200	>200	quit<5 yrs	>8.5	<0.9
HEI	56	N/A	122/84	N/A	N/A	N/A	N/A	Non-Sm	N/A	1.01
TIA1	50	N/A	118/80	N/A	N/A	N/A	N/A	Non-Sm	N/A	1.15
TTA2	32	N/A	112/76	N/A	N/A	N/A	N/A	Non-Sm	N/A	1.0
LRD1	55	2	130/64	48	96	180	165	Non-Sm	7.1	1.03
LRD2	55	2	130/56	86	65	53	162	Non-Sm	7.4	1.13
HRD1	63	2	140/86	52	124	146	205	Non-Sm	9.7	0.98
HRD2	64	2	140/80	N/A	N/A	N/A	234	Quit >10 yrs ago	8.5	0.67*
VTA1	75	N/A	131 /94	N/A	N/A	N/A	N/A	Quit >10 yrs ago	N/A	0.51

Values that are indicative of high risk of vascular disease for the diabetic and amputee subjects are in bold. *indicates toe-brachial, not ankle-brachial, pressure; high-risk threshold <0.7.

The variability in the perfusion parameters within each of the four trials (intratrial repeatability, shaded bars) and between four trials (intertrial repeatability, unfilled bar) at 1 mm/s is shown for a representative subject in Fig. 2 for both the proximal and distal test sites. All subjects demonstrated variability (both intratrial and intertrial) similar to these representative data. The first four mean values and standard deviations represent the mean and standard deviation of that parameter during the last five cycles of rate-controlled loading at 1 mm/s, and represent intercycle or intratrial repeatability; increased standard deviations reflect greater variability. As seen in Fig. 2, the intratrial variability in the percent perfusion drop at the two sites was low (1%–2% for distal and 5%–10% for the proximal sites), with only one trial demonstrating variability greater than 10%. The proximal test site demonstrated greater intratrial variability than the distal site for the perfusion decrease for this subject, although this was not observed for all subjects. The fifth (unfilled) bar corresponds to the intertrial mean and standard deviation, and represents intertrial variability or the consistency of each measure on a week-to-week or trial-to-trial basis. The perfusion decrease was relatively consistent between trials, varying by approximately 10% for each of the two sites. The distal site values were consistent between trials, with the exception of the fourth trial. The unloading delay demonstrated 5%–10% intratrial variability and approximately 10% intertrial variability for both sites. Similar data are summarized in Figs. 3 and 4 for all subjects for the various indentation rates.

Fig. 2. Representative perfusion data (perfusion decrease and unloading delay) during cyclic loading at 1 mm/s (subject LRD1) for both the (top) proximal and (bottom) distal test sites.

Fig. 3. Perfusion decrease during cyclic loading for all subjects at (solid) 1 mm/s, (slant up) 5 mm/s, and (slant down) 10 mm/s. Subject groups in order of expected increasing vascular impairment are: HE control, TTA, LRD, HRD, and VTA.

Fig. 4. Unloading delay during cyclic loading for all subjects at (solid) 1 mm/s, (slant up) 5 mm/s, and (slant down) 10 mm/s. Subject groups are in order of expected increasing vascular impairment are: HE control, TTA, LRD, HRD, and VTA.

The skin temperature variations over the course of an individual trial session varied by less than 0.5 °C. Skin temperature variations for a specific individual over the four separate trials varied by less than 3.0 °C. Skin temperatures were not identical for all subjects; the average skin temperature for all subjects ranged from 32.0 °C to 33.7 °C. Some subjects had higher skin temperature, which may have resulted in higher baseline perfusion values than for subjects with lower skin temperature. There was little variation for each subject in either the ambient temperature or skin temperature over the test duration. Overall, the skin temperatures ranged from 30 °C to 35 °C, while the ambient temperatures ranged from 24 °C to 28 °C.

SECTION IV. Discussion

Given the small sample sizes of each of the five test groups, statistical significance cannot be demonstrated readily. Both new perfusion parameters (e.g., perfusion decrease and unloading delay) demonstrated comparable or enhanced repeatability with respect to the ABI. The parameter variability may reflect physiological or pathological changes, other than solely perfusion, in patient characteristics over time. The unloading delay also showed potentially increased resolution (e.g., ability to differentiate subject groups) compared to the ABI.

A. Cyclic Loading Repeatability

The perfusion measures of interest during cyclic loading included the perfusion decrease during loading and unloading delay. The intertrial variability of each of these parameters was examined and compared to that of the ABI (10%–20% interrater variability) [4]. This comparison was conducted for each indentation rate (1, 5, 10

mm/s) and each site. The perfusion decrease during cyclic loading showed better repeatability than the ABI with 31% of the tests demonstrating less than 10% variance and 77% of tests demonstrating less than 20% variance. This variability was dependent on the respective indentation depth and the indentation rate (e.g., less variability was observed at slower indentation rates). Other potential sources of variability included tissue temperature (variability of 1.3 °C over the duration of the four trials), peak tissue reaction force (mean variability of 17% for each subject between each successive trial), subject medication, subject's recent activity level, and variations in the subject's diet before testing. Similar sources of variability exist for the unloading delays. The delay in perfusion response after unloading (e.g., unloading delay) demonstrated comparable repeatability with respect to the ABI, with 19% of the tests demonstrating less than 10% variance and 71% of tests demonstrating less than 20% variance.

While skin and/or ambient temperature may influence the perfusions measures, the temperature variations were consistently less than 2 °C over the course of the four-week trial duration, and did not exceed 0.5 °C during any given trial. As such, thermal variability did not appear to influence the observed intertrial variability in the new perfusion parameters.

B. Resolution of Perfusion Measures Contrasted with ABI

The resolution of each perfusion parameter was also contrasted with that of the ABI, to assess the respective potential of that parameter to differentiate variations in vascular health. As the high-risk diabetic subjects were expected to be at greater risk of vascular impairment and/or subsequent limb amputation than the low-risk diabetic subjects, the ABI measures of these two groups were contrasted. While differences in the ABI measures were observed for these two subject groups [low risk: 1.03 and 1.13; high risk: 0.98 and 0.67 (toe)], only the toe ABI for the second high-risk diabetic subject was indicative of low-to-moderate vascular impairment. Therefore, the ABI itself does not appear to have sufficient resolution to differentiate vascular health between these two groups.

The new perfusion measures (e.g., perfusion decrease and unloading delay) were similarly examined to see if they could differentiate the expected differences in vascular health for these two populations. At least one high-risk diabetic subject demonstrated stiffer vessels, as noted from the need to take the ABI at the toe. Due to stiffer vessels and other possible vascular impairments associated with diabetes, the high-risk diabetic subjects were expected to demonstrate less perfusion decrease, increased perfusion response time (i.e., prolonged unloading delays [3]), and increased force required to occlude blood vessels when compared to the low-risk diabetic subjects. Also of note is the difference in blood sugar control between the high-risk (HbA1c = 8.5%–9.7%) and the low-risk diabetic (7.1%–7.4%) subjects. The less effectively controlled blood sugar in the high-risk group may inhibit vasodilative agent (e.g., nitrous oxide) release, perhaps slowing reperfusion [10]. However, for all three cyclic loading rates, no significant differences in the perfusion decrease or unloading delay were observed between the high- and low-risk diabetic groups.

A second intergroup comparison was conducted between the high-risk diabetic subjects and the vascular amputee subject. These diabetic individuals have many risk factors that may necessitate future lower extremity amputation. Substantial differences in the ABI were observed between the high-risk diabetic subjects (0.98 ankle and 0.67 toe) and the vascular amputee subject (0.51). The blood pressure of the high-risk diabetic subjects was somewhat elevated with respect to the amputee subject (140/83 versus 131/94); the vascular amputee subject was not diabetic.

No significant differences in the perfusion parameters were observed between the vascular amputee subject and high-risk diabetic subjects during cyclic loading, although greater intersite variability in each perfusion parameter was observed for the vascular amputee subject. This increased intersite variability may reflect vascular health changes distally versus proximally, perhaps due to vascular disease and/or amputation surgery.

Despite these site differences, the perfusion decrease did not differ significantly between these subject groups at any indentation rate. This apparent lack of intergroup differences was unexpected, as the vascular amputee subject had an ABI that was much lower than the high-risk diabetic subject group. The vascular amputee subject was expected to demonstrate a lower baseline perfusion level that would then result in a decrease in the percent perfusion drop.

A third intergroup comparison was conducted between the vascular and traumatic amputee subjects to examine differing levels of vascular health (ABI of 0.51 for the vascular amputee; ABIs of 1.01 and 1.15 for the traumatic amputees) with common vascular changes due to amputation surgery. Each subject had undergone surgery for transtibial amputation, although surgical procedures may vary admittedly. In addition to differences in vascular health as indicated by their ABIs, the subject groups also differed with respect to blood pressure (vascular amputee: 131/94; traumatic amputee subjects: 115/78). This variation in blood pressure is consistent with greater vascular impairment for the vascular amputee.

Despite the apparent differences in vascular health between these subject groups, no significant intergroup differences were observed in the perfusion parameters during cyclic loading. Tissues with poor vascular health might be expected to show reduced perfusion decreases due to lower baseline perfusion levels. However, the perfusion levels during loading may fall to lower minimum values for unhealthy tissues, and may therefore yield comparable perfusion decreases.

Finally, intergroup comparison was conducted between the HE subject and each of the test subject groups to examine the effect of varying levels of vascular health on these new perfusion parameters. During cyclic loading, the perfusion drop did not vary significantly between the HE subject and any of the other groups. The diabetic subjects, both low and high risk, may possess stiffer blood vessels resulting in smaller perfusion decreases, particularly at faster indentation rates; these subjects may also show smaller perfusion decreases due to elevated blood pressure, although this was not observed in the current study.

The unloading delays were prolonged with respect to the HE subject for the low-risk diabetic subjects; similar prolonged unloading delays were observed for the high-risk diabetic subjects. The high-risk diabetic subjects also had poor blood sugar control, which may have limited the vasodilative response, delayed the reperfusion response, and increased reperfusion times. The blood sugar regulation was impaired for the low-risk diabetic subjects too, but not as much as for the high-risk diabetic subjects; this may still affect the reperfusion response through restriction of nitrous oxide release. The traumatic amputee subjects, who exhibited results similar to that of the HE control for the perfusion decrease and loading delay at all indentation rates, demonstrated prolonged unloading delays with respect to the healthy subject at each indentation rate, reflecting longer reperfusion times. While these differences were consistent with expected variations in vascular impairment, none of these intergroup differences in the unloading delays were significant, largely due to the small sample size.

In summary, neither the unloading delays nor the perfusion decrease during cyclic loading protocol consistently demonstrated significant intergroup differences that support the expected changes with vascular health. However, both parameters demonstrated potential to differentiate vascular health and should be investigated more fully with a larger test population. Note that the preliminary results of this pilot study were used to estimate sample sizes necessary to detect possible significant ($P < 0.05$) differences between subject groups for all measured perfusion parameters. These values were calculated using 95% confidence and the standard deviation of each parameter within each subject group. These parameter values were then normalized against the standard deviation of the parameter for all the subjects. From these calculations, at least 30 subjects are needed in each of the five subject groups. This number varies based on the selected perfusion parameter [12].

Some challenges were encountered in this pilot study. This included difficulty in assuring that the same test sites were used in each successive trial; the markers used to identify the two test sites often wore off between the tests. While the same method was used to find the sites for each trial, some inconsistency (perhaps as large as 1 cm in lateral direction) may have occurred in identifying each test site. Another difficulty was the changing backscatter in the LDF signal due to a loss of skin contact during cyclic loading; additional postprocessing steps were taken to identify and remove questionable data during this period of lost contact.

SECTION V. Conclusion

As one might expect from a pilot study, few definitive conclusions can be drawn from the limited sample size; future studies with group sample sizes of at least 30 subjects are recommended for future study. The unloading delay associated with the reperfusion response during cyclic loading displayed the greatest combination of repeatability and resolution between subject groups of varying levels of vascular impairment.

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