Near-infrared spectroscopy with a provocative maneuver to detect the presence of severe peripheral arterial disease

Q3 Q2

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ABSTRACT

Current assessment standards for peripheral arterial disease (PAD), such as the ankle brachial index, are limited in their utility and portability. Near-infrared spectroscopy (NIRS) has shown some promise in diagnosing PAD when used in conjunction with a provocative maneuver. The purpose of this study was to assess the viability of NIRS in conjunction with a transient leg elevation provocative maneuver for detecting severe PAD. This retrospective observational cross-sectional study assessed 57 limbs in 34 patients receiving routine vascular screening for PAD at Madigan Army Medical Center. The patient limbs were stratified into normal (n = 17), mild (n = 9), moderate (n = 16), and severe (n = 15) PAD groups based on the clinician assessments. Additionally, the patients were assessed with NIRS measurements taken with the patient in the supine position at rest and using a provocative leg raise maneuver of transient leg elevation of 45° for 60 seconds. The resting tissue oxygen saturation (StO_2) and the change in StO_2 (ΔStO_2) from rest to elevation were recorded and compared between the PAD severity groups via independent measures analysis of variance with the Tukey honest significant difference post hoc test. The supine resting StO_2 was not different between the normal (77.5% ± 7.7%), mild (72.5% ± 7.4%), moderate (72.0% ± 10.3%), and severe (74.2% ± 5.4%) PAD groups ($P = .23$). However, the ΔStO_2 with transient leg elevation was significantly greater in the severe PAD group (−17.2% ± 6.0%) compared with the normal (−3.9% ± 4.8%), mild (−6.9% ± 4.7%), and moderate (−9.7% ± 5.2%) PAD groups ($P < .002$ for all). Similar results were observed in the changes in oxyhemoglobin and deoxyhemoglobin. The leg elevation protocol was also used for two patients before and after lower limb revascularization, which demonstrated that the ΔStO_2 corresponded with the clinical assessment of PAD severity. Resting supine NIRS images were unable to detect any differences among normal and limbs with different PAD severity. However, NIRS imaging with 45° leg elevation for 60 seconds showed a significant difference between severe PAD compared healthy patients and those with mild to moderate PAD in a fast, precise, and accurate manner. These preliminary data support the use of NIRS and transient leg elevation as a tool to diagnose severe PAD but do not support the use of NIRS alone as a screening test for PAD. NIRS measurements with leg elevation might be a viable noninvasive, noncontact, and portable method of assessing severe PAD for home monitoring, in rural communities, and/or in standard clinical practice. (J Vasc Surg Cases Innov Tech 2023;■:101379.) Q5

Keywords: Critical limb ischemia; Near-infrared spectroscopy; Peripheral vascular disease; Revascularization; Vascular screening

Recent joint guidelines from the American College of Cardiologists and American Heart Association provide recommendations for diagnostic testing for patients suspected of having peripheral arterial disease (PAD).[1] The resting ankle brachial index (ABI) is the primary diagnostic assessment used, with a decreasing ABI denoting increasing PAD severity indicative of critical limb ischemia (CLI).[2] Should the clinical presentation be inconclusive, alternative or complimentary assessments such as the toe brachial index (TBI), transcutaneous oxygen pressure ($TcPO_2$), or skin perfusion pressure (SPP) assessments can be performed.[1] However, these assessment methods are time intensive ($TcPO_2$), involve recurring costs ($TcPO_2$, SPP), are not always feasible (TBI), not always diagnostically accurate (ABI), or are no longer on the market (SPP). This is further supported by recent guidelines from the International Working Group on the Diabetic Foot, which espouse that no single modality has been shown to be optimal, with no definite threshold value above which CLI can be reliably excluded.[3] Collectively, a true consensus is lacking on how to best screen for CLI, highlighting the need for new robust diagnostic methods or a combination of diagnostic methods to screen for CLI.

Near-infrared spectroscopy (NIRS) might help fill this unmet need, because it provides a fast, noninvasive, and noncontact quantitative assessment of oxygenation

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in the dermal microcirculation.[4,5] More recently, NIRS has been used for the evaluation of CLI, which primarily relied on the NIRS-derived measures of tissue oxygen saturation (StO_2).[6-9] These studies have often focused on comparing healthy controls to patients with a CLI diagnosis after a clinical assessment using the ABI, Rutherford classification, or Fontaine classification[7] or, alternatively, by quantifying the StO_2 dynamics after exercise[10] or postocclusive reactive hyperemia (PORH).[6] Prior research has suggested that provocative maneuvers can assist in diagnostic measurements.[6] Given this diagnostic potential, it is of interest to determine whether NIRS measurements, in conjunction with a leg raise maneuver, could be used to evaluate PAD status and severity. A particular area of interest is the assessment of CLI, because CLI requires urgent attention to prevent limb loss and potential complications.

Our current proof-of-concept research objective is to determine whether noncontact NIRS imaging during a provocative maneuver that affects limb perfusion could be used as an assessment tool to stratify patients by PAD severity and, specifically, to detect the presence of severe PAD or CLI. To the best of our knowledge, this would be the first report of NIRS imaging used in conjunction with leg elevation as a possible method to identify CLI. We hypothesized that NIRS would be capable of stratifying PAD severity (as assessed via a standard clinical assessment) based on the change in the score observed during a provocative maneuver of the lower limb.

METHODS

Participants and study design. This retrospective noninterventional observational cross-sectional study included patients suspected of having PAD who underwent a vascular evaluation at a vascular center (Madigan Army Medical Center, Tacoma, WA) between September 2021 and April 2023. A total of 57 limbs were assessed in 34 patients during the study period. Formal institutional review board approval was waived due to the retrospective and observational nature of the study. All demographic data were derived from the standard electronic medical records available to the investigators.

Protocol and data analysis. Patients suspected of having PAD were assessed using a provocative leg raise maneuver during the standard assessment. All assessments were conducted in a temperature-controlled room (20°C). During the provocative leg raise maneuver, the patients underwent imaging with a noncontact, portable NIRS camera (SnapshotNIR; Kent Imaging Inc) while resting supine and after 60 seconds of transient leg elevation at 45°. Because this is a preliminary report with no prior protocol of leg elevation on which to base our work, 45° was used as the designated metric due to the ease of visual measurement. Future work at different limb angles (eg, 60°) might help better distinguish PAD severity, but that was not the objective of the present study. The procedure requires ~2 minutes to conduct. The room temperature was controlled to maintain consistent surface temperatures of the patients' skin that might affect superficial vasodilation. At the end of both the resting supine and the leg elevation measurements, the plantar and dorsal surfaces of the foot were imaged for indexes of StO_2, oxyhemoglobin (HbO), deoxyhemoglobin (Hb), and total hemoglobin. The plantar surface of the foot was chosen, because previous work supports the plantar surface as a more reproducible monitoring area than the dorsal surface.[11,12] This also avoided the issue of marked variations in pigmentation between different races, allowing for more similar Fitzpatrick scores and precise NIRS readings. These metrics were evaluated at the hallux, second metatarsal head, and fifth metatarsal head before being averaged as a comprehensive reading of oxygenation within the forefoot. Changes (Δ) in StO_2, HbO, and Hb were calculated from the supine resting position to leg elevation to determine whether a relationship existed between arterial insufficiency and oxygenation.

To determine the relationship between PAD severity and NIRS measures, the patients were classified via clinical assessment into groups of normal, mild, moderate, and severe PAD. These groups were stratified by descending importance of clinical history, physical examination findings, pulse examination findings, ABIs, and TBIs, as suggested by recent guidelines.[3] Pulse examinations, ABIs, and TBIs were only performed if the physician determined these studies were necessary for an accurate diagnosis. These tests were not performed for every patient because they were not always indicated by the clinical examination findings. Although the ABI and TBI are arguably the most objective, they can still be skewed by calcification or noncompressible arteries, which can elevate the results. A single evaluator, a trained vascular surgeon with >40 years of practice, established the clinical criteria. In the clinic where our study was performed, pulse examinations are the standard of care if indicated by the clinical examination. The clinical history findings could be normal or abnormal based on the surgical history, a history of vascular disease, or other confounding factors. The physical examination findings were classified as normal or abnormal by the presence of palpable pulses, the presence of nonhealing wounds, temperature of the extremities, and any other observable symptoms of disease. The pulse Doppler signals were classified as normal if triphasic, mild to moderate disease if biphasic, and severe disease if monophasic or no Doppler signal was present. The thresholds for the disease level for the ABI were as follows: severe, an ABI of ≤0.49; moderate, an ABI of 0.50 to 0.74; mild, an ABI of 0.75 to 0.96; and normal, an ABI

Table I. Documented demographics and risk factors (n = 38 patients)

	PAD severity			
Variable	Normal (n = 12)	Mild (n = 5)	Moderate (n = 10)	Severe (n = 11)
Age, years	75 ± 7	83 ± 6	76 ± 8	75 ± 8
Comorbidities				
Diabetes mellitus	7 (62)	3 (60)	7 (70)	10 (91)
Hypertension	10 (77)	5 (100)	10 (100)	10 (91)
Chronic kidney disease	2 (15)	1 (20)	3 (30)	5 (45)
Coronary artery disease	5 (46)	0 (0)	3 (30)	3 (27)
Other risk factors				
History of tobacco	4 (31)	5 (100)	10 (100)	9 (82)
History of vascular surgery	3 (23)	2 (40)	8 (80)	7 (64)
Race				
White	12 (100)	4 (80)	7 (70)	5 (45)
Black	0 (0)	0 (0)	2 (20)	3 (27)
Asian	0 (0)	0 (0)	0 (0)	0 (0)
Hispanic	0 (0)	1 (20)	1 (10)	1 (9)
Native American	0 (0)	0 (0)	0 (0)	1 (9)
Hawaiian/Pacific Islander	0 (0)	0 (0)	0 (0)	1 (9)

NIRS, Near-infrared spectroscopy; *PAD*, peripheral arterial disease; *StO_2*, tissue oxygen saturation.
Data presented as mean ± standard deviation or number (%).

of ≥0.97. A TBI of <0.60 was classified as abnormal and a TBI of ≥0.60 as normal.

Statistical analysis. Statistical analyses were performed using R statistical language (R Foundation for Statistical Computing). Data are presented as the mean ± standard deviation. The between group contrasts are presented as the mean and 95% confidence intervals (CIs). Statistical significance was considered present at $P < .05$. The normality of data was assessed via the Shapiro-Wilk test and quantile-quantile plots. One-way independent measures analysis of variance was used to compare NIRS measurements between the different levels of PAD severity (ie, normal, mild, moderate, and severe). When significant F ratios were detected, the Tukey honestly significant difference post hoc analysis was used to identify pairwise differences.

RESULTS

Demographic data are presented in Table I. We included 57 limbs (34 patients) in the final analysis. Of the 57 limbs, 17 were categorized as normal, 9 with mild disease, 16 with moderate disease, and 15 with severe disease. In addition, 19 limbs had previously undergone surgical interventions. One patient was included who had been classified as having severe PAD from the initial leg raise protocol. This patient subsequently underwent bilateral stenting of their common iliac arteries and then underwent repeat imaging with the leg raise protocol postoperatively after being classified as having normal vascular studies (Fig 1).

The average NIRS-derived variables are presented in Table II. The supine resting StO_2 values for mild (−4.9%; 95% CI, −13.6% to 3.8%; $P = .44$), moderate (−5.5%; 95% CI, −12.8% to 1.9%; $P = .21$), and severe (−3.3; 95% CI, −10.8% to 4.2%; $P = .65$) PAD groups were not significantly different from those for the normal group (Fig 2, *A*). The ΔStO_2 from supine to leg elevation was significantly reduced in the moderate (−5.8; 95% CI, −10.7% to −1.0%; $P = .013$) and severe (−13.3; 95% CI, −18.2% to −8.3%; $P < .0001$) PAD groups compared with the change in the normal patients (Fig 2, *B*). However, the ΔStO_2 in the mild PAD group was not significantly reduced compared with the normal group (mean, −2.9; 95% CI, −8.7% to 2.9%; $P = .56$). Moreover, no difference was found between the mild and moderate groups (mean, −2.9; 95% CI, −8.7% to 2.9%; $P = .56$), although a significant difference was found between the moderate and severe groups (mean, −7.4; 95% CI, −12.4% to −2.4%; $P = .001$).

Similarly, the supine resting HbO (Fig 2, *C*) and Hb values did not show differences in any of the group comparisons ($P > .07$). However, the ΔHbO was significantly less in the normal (mean, −0.09 a.u.; 95% CI, −0.17 to 0.00; $P = .05$), mild (mean, −0.13 a.u.; 95% CI, −0.23 to −0.03; $P = .009$), and moderate (mean, −0.10 a.u.; 95% CI, −0.19 to −0.01; $P = .03$) PAD groups than in the severe PAD group (Fig 2, *D*). There was no significant difference in the ΔHbO between the normal, mild, and moderate PAD groups ($P > .68$). The ΔHb was also significantly less for the normal (mean, 0.06 a.u.; 95% CI, 0.0.03-0.09; $P < .0001$), mild (mean, 0.04 a.u.; 95% CI,

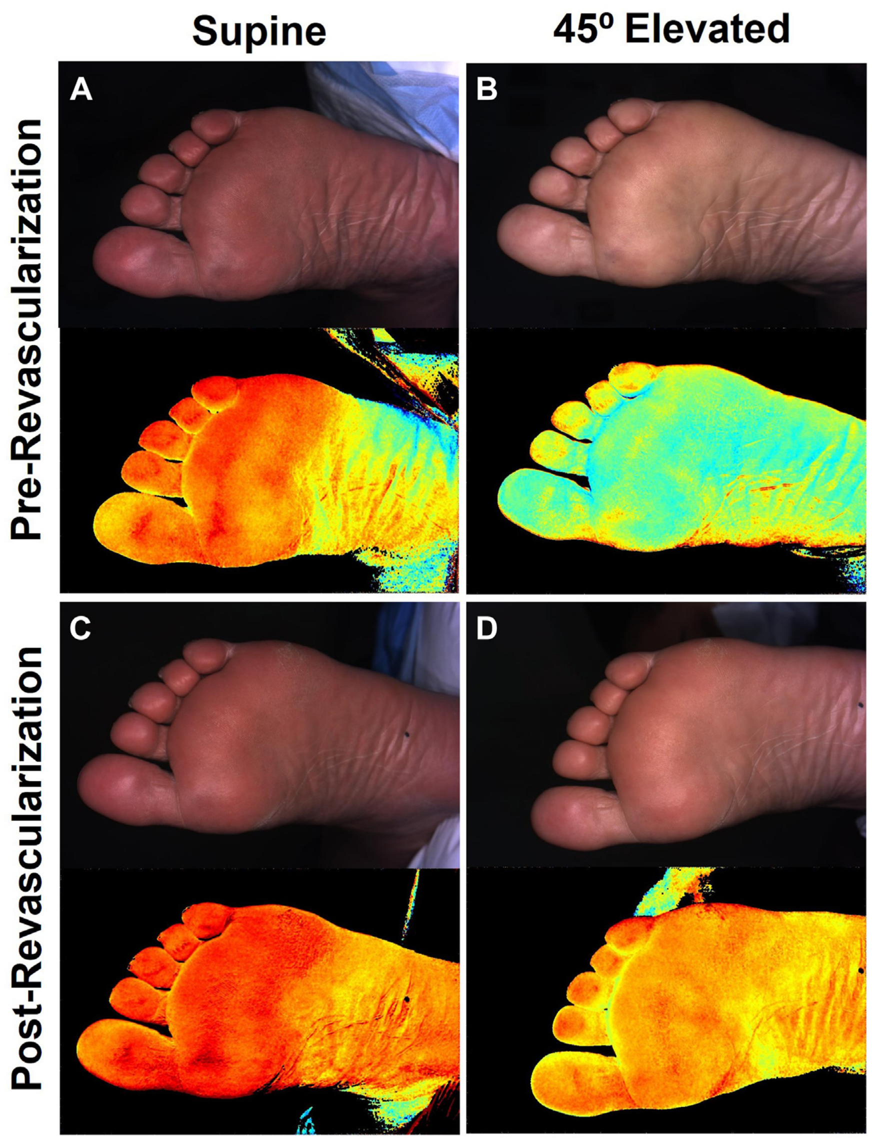

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Fig 1. Clinical photograph and tissue oxygen saturation (StO_2) images of a patient with severe critical limb ischemia before lower limb revascularization **(A and B)** and 5 days after bilateral stenting of the common iliac arteries (**C,D**). The imaging protocol involved measurements after both supine resting **(A and C)** and 60 seconds of 45° leg elevation **(B and D)**.

0.01-0.07; *P* = .02), and moderate (mean, 0.03; 95% CI, 0.00-0.06; *P* = .047) PAD groups than for the severe PAD group (Fig 3). We also found a difference in the ΔHb between the normal and moderate groups (mean, 0.03 a.u.; 95% CI, 0.00-0.06; *P* = .02).

DISCUSSION

The principal findings from our study are that (1) the supine resting StO_2 values were not different among the normal and PAD groups of various severity; and (2) a 60-second leg elevation maneuver was able to identify patients with CLI but not those with mild or moderate PAD. Furthermore, NIRS was used in some cases both before and after revascularization of the lower limb and was a precise determiner of postoperative outcomes. Our findings suggest that NIRS as a standalone modality might not accurately screen for PAD using a single imaging timepoint in a dependent position. Alternatively, the findings support that NIRS imaging could serve as a fast, precise, and accurate tool to diagnose severe PAD and might have utility in assessing postoperative outcomes if used in conjunction with a provocative maneuver.

To the best of our knowledge, this is the first known study using a leg elevation protocol with NIRS as a screening test for severe PAD. The leg raise protocol has multiple advantages over exercise and PORH maneuvers and other routine PAD assessments. First, a recent systematic review on tissue perfusion tests to diagnose

Table II. Near-infrared spectroscopy (NIRS) measurements (n = 57 limbs)

NIRS measure	PAD severity				*P* value
	Normal (n = 17)	Mild (n = 9)	Moderate (n = 16)	Severe (n = 15)	
StO_2, %					
Supine	77.5 ± 7.7	72.5 ± 7.4	72.0 ± 10.3	74.2 ± 5.4	.23
Elevated	73.5 ± 7.6	65.7 ± 5.8	62.3 ± 12.8	57.0 ± 6.2	<.0001
Change	−3.9 ± 4.8	−6.9 ± 4.7	−9.7 ± 5.2	−17.2 ± 6.0	<.0001
Oxyhemoglobin, a.u.					
Supine	0.69 ± 0.14	0.55 ± 0.13	0.56 ± 0.17	0.64 ± 0.11	.07
Elevated	0.50 ± 0.09	0.40 ± 0.07	0.38 ± 0.12	0.37 ± 0.10	.002
Change	−0.19 ± 0.08	−0.15 ± 0.09	−0.18 ± 0.09	−0.28 ± 0.12	.006
Deoxyhemoglobin, a.u.					
Supine	0.19 ± 0.05	0.20 ± 0.04	0.20 ± 0.04	0.22 ± 0.05	.27
Elevated	0.18 ± 0.05	0.21 ± 0.03	0.22 ± 0.05	0.27 ± 0.04	<.0001
Change	−0.01 ± 0.03	0.008 ± 0.04	0.02 ± 0.02	0.05 ± 0.02	<.0001

PAD, Peripheral arterial disease; *StO_2,* tissue oxygen saturation.
Data presented as mean ± standard deviation.

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PAD highlighted the need for noninvasive, contact-free, and quick diagnostic tests that could be implemented for home monitoring.[7] The NIRS device used in the present study fulfills these criteria, because it is portable, noninvasive, and contact-free device. Also, the leg elevation protocol takes <5 minutes to perform. This is considerably shorter than the gold standard ABI, which require, on average, 10 to 20 minutes to perform. Second, the leg elevation protocol does not involve the extra equipment (eg, treadmills, occlusion cuffs) that exercise and PORH protocols require. Third, NIRS has good to excellent reliability and provides reproducible measurements.[12,24] Compared with the ABI, which is user dependent, NIRS might be a more objective measurement. Future work assessing device-specific reliability, reproducibility, and multisite implementation is warranted, however, to confirm this assertion. Finally, NIRS can give a comprehensive examination of tissue oxygenation within the foot (Fig 1). In our experience regarding the sensitivity for detecting severe PAD, NIRS with leg elevation is more effective than the common ABI, which can be falsely elevated and cannot measure focal perfusion in the lower extremity or within a wound bed. This is supported by other work in which the NIRS detected lateral hypoxemia of the dorsum of the foot both before and after revascularization surgery.[4] As such, NIRS gives a global view of the foot or lower leg that can more precisely identify areas of concern when used in conjunction with a leg raise.

Although ours might be the first study to use a provocative leg raise maneuver in combination with NIRS, the idea of identifying PAD using NIRS is not new. Multiple systematic reviews have been reported in recent years focusing on NIRS for the diagnosis of PAD.[7-9,19,25] The unifying theme has been that evidence is currently lacking regarding "the clinical relevance of routine use of NIRS to diagnose PAD is unproven"[25] or that, "evidence seems too low to define this technique as a gold standard."[7] This, however, comes from the lack of standardization in the metrics, protocols, and devices for assessing PAD.[6] Regardless, it is clear that provocative maneuvers can identify statistically significant differences in those with PAD vs those without PAD,[12,18,20,22,23] suggesting the potential viability of NIRS for identifying PAD. Our present work builds on these findings, because we found statistically significant differences in the ΔStO_2 (Fig 2, *B*), ΔHbO (Fig 2, *D*), and ΔHb (Fig 3, *B*) between severe PAD and mildly diseased or healthy limbs when elevated by 45° for 60 seconds. Although the data are variable, we found many patients with severe PAD who had a ΔStO_2 of at least −18%, which was markedly different from that of the other groups (Fig 2, *B*). Furthermore, all the patients with severe PAD had an increase in ΔHb (Fig 3, *B*), which was not always seen in the other groups. Thus, we suggest that although NIRS might not be an adequate standalone screening test for PAD, it could be effective in identifying severe PAD in a fast and precise manner when used with a leg elevation protocol. Currently, the cutoff values to discriminate severe PAD from healthy limbs does not seem readily apparent but warrant future investigation.

Study limitations. The present study has multiple methodologic considerations and limitations that are important to address. First, it is well known that melanin affects NIRS and other light-based technologies.[27-29] The present study did not account for the melanin content, which could have contributed to the baseline variability in our patients. However, because our measurements of interest are the changes in oxygenation metrics, the

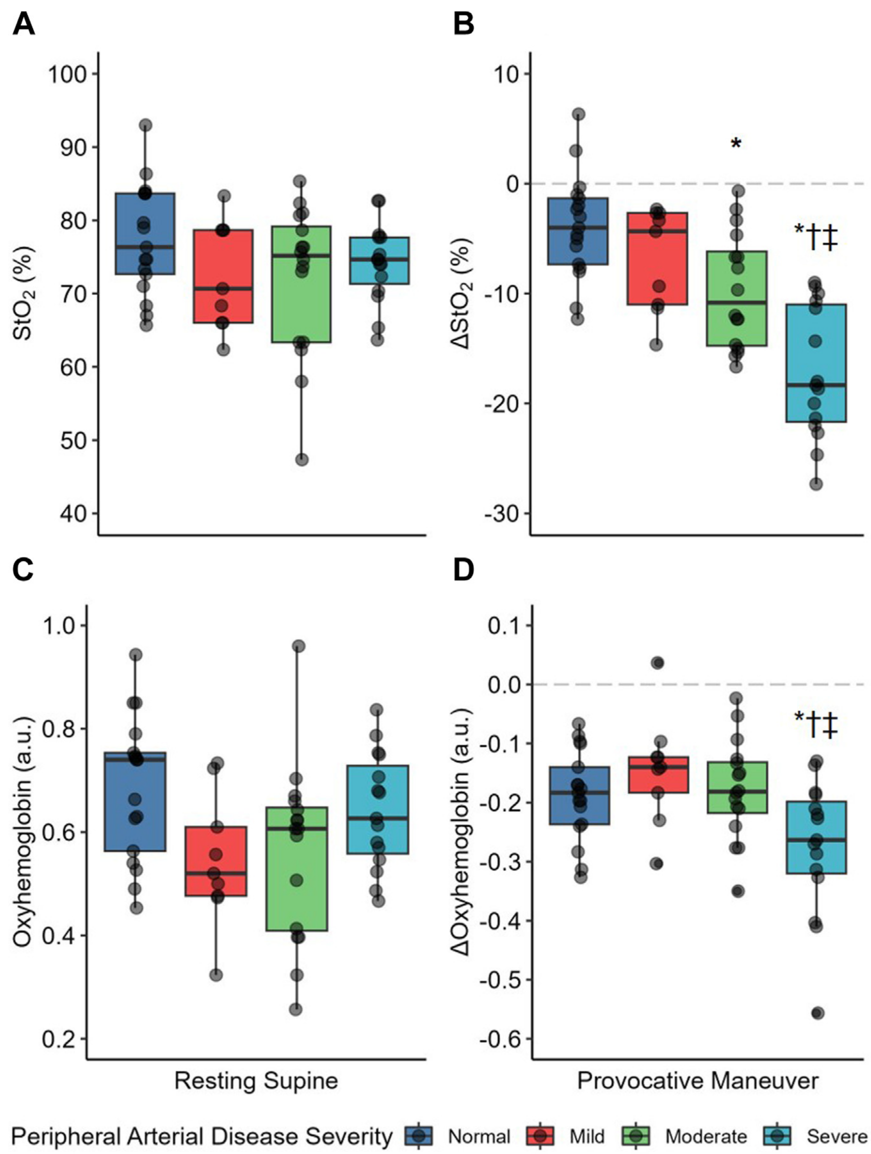

Fig 2. Comparison of supine resting tissue oxygen saturation (StO_2; **A**) and oxyhemoglobin (HbO; **C**) values in normal, mild, moderate, and severe peripheral arterial disease (PAD) groups and delta values for StO_2 **(B)** and HbO **(D)** taken as part of a provocative leg raise maneuver of 45° elevation for 60 seconds. Presented as individual data scatter and box plots for transparency. *$P < .05$ compared with normal; †$P < .05$ compared with mild PAD; and ‡$P < .05$ compared with moderate PAD.

absolute baseline value for each of our patients is not as important as the relative change that occurs with our leg raise protocol. Black patients were studied in this cohort. By only including plantar images of the foot, we did not find a significant difference in hemoglobin for most black patients compared with patients of other races. Next, this was an observational study with uneven numbers of participants in each PAD group and incomplete demographics. Because this is a preliminary study, it does not have the number of participants needed to stratify for different comorbidities or conditions. As an example, previous work has found that diabetes inflates StO_2 values.[6,8,30] To offset this, we suggest that the relative variability with each comorbidity will remain the same on an intraindividual basis because the relative changes should be consistent in their level of error. Despite this shortcoming, the P values for ΔStO_2 were very small when comparing the severe PAD group and the other groups, which strengthens our confidence that we found a real difference and not strictly an exacerbation of comorbidities or a small value. Next, two patients were included in the dataset who had both pre- and postrevascularization leg raise data available. Because of the mix of individuals who had undergone previous

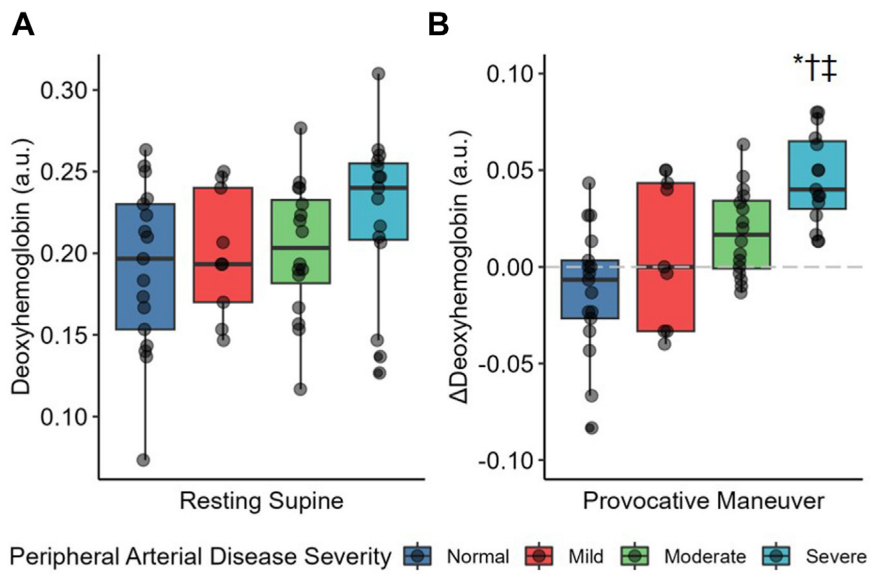

Fig 3. Comparison of supine resting deoxyhemoglobin (Hb) values **(A)** for normal, mild, moderate, and severe peripheral arterial disease (PAD) groups and delta values for Hb taken as part of a provocative leg raise maneuver of 45° elevation for 60 seconds **(B)**. Presented as individual data scatter and box plots for transparency. *$P < .05$ compared with normal; †$P < .05$ compared with mild PAD; and ‡$P < .05$ compared with moderate PAD.

revascularization, we decided to include the post-revascularization data in our dataset. Based on the independent measures analysis of variance, they would be considered independent samples because they changed groups after revascularization. Because ours is a preliminary analysis, we did not want to exclude the limbs with postintervention data and reduce our dataset by ~33%; thus, we included them in the dataset for transparency. Finally, this study only used patients who had attended for a routine vascular screening and did not have a control group as a comparator. Having a strict control group would help isolate the normal vascular responses from "normal" patients who might have some degree of vascular compromise due to them requiring screening to begin with.

CONCLUSIONS

NIRS with a 45° leg elevation for 60 seconds resulted in significant decreases in StO_2 and HbO for patients with severe PAD compared with patients with normal, mild, or moderate PAD. Although these groups differ slightly from the literature, during the study, we observed a range of non-normal StO_2 values that did not constitute severe disease. These were grouped into the mild and moderate PAD groups. Grouping them together into moderate would not have changed the resultant data because neither mild nor moderate disease could be diagnosed with significance using NIRS alone. Only CLI can be diagnosed with significance. Such differences in oxygenation were not detectable during the resting supine assessment. Our data indicate that a simple leg raise maneuver used in conjunction with NIRS can delineate patients with severe PAD from healthy patients and those with mild PAD in a fast, noncontact, and noninvasive way. These findings highlight the potential utility of a portable NIRS camera for quick and efficient detection of severe PAD in the clinic or home monitoring setting. Other findings suggest that the same leg raise protocol could be useful in determining revascularization surgery outcomes. Future work investigating the range of values for a severe PAD diagnosis and surgical success is warranted.

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13; 14; 15; 16; 17; 21; 26.

DISCLOSURES

None.

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