Eur J Vasc Endovasc Surg **35**, 68–74 (2008)
doi:10.1016/j.ejvs.2007.07.015, available online at http://www.sciencedirect.com on ScienceDirect

REVIEW

Near-infrared Spectroscopy for Evaluation of Peripheral Vascular Disease. A Systematic Review of Literature

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Objectives. *To assess near-infrared spectroscopy (NIRS) as a method for the diagnosis and evaluation of peripheral vascular disease.*
Search strategy. *MEDLINE and CENTRAL were searched with a search protocol presented below. Handsearching through reference lists of the retrieved articles and reviews was conducted.*
Main results. *224 and 57 abstracts from MEDLINE and CENTRAL respectively were retrieved from which 21 studies were selected. NIRS was evaluated for the diagnosis and severity evaluation in patients with peripheral vascular disease. Its parameters were shown to reflect the clinical status of patients, with good correlation to existing methods.*
Conclusions. *Currently NIRS technology can serve as an adjunct method for the diagnosis and evaluation of patients with peripheral vascular disease.*

Keywords: Peripheral vascular diseases; Spectroscopy; Near-infrared; Review [Publication Type].

Background

Peripheral vascular disease (PVD) is a common disease of the elderly, resulting in compromise of blood flow to the lower limbs. Several techniques are currently being used to aid the diagnosis and severity assessment of patients with PVD. These include ankle-brachial index, segmental limb pressure and plethysmography, Duplex ultrasound, multidetector computed tomography,[1] and magnetic resonance spectroscopy or imaging. These techniques assess blood supply but not oxygen and nutrient transport, essential for limb vitality and functionality. Transcutaneous oximetry (TcpO2) and laser Doppler fluximetry measure local oxygen tension at the surface of the skin and total skin perfusion, respectively, and serve as adjuncts in the assessment of PVD severity.

Near infrared spectroscopy is a technology in which oxygen saturation of haemoglobin is measured using near infrared (NIR) light. The percentage of haemoglobin saturated with oxygen is determined by passing specific wavelengths of light through blood and measuring its absorption. Since the amounts of light absorbed by oxygenated haemoglobin and by deoxygenated haemoglobin are different, the relative concentration of oxygenated haemoglobin can be determined. Near-infrared spectroscopy has been used since the eighties, mostly for the assessment of cerebral circulation. Animal experiments have indicated that skeletal muscle oxygen consumption ($V0_2$) is proportional to blood flow.[2]

The aim of this systematic review of literature is to assess the clinical efficacy of NIRS for the diagnosis and evaluation of peripheral vascular disease.

Methods

Criteria for considering studies for this review

Prospective clinical trials were sought, in which NIRS was used for the diagnosis and severity evaluation of patients with peripheral vascular disease from any etiology, and of any age and gender. Studies designed to evaluate a therapeutic intervention were excluded.

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1078–5884/000068 + 07 $32.00/0

Retrospective trials and case reports were not considered. We searched MEDLINE and CENTRAL (until June 2007) with the following search strategy: ((''Spectroscopy, Near-Infrared''[MeSH]) OR (NIR*) OR (tissue spectroscopy*) OR (tissue oxygen*) OR (tissue hypox*) OR (muscle spectroscopy) OR (muscle oxygen*) OR (muscle hypox*) OR (muscle oxygen consumption) OR (''Oxygen Consumption/analysis''[MeSH])) AND ((''Peripheral Vascular Diseases'' [MeSH]) OR (PVD*) OR (Peripheral arterial Disease) OR (PAOD) OR (leg ischemia) OR (''Intermittent Claudication'' [MeSH]). We tried to identify additional studies by searching the reference lists of relevant trials and reviews identified.

Two independent reviewers scanned the titles and abstracts of the studies retrieved. Full articles were retrieved for further assessment when appropriate. Doubts and differences of opinion were resolved by open discussion.

Results

224 and 57 abstracts from MEDLINE and CENTRAL, respectively, were retrieved. 29 studies were further assessed. 25 trials met the inclusion criteria specified above. Four studies were excluded. One study reported a different technology for tissue oxygen measurements, and one reported on pulmonary oxygen uptake. Two used NIRS alongside other modalities for the assessment of different interventions [Fig. 1].

NIRS for the diagnosis of PVD

The first study aimed to assess whether VO_2 was reduced in patients suffering from intermittent claudication was conducted by Cheatle *et al.*[3] NIRS was employed on the calf muscles of 17 patients and 21 controls, while oxygen consumption was measured during and after a tourniquet-induced ischemia. The authors found a significant difference in resting oxygen consumption between claudicants and controls. However, there was a broad overlap between the groups. Correlation between VO_2 and ankle-brachial index (ABI) was reported to be poor. Median time to reach 95% maximal level of saturated haemoglobin (measured during post-obstructive hyperemia) was 40 seconds in claudicants compared to 20 seconds in controls, again with a broad overlap between the groups. McCully *et al.*[4] compared the rate of oxygen desaturation and resaturation during and after exercise of calf muscles of people with PVD, with that of healthy young as well as older subjects. Oxygen desaturation during an exercise test was near-maximal in the PVD group compared to healthy subjects. The investigators found that the rate of oxygen resaturation after exercise was a reproducible measurement, with a good correlation between this parameter and the ankle-brachial pressure index ($r^2 = .63$, $p < 0.01$). However, their report included only 8 patients and 26 controls. In a subsequent report from this group on a larger cohort ($n = 117$),[5] clinical evidence of PVD was compared to NIRS half time of recovery to baseline parameters (T_{50}), reflecting tissue oxygenation. Half time to recovery values for participants with PVD was significantly longer. The sensitivity and specificity of two threshold values were assessed (40 and 50 seconds) to estimate the usefulness of NIRS as a screening tool for PVD. Sensitivity and specificity ranged from 50 to 80% for both thresholds. Lee *et al.*[6] reported 11 claudicants and 12 healthy controls assessed with NIRS at rest, while standing, and during and post exercise. During the postexercise recovery period, all but one of the subjects without claudication showed an increase in oxygenation index (log difference of red reflectance from infrared reflectance). In the patients with claudication, the oxygenation index in three limbs decreased in the immediate postexercise recovery period, while it increased slowly in six limbs and rapidly in two limbs. Harrison *et al.*[7] investigated NIRS potential to diagnose PVD, during and after standard treadmill exercise in 19 patients and nine healthy controls. T_{50} was significantly longer for the patients than controls. No threshold was reported. Cassavola *et al.*[8] investigated the application of NIRS for the diagnosis of PVD in four patients. They found that T_{50} was in the range of seconds in healthy legs, and minutes for legs affected by peripheral vascular disease. No threshold for this distinction was advised. Another report from Kooijman *et al.*[9] evaluating 11 patients and 15 healthy controls, demonstrated that during rest VO_2 was similar for the

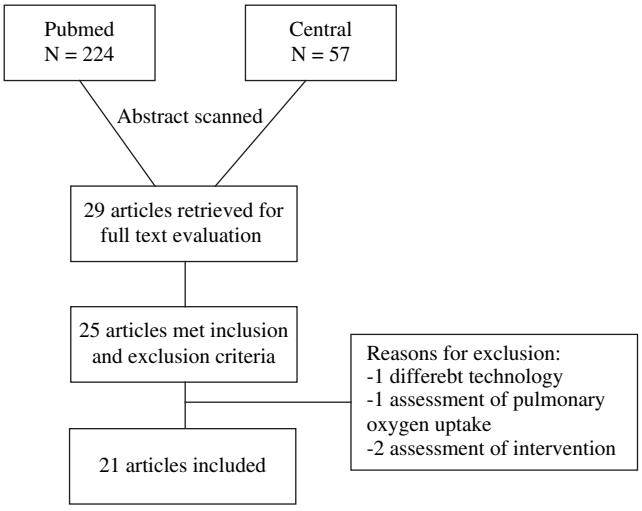

Fig. 1. Flow chart for the search strategy and reasons for exclusion.

different groups, while one minute after a standard walking exercise it declined significantly more in claudicants. In addition the report showed that claudicants exhibited a lower resaturation rate of oxyhaemoglobin (HbO_2) and longer recovery times, after both walking and arterial occlusion. These parameters were correlated to ABI measurements. Seifalian *et al.*[10] evaluated the changes in NIRS in 14 patients with intermittent claudication and 10 controls, pre- and postexercise. There was a significant ($p < 0.001$) difference in the degree and rate of HbO_2 deoxygenation between claudicants and controls. The period of recovery of HbO_2 postexercise was also significantly slower in claudicants. Comerota *et al.*[11] explored the diagnostic sensitivity of quantified muscle saturation (StO_2) for PVD, and the correlation between StO_2 dynamics and ABI, on 14 patients with PVD and 35 controls. They found that peak exercise StO_2, absolute change between baseline and peak StO_2, percent change between baseline and peak StO_2, half time to recovery of StO_2 and full time of recovery of StO_2 (T100) were all significantly different between PVD patients and controls. A significant correlation between half time and full time of recovery of StO_2 to ABI was found ($r = -.65$, $p < 0.001$, $r = -.48$, $p = 0.035$, respectively). They report a cut-point for T_{50} maximizing sensitivity without loosing specificity of >70 seconds (89% and 75% respectively). For T_{100} a cut-point of 165 seconds yielded a sensitivity and specificity of 88% and 81% respectively. Wolf *et al.*[12] found significant differences between patients with documented PVD, patients with risk factor for PVD, and healthy subjects, with respect to oxygen consumption, venous oxygen saturation, as well as changes in oxyhaemoglobin, deoxyhaemoglobin and total haemoglobin after venous occlusions of 60 and 180 seconds. Some of these indicators were significant for differentiating PVD patients from patients with risk factors, some between patients with risk factors and healthy volunteers, and some between PVD patients and healthy volunteers. ABI was correlated with SVO_2, haemoglobin flow, oxy- and total-haemoglobin concentration differences after 60 seconds of venous occlusion. Mapping areas of reduced oxygenation and flow was also possible. Watanabe *et al.*[13] evaluated NIRS in 62 limbs from patients with peripheral occlusive disease and reported highly significant correlation in the recovery time between the ABI and StO_2, Oxy- and deoxy-haemoglobin. The recovery time for NIRS parameters were shorter than for ABI, reflecting the different physiological events monitored by these two modalities. Ubbink *et al.*,[14] in a study with 45 patients and 20 controls, reported StO_2 as being able to discriminate controls from claudicants in response to treadmill exercise but not during rest. The post exercise StO_2 as well as the decrease in StO_2 during exercise correlated with lower ABI.

Post occlusive reactive hyperemia (PORH) is one of the well-known clinical tests for lower limb ischaemia. Kragelj *et al.*[15] used NIRS during a PORH test on 24 PVD patients and 18 healthy volunteers and compared it to TcpO2 readings and baseline ABI. Recovery time parameters (including the time interval from the release of the cuff until the initial values from NIRS recording are reached; the time to reach 95% of the maximal signals) and reoxygenation rates (the maximal change in the signal after the release of the cuff expressed as the percentage of the signal change during arterial occlusion, and the maximal change in signals during the reactive hyperemia) all differed significantly between PVD patients and controls. Some of these parameters also correlated well with baseline ABI and $TcpO_2$ values. Interestingly, diabetic patients had a delayed hyperemic response and lower reoxygenation rates than non diabetics, with a broad overlap between the two groups. Jarm *et al.*[16] reported the use of three non-invasive methods for the distinction between three healthy volunteers and patients with PVD: $TcPO_2$, near-infrared spectroscopy, and LDF measurements during PORH. Results of all three methods provided distinction between healthy volunteers and patients. NIRS and LDF demonstrated the difference between healthy volunteers and patients more clearly than $TcPO_2$. The dynamics of the PORH response detected by NIRS and LDF proved to be a better indicator of peripheral vascular disease than the amplitude of responses. Cheng *et al.*[17] utilized StO_2 changes during and post PORH test for the assessment of PVD in nine patients and 10 controls. They assessed [Δt]phase-*i* as the time required for 80% change in StO_2 in phase *i* of the four phases of the PORH test (accumulation, ischemia, reperfusion and dispersion), and [ΔStO_2]phase-*i* as the StO_2 change rate at the middle value of StO_2 in phase *i*. Three parameters were found to qualify as indicators of PVD: [Δt]reperfusion, [ΔStO_2]reperfusion, and [ΔStO_2]dispersion with a *p-value* < 0.001 for the differentiation between the control and PVD groups. As a diagnostic tool, a subject may have higher risk for PVD if [Δt]reperfusion >40 seconds and [ΔStO_2]reperfusion <50%/minute, and [ΔStO_2]dispersion <5%/minute. The sensitivity and specificity were between 80 and 100%.

NIRS for evaluation of the severity of PVD

NIRS as a method for assessing PVD severity was the subject of four trials. Komiyama *et al.*[18] studied the changes in tissue oxygenation in the calf muscle in

62 patients who complained of intermittent claudication in the calf during a treadmill test. Three distinctive patterns of oxygenated and deoxygenated haemoglobin ratios were observed. The findings correlated with disease severity as assessed by the ability to walk for more than five minutes, the mean maximum walking distance and the mean ankle-brachial pressure index at rest. They were referred to as types 0, 1 and 2. A subsequent report[19] evaluated NIRS with treadmill walking as a method for assessing PVD in diabetics. All type 0 legs completed a five minutes treadmill walking test, while none of the type 2 legs were able to do so. These authors also reported the ability to evaluate absolute muscle saturation with spatially resolved spectroscopy (SRS).[20] This measure differentiated normal controls from three groups of claudicants according to clinical status.

NIRS for the evaluation of patients with PVD and diabetes mellitus

Kragelj *et al*.[15] reported a post-hoc analysis in which non-significant delayed recovery times and lower reoxygenation rates after PORH in diabetics with PVD compared to non-diabetics with PVD were observed. Komiyama *et al*.[19] evaluated NIRS with treadmill walking as a method for assessing PVD in diabetics, compared with resting ABI, on 208 symptomatic legs from 153 patients. They concluded that recovery time measured with NIRS is a better marker than resting ABI for the diagnosis and assessment of severity of claudication in diabetics. Mohler *et al*.[22] recently published a study aimed at determining whether NIRS hemodynamic measurements are perturbed in patients with diabetes before the development of clinically significant PVD. 25 healthy controls, 17 diabetics, 13 claudicants and 19 claudicants with concomitant diabetes were enrolled. Blood volume expansion did not differ between controls and diabetics, but was increased in PVD patients. PVD patients with diabetes had an attenuated blood volume response compared to PVD only patients. Diabetes had no effect on T_{50} or percentage of deoxygenation, unlike the presence of PVD, which significantly increased both values. These results are argued to reflect a decrease in the vasodilatation capacity of patients with diabetes, presumably due to endothelial dysfunction.

Combining NIRS with other modalities

Other modalities for assessing patients suffering from PVD exist. In 2001, Kemp *et al*.[24] evaluated the simultaneous use of NIRS and magnetic resonance spectroscopy (MRS) during an exercise test. Both NIRS and MRS signals fell during exercise and then recovered. Claudicants showed faster and greater deoxygenation during exercise, despite reduced oxygen consumption, and slower resaturation afterwards. This supports the idea that oxidative metabolism impairment in peripheral arterial disease is a result of impaired oxygen delivery.

Reproducibility

McCully *et al*.[4] found the rate of oxygen resaturation after exercise is a reproducible measurement. Ubbink *et al*.[14] studied twenty healthy volunteers to assess the reproducibility of NIRS. Calf measurements had good reproducibility (intraclass correlation coefficient of 0.91 before treadmill and 0.90 after treadmill) but those performed on the dorsum of the foot were less reliable.

New NIRS based technology

New NIRS based technology has emerged in recent years to expand its clinical and experimental utility. Three reports demonstrated these novel approaches on patients with peripheral arterial disease. Komiyama *et al*. have used spatially resolved spectroscopy, which is based on intensity changes at multiple spacing, and provides an absolute tissue oxygen saturation index in addition to changes in oxygenation.[20] Wolf *et al*.[12] used NIRS to demonstrate maps and spatial distribution of haemoglobin flow, concentration and oxygenation, enabling identification of local irregularities in haemoglobin flow, concentration and oxygenation. Yu *et al*.[25] have used near-infrared diffuse correlation spectroscopy (DCS), a technique for continuous noninvasive measurement of relative blood flow in deep tissues, and diffuse reflectance spectroscopy (DRS), to measure blood flow and oxygenation in cuffed and exercising human muscle. These techniques may be applicable in the future but are currently not clinically useful in the setting of PVD.

Assessment of parameters for evaluation of patients with peripheral arterial disease

Many parameters were evaluated as being efficient indicators for PVD existence and severity. The parameters are mostly derivatives of changes in tissue oxy- and deoxyhaemoglobin saturation, during rest, venous occlusion, muscle ischemia, exercise challenge, and recovery phases. Standard exercise protocols, post obstructive reactive hyperemia test, as well as modified techniques to induce muscle hypoxia were employed [Table 1].

Table 1. NIRS parameters assessed

Parameter	Study	Outcome
Oxygen consumption	Cheatle *et al.*[3]	Resting VO2 significantly different between claudicants and controls with a broad overlap between the groups
	Kooijman *et al.*[9]	Resting VO_2 not significantly different between their groups VO2 differed significantly one minute after a standard walking exercise
	Wolf *et al.*[12]	VO2 after venous occlusion differed between patients and controls.
Saturation recovery times	Cheatle *et al.*[3]	median time to reach 95 per cent maximal saturated haemoglobin level was 40 seconds in claudicants compared to 20 seconds in controls, with a broad overlap between the groups
	Harrison *et al.*[7]	T_{50} – best indicator for differentiating PVD patients from controls, after exercise test
	Cassavola *et al.*[8]	T_{50} – in the range of seconds in healthy legs, and minutes for legs with PVD.
	McCully *et al.*[5]	Time to recovery values for PVD patients- significantly longer
	Kooijman *et al.*[9]	Higher recovery times of HbO_2, after walking and after arterial occlusion.
	Seifalian *et al.*[10]	Recovery of HbO_2 postexercise significantly slower among claudicants.
	Comerota *et al.*[11]	Half time and full time to recovery of StO_2 significantly different between PVD patients and controls
	Wantanabe *et al.*[13]	Good correlation in recovery time of StO_2 and ABI, although shorter time for StO_2 was noted.
	Ubbink *et al.*[14]	Good correlation between StO_2 during and after exercise and post-exercise ABI.
Saturation recovery times during PORH test	Kragelj *et al.*[15]	Time interval between the release of cuff until the initial values from NIRS recording were reached, and the time to reach 95% of the maximal signals, differed with statistical significance between PVD patients and controls.
	Jarm *et al.*[16]	Time intervals for recovery to initial values, maximum values and half of the initial values – the best indicators of disease.
	Cheng *et al.*[17]	Time required for 80% change in StO_2 during PORH reperfusion phase- significantly different between patients and controls.
StO2 kinteics under low work rates*	Bauer *et al.*[32]	StO2 responses were similar under these conditions, yet the time course of muscle oxygen desaturation was prolonged in the PVD group, reflecting slower dynamic increase in oxygen consumption.
Rate of resaturation after exercise	McCully *et al.*[4]	Rate of oxygen resaturation after exercise is a reproducible measurement, and significantly slower in PVD patients compared to controls
	Kooijman *et al.*[9]	Resaturation rate of O_2Hb lower after walking after arterial occlusion.
	Kragelj *et al.*[15]	Reoxygenation rates significantly different between groups
O_2 desaturation rate and time	McCully *et al*[4]	Oxygen desaturation during an exercise test to be near-maximal in the PVD group compared to healthy subjects.
	Seifalian *et al.*[10]	Significant difference in the degree and rate of HbO_2 deoxygenation between claudicants and controls.
Changes of tissue saturation:	Comerota *et al.*[11]	Absolute change between baseline and peak StO_2 and percent change between baseline and peak StO_2 – differentiating controls from patients.
	Wolf *et al.*[12]	Changes in oxyhaemoglobin, deoxyhaemoglobin and total haemoglobin after venous occlusion of 60 and 180 second- significantly different between groups.
Quantitative measures of tissue saturation:	Comerota *et al.*[11]	Peak exercise StO_2- a significant marker for PVD

* In low work rates blood flow response is presumably similar in healthy and occluded limbs.

Safety

Only one report[11] employing NIRS technology on patients with PVD referred to safety issue. They reported no adverse events.

Discussion and Conclusion

Several methods exist to diagnose and assess the severity of peripheral vascular disease. The most common of all is measurement of ankle-brachial pressure index.[26] This method lacks the ability to measure blood flows. Doppler ultrasound can be used for this purpose,[27] but previous reports have demonstrated that femoral artery flow is not sufficiently reliable to assess tissue ischemia.[28] Venous occlusion plethysmography indirectly quantifies and detects vascular abnormalities based on volume change in the leg.[27,29] Magnetic resonance spectroscopy has been applied to evaluate PVD,[30] but its clinical use is limited due to high costs and lack of availability. Doppler fluximetry and transcutaneous oxygen tension measurement are also available for microcirculatory evaluation, but should be interpreted cautiously in patients with PVD.[31] Near-infrared spectroscopy monitors the key pathophysiological determinant of PVD, i.e. oxygen delivery to tissues themselves. It is designed to allow an objective assessment of muscle blood flow and oxygenation level, which gives rise to assessment of mismatch between oxygen demand and delivery to tissue. Therefore, information yielded by NIRS is a valuable measure of PVD.

In this systematic review we have summarized results from 21 prospective clinical trials, assessing the

application of NIRS for the evaluation of PVD. No gold standard for this evaluation is available, as the clinical presentation is a derivative of a combination of flow, tissue oxygenation, oxygen extraction and utilization. It seems from the reports presented above that NIRS is a promising evolving technique for this purpose, encompassing the ability to reflect tissue dynamics. Many parameters extracted by NIRS can be retrieved as indicators for PVD presence, severity, and response to treatment. Indeed, many parameters were evaluated over the years, a reflection of the search for the best indicators for clinical purposes. It seems that the best reported parameters to this date are a reflection of oxygen consumption and tissue post-hypoxia resaturation times or rates. These parameters mostly correlated well with ankle-brachial index. Trying to summarize the effectiveness of NIRS in this clinical setting in a meta-analysis is not statistically nor clinically sound, and therefore it remains to be determined how many patients with PVD requiring treatment would have been missed without the more traditional diagnostic modalities, or on the other hand without NIRS. NIRS has not yet gained widespread use as a tool in PVD diagnosis. Therefore, issues of efficiency and cost of the technique have not been addressed in the works reviewed. However, NIRS is a simple, easy to learn, painless and complication-free technique. Its utilization is still awaiting refinement.

Financial Disclosure

Dr. Moshe Vardi received consultant fees From Or-Nim Ltd. Dr. Asaph Nini is the Medical Director of Or-Nim Ltd.

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Accepted 24 July 2007
Available online 4 October 2007