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Systematic Review

Muscle Oxygenation During Exercise in Patients with Peripheral Artery Disease: A Systematic Review

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Abstract

Peripheral artery disease (PAD) involves atherosclerotic obstruction of the leg arteries and impairs function and structure of lower-limb tissues. Although traditionally regarded as a large-artery (macrovascular) disorder, PAD includes significant microvascular disease in the affected musculature, together leading to impaired leg perfusion. Monitoring muscle oxygenation during exercise provides an indirect index of limb perfusion and exercise capacity, and tracking its kinetics with near-infrared spectroscopy (NIRS; a portable, non-invasive technique measuring real-time tissue oxygen saturation) helps elucidate mechanisms underlying walking limitations in PAD. We systematically searched PubMed, Web of Science, and the Cochrane Library (1985–2025) for studies employing NIRS to monitor muscle oxygenation in PAD patients before, during, and after exercise. Of 628 articles screened, 11 met the inclusion criteria. NIRS demonstrated reliability and validity for monitoring muscle oxygenation in PAD. During walking, PAD patients showed a much steeper decline in muscle oxygenation and delayed recovery to baseline. Resting muscle oxygenation did not differ between patients with PAD and controls. These dynamics reveal the pathophysiological interplay in which proximal/macrovascular and distal/microvascular disease limit oxygen delivery and utilization in skeletal muscle. Accordingly, NIRS offers a sensitive, non-invasive tool to evaluate macro- and microvascular disease burden and monitor therapeutic response in PAD.

Keywords: claudication; ischemia; macrovascular disease; microvascular disease; near-infrared spectroscopy (NIRS)

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1. Introduction

Peripheral artery disease (PAD) is a cardiovascular condition that occurs when atherosclerosis narrows or obstructs the arteries supplying the lower extremities [1–4]. Muscle oxygenation is a valuable indicator of oxygen delivery and utilization, particularly in the calf muscles of patients with PAD, who experience reduced blood flow from large-artery blockages (macrovascular disease) as well as microvascular pathology and

dysfunction [5–10]. PAD is a chronic disease in which oxygen supply to the leg tissues, especially during walking, cannot meet oxygen demand [11]. This persistent imbalance over months and years causes progressive structural, physiological, and functional injury to skeletal muscle, skin, adipose tissue, blood vessels, and nerves [11,12]. Together, this ischemic mismatch and tissue damage produce the hallmark manifestations of PAD, namely, intermittent claudication and chronic limb-threatening ischemia [13,14]. Claudication, the most common clinical symptom of PAD [15,16], occurs because patients cannot increase blood flow to skeletal muscle during walking, owing to macro- and microvascular disease [15,17]. This leads to muscle dysfunction, disabling leg pain, and severe walking impairment. Given that impaired perfusion underlies these symptoms and that skeletal muscle is the most active, oxygen-consuming tissue during walking, monitoring muscle oxygenation provides a practical and non-invasive way to assess both regional blood flow and balance between oxygen delivery and utilization [18–20]. During walking, rising metabolic demand in the working muscles pushes oxygen consumption beyond supply, so tissue oxygen saturation (StO_2) falls (ischemia) [21]. Once activity stops, oxygen supply once again exceeds demand, and StO_2 returns toward baseline (reperfusion). Calf muscle StO_2 is influenced by several factors, including macro- and microvascular lesions, endothelial function, the efficiency of oxygen extraction by myofibers, and the efficiency of oxygen utilization by mitochondria [10].

Patients with PAD show altered physiological responses to physical activity [20,22,23], including reduced oxygen levels in the active skeletal muscles and delayed post-exercise calf muscle reoxygenation [24–28], with recovery rates slower than healthy individuals [29,30]. Monitoring dynamic changes in StO_2 from rest to exercise and into recovery may therefore illuminate the pathophysiological basis of exercise limitation in patients with PAD [20]. Figure 1 illustrates a representative StO_2 pattern in a patient with PAD during walking and recovery, highlighting commonly analyzed metrics.

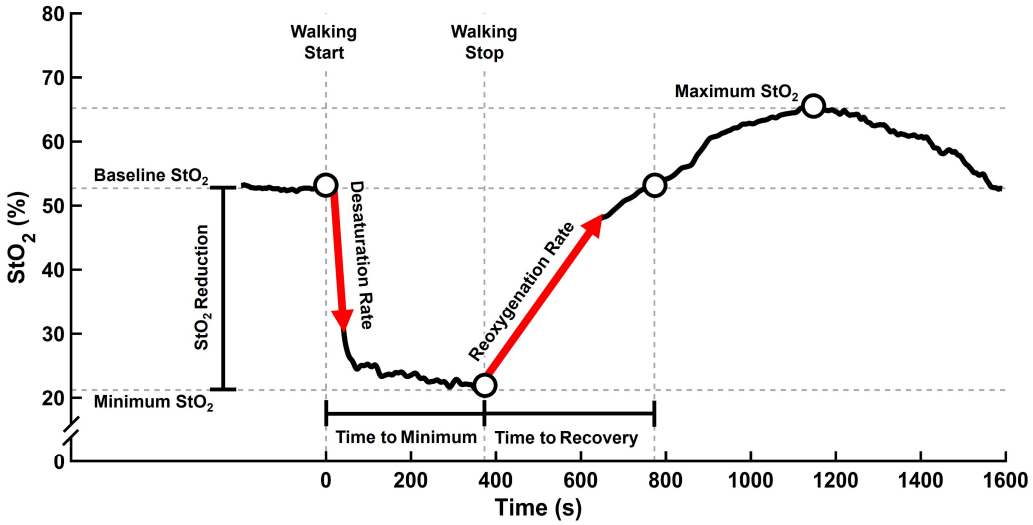

Figure 1. Representative StO_2 trace for a patient with claudication due to peripheral artery disease during walking and common outcome measures. StO_2 is the percentage of hemoglobin/myoglobin in the near-infrared spectroscopy sampling volume that is oxygenated. An StO_2 of 100% indicates that all hemoglobin/myoglobin in the sampling volume is oxygenated, and an StO_2 of 0% indicates that no hemoglobin/myoglobin in the sampling volume is oxygenated [31]. However, when using continuous-wave near-infrared spectroscopy systems, absolute StO_2 values should be interpreted with discretion due to assumed scattering coefficients. Therefore, it cannot be assumed that full oxygen desaturation during walking occurs at an StO_2 of 0% for all patients. In experiments in patients with peripheral artery disease, the near-infrared spectroscopy sensor is commonly adhered

to the skin superficial to the medial gastrocnemius muscle. Prior to walking, the baseline StO_2 is assessed as the steady-state StO_2 in the standing position. Muscle oxygen desaturation during walking is captured with several outcome variables, such as StO_2 reduction, desaturation rate, and time to minimum StO_2. StO_2 reduction is the difference between the baseline StO_2 and the minimum StO_2 achieved during walking. The desaturation rate is quantified as the slope of the linear portion of StO_2 descent at the beginning of walking. Finally, time to minimum StO_2 is the time elapsed from the onset of walking to when the minimum StO_2 is achieved. StO_2 recovery after walking is captured with several outcome measures, such as reoxygenation rate, time to StO_2 recovery, and maximum StO_2. The reoxygenation rate is the slope of the linear portion of StO_2 ascent after walking cessation. Time to StO_2 recovery is the time elapsed to achieve the baseline StO_2 after walking cessation. Finally, maximum StO_2 is assessed as the maximum StO_2 achieved during the recovery period after exercise.

Near-infrared spectroscopy (NIRS) is a well-validated, non-invasive method for measuring muscle (tissue) oxygenation, and it has been incorporated into wearable devices [32]. NIRS provides real-time insight into the balance between oxygen supply and demand in various conditions, including exercise [19,33,34], and low-flow states, including hypoperfusion of organs and limbs due to different types of shock and blood flow limitations [33,35–38]. NIRS cannot differentiate between oxygen bound to myoglobin (Mb) and oxygen bound to hemoglobin (Hb) (Table 1). As a result, researchers report composite measures to represent overall tissue oxygenation [10,33,34,39]. Common NIRS-derived variables include StO_2 (tissue oxygen saturation), SmO_2 (muscle oxygen saturation), tissue oxygenation index (TOI), and tissue saturation index (TSI) (Table 1) [34,40–42]. In this manuscript, we use StO_2, oxyhemoglobin (O_2Hb), and deoxyhemoglobin (HHb) as primary indicators of muscle oxygenation, representing the combined oxygen content of Hb in blood and Mb in muscle cells [10,33,34,39]. Although this aggregate view cannot separate the individual contributions of oxygen bound to Hb versus Mb, it remains essential for monitoring tissue oxygen levels during exercise.

Table 1. Definition of frequent terms used for muscle oxygenation measurements in different studies. Hem: hemoglobin [40]; Hb: hemoglobin [40]; Mb: myoglobin [40]; HbO_2: oxyhemoglobin [40]; O_2Hb: oxyhemoglobin [40]; HHb: deoxyhemoglobin [40].

NIRS-Derived Variables	Frequent Terms and Equations
Total hemoglobin	Total [hem]; total [Hb + Mb]; [tHb] [40]
Oxyhemoglobin	Oxy [hem]; oxy [Hb + Mb]; O_2Hb; HbO_2 [40]
Deoxyhemoglobin	Deoxy [hem]; deoxy [Hb + Mb]; HHb [40]
Muscle Oxygenation	Tissue oxygen saturation (StO_2) [43]; $StO_2\% = (O_2Hb/O_2Hb + HHb) \times 100$ Muscle oxygen saturation (SmO_2) [44]; $SmO_2\% = (O_2Hb/O_2Hb + HHb) \times 100$ Tissue oxygenation index (TOI) [41]; $TOI\% = (O_2Hb/O_2Hb + Hb) \times 100$ Tissue saturation index (TSI) [42,45]; $TSI\% = (O_2Hb/O_2Hb + HHb) \times 100$

NIRS has been used to monitor muscle oxygenation at rest, during walking, and in recovery [29,46–52]. Monitoring muscle oxygenation changes with NIRS can help clinicians and researchers assess the effects of exercise in both healthy and clinical populations [51–57]. Studies have examined a range of skeletal muscles to reveal physiological adjustments during activity [47,58–65]. A few studies have investigated muscle oxygenation responses

to high-intensity or resistance exercise training, showing variations in oxidative responses across different muscle groups [47–49,66]. Age-related comparisons indicate slower recovery in older adults [67–69]. Finally, marked alterations in muscle oxygenation have been observed in patients with PAD, before, during, and after exercise [20,70]. This review summarizes the effects of exercise on muscle oxygenation across different muscle groups, identifies gaps in current knowledge, and outlines future applications of muscle oxygenation monitoring in patients with PAD.

2. Materials and Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) is a guideline designed to ensure transparency, completeness, and accuracy in systematic reviews [45]. According to the PRISMA checklist, we conducted a systematic review of studies reporting StO_2 during exercise in patients with PAD. The research question was formulated according to the Population, Intervention, Comparison, and Outcomes (PICO) strategy (Table 2) [71,72]. The review protocol was registered in the PROSPERO database (ID: CRD420251061973).

Table 2. PICO terms used to find articles for this systematic review.

Acronym	Definition	Description
P	Population	Patients with PAD.
I	Intervention	Exercise (typically this means an acute exercise session).
C	Comparison	Baseline (resting) versus exercise and post-exercise (recovery) values, and healthy versus PAD.
O	Outcomes	NIRS muscle oxygenation measurements.

Search Strategy

Relevant articles between 1 January 1985 and 20 March 2025 were searched using the PubMed, Web of Science, and Cochrane Library databases. The MeSH terms included "Infrared Spectroscopy," "Muscle Oxygenation," "Perfusion," "Peripheral Artery Disease," "Exercise Therapy," "Gait Analysis," "Intermittent Claudication," "Lower Extremity Artery Disease," "Supervised Exercise Therapy," "Vascular Disease," "Oxygen Consumption," "Non-invasive Measurements," "Muscle Oxidative Metabolism," and "Exercise Physiology".

Inclusion and exclusion

Manuscripts were eligible for inclusion if they: (1) used NIRS to monitor muscle oxygenation during exercise; (2) included comparisons of patients with PAD and non-PAD controls; (3) evaluated at least three claudicating patients; (4) were written in English; (5) studied human subjects; and (6) included participants aged 60 years or older. Exclusions were based on screening the abstract and then the full manuscript to confirm lack of relevance. Articles that used magnetic resonance, ultrasound, and biopsy to assess muscle oxygenation without also using NIRS were excluded.

Primary and secondary outcomes

The primary outcome of this manuscript was muscle oxygenation in patients with PAD compared with healthy age-matched individuals, as measured by NIRS before, during, and/or after exercise. The secondary outcome was the validity and reliability of NIRS for measuring muscle oxygenation.

Quality control

Each article's methodological quality was examined using the "Critical review form: quantitative studies" [73–75].

3. Results

Keyword searches identified 628 potential articles in the selected databases (Figure 2). After screening the titles, abstracts, and full contents, 11 articles met the inclusion criteria. No additional articles were identified through reference list searches.

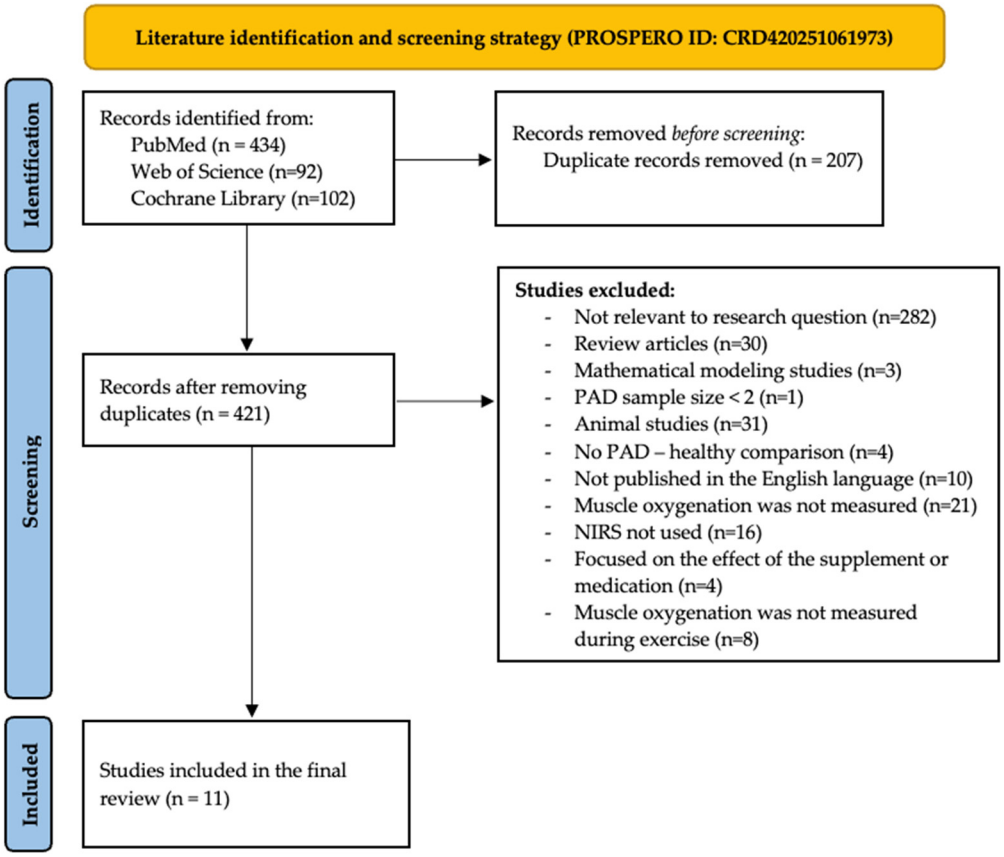

Figure 2. Flowchart of the search and article selection strategy. After searching for keywords in the selected databases, 11 articles remained. No additional articles were added by searching the reference lists.

Descriptive Analysis

Table 3 summarizes the detailed methodological quality of the included studies. All 11 studies clearly stated the purpose, used the relevant literature, justified the sample size, reported the statistical significance, conducted an appropriate analysis, and reported the conclusion based on methods and results. However, the sample size justification was not reported in nine studies. Additionally, the number of dropouts was not reported in five studies [9,46,76–78].

Table 3. Overview of the methodological quality of articles based on the Critical Review Form: Quantitative Studies. This form assesses the key methodological components, such as the purpose of the study, method, statistical analysis, results, and conclusion. N/A: Not applicable. 1: Was the purpose stated clearly? 2: Literature: Was the relevant and background literature reviewed? 3: Was the sample described in detail? 4: Was the sample size justified? 5: Was the statistical significance reported for the results? 6: Were the analysis method(s) appropriate? 7: Were clinical characteristics reported? 8: Were dropouts reported? 9: Were the conclusions appropriate based on the study results?

Authors	1	2	3	4	5	6	7	8	9
Song-Young Park, et al. 2022 [9].	Yes	Yes	Yes	N/A	Yes	Yes	Yes	N/A	Yes
Matthew Fuglestad, et al. 2020 [32].	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes
J. Carter Luck, et al. 2017 [79].	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes
F Manfredini, et al., 2017 [80].	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes
F Manfredini, et al. 2009 [46].	Yes	Yes	Yes	N/A	Yes	Yes	Yes	N/A	Yes
DT Ubbink, et al. 2006 [81].	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes
Anthony J. Comerota, et al. 2003 [77].	Yes	Yes	Yes	N/A	Yes	Yes	Yes	N/A	Yes
Anselm Egun, et al. 2002 [76].	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes
G.J. Kemp, et al. 2001 [82].	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes
H. Miriam Kooijman, et al. 1997 [78].	Yes	Yes	Yes	N/A	Yes	Yes	Yes	N/A	Yes
Kevin K. McCully, et al. 1994 [83].	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes

Table 4 provides detailed information on participant numbers, study objectives, targeted muscles, measured parameters, and primary outcomes. Among the included studies, the most common study design was observational (n = 4) [9,32,46,80]. The remaining seven studies used prospective comparative (n = 1) [81], cross-sectional (n = 1) [77], comparative (n = 1) [83], case–control (n = 1) [82], and controlled experimental (n = 1) [79] study designs. In total, 317 patients with PAD and 196 healthy controls were included. Treadmill walking was the exercise modality in seven studies [9,32,46,76–78,81]. One study used both plantar flexion and treadmill protocols [83]; two studies focused on plantar flexion exercise [79,82]; and one study used a toe flexion protocol [80]. In all the studies, NIRS was used during exercise to measure muscle oxygenation in one or more lower-extremity muscles. Compared with healthy controls, patients with PAD consistently demonstrated prolonged recovery times and greater variability in muscle oxygenation during post-exercise recovery [9,32,46,77–80,82,83].

Table 4. Reference table. Characteristics (summary and details) of the articles included. NIRS: near-infrared spectroscopy. ABI: ankle-brachial index. ICT: initial claudication time. ACT: absolute claudication time. Gardner treadmill test: Patients perform eight 2 min walking sessions for a maximum of 16 min at a constant 2 mph speed. The incline started at 0% and increased by 2% every 2 min until it reached 14% [77]. O_2Hb: oxyhemoglobin [40,76]. Oxygen index: difference between oxygenated and deoxygenated hemoglobin [76]. HHb: deoxyhemoglobin [34,76]. tHb: total hemoglobin. Hb: hemoglobin.

Article	Sample (n)	Study	Study Objective	Outcome Measurements	Results
Song-Young Park, et al. 2022 [9].	10 patients with claudication pain and 11 healthy subjects	Observational study	(1) Determine the effect of chronic ischemia on skeletal microcirculatory function. (2) Determine the correlation between leg ischemia and muscle mitochondrial function and StO_2.	An NIRS device was attached to the calf muscle to measure StO_2 at baseline and during walking and recovery using the Gardner–Skinner protocol.	Patients with PAD and healthy subjects showed no significant difference between baseline StO_2 prior to exercise and maximum StO_2 after exercise. However, patients with PAD showed greater StO_2 reduction during walking and slower StO_2 recovery compared with healthy subjects. Minimum StO_2 during walking did not differ between patients with PAD and healthy subjects.

Table 4. *Cont.*

Article	Sample (n)	Study	Study Objective	Outcome Measurements	Results
Matthew Fuglestad, et al. 2020 [32].	40 patients with PAD and 10 control subjects	Observational study	(1) Examine NIRS profile differences in patients with PAD vs. healthy subjects. (2) Determine how walking limitations relate to NIRS parameters during exercise training.	Calf muscle StO_2 was measured for 3 min at baseline/rest, during the graded treadmill test, and 30 min after the test. Healthy control subjects performed a 540 s treadmill test. Additionally, all subjects performed computerized angiography and a 6 min walking test.	Patients with PAD and healthy subjects showed similar baseline StO_2 levels. However, patients with PAD showed faster StO_2 drop, greater StO_2 fluctuation, greater decrease in StO_2 during, and longer recovery after treadmill walking compared with healthy subjects. In patients with PAD, a strong correlation between calf muscle hypoxia and walking capacity during the 6 min walking test was observed.
J. Carter Luck, et al. 2017 [79]	Experiment 1: 8 patients with PAD and 8 healthy subjects. Experiment 2: 7 patients with PAD and 7 healthy subjects.	Controlled experimental study	Compare blood pressure (BP) and StO_2 responses to different exercise intensities during plantar flexion exercise in patients with PAD vs. healthy subjects.	NIRS assessed calf muscle StO_2 in the most symptomatic leg of patients with PAD. Experiment 1: After a 3 min baseline, subjects performed supine single-leg contraction (most symptomatic leg) at 30 contractions/min with progressive weights (0.5–7kg) for up to 14 min, stopping if fatigue or pain exceed 5/10. Experiment 2: The same exercise was performed but at 20 contraction/min, short pauses during exercise, and constant weights for 14 min.	Experiment 1: Patients with PAD showed significantly greater StO_2 reduction during exercise compared with healthy subjects. At the time of fatigue, patients with PAD showed threefold greater StO_2 reduction compared with healthy subjects. Experiment 2: Due to the lower StO_2 level at baseline in patients with PAD compared with healthy subjects, StO_2 was measured as the percentage relative changes with respect to the baseline at 1 min and 14 min. No significant changes were observed at 1 min, while a significant change was observed at 14 min during exercise.
F. Manfredini, et al. 2017 [80]	80 patients with PAD and 13 healthy subjects	Observational study	Assess NIRS feasibility, validity, and diagnostic accuracy during dynamic ambulatory test to diagnose foot perfusion in PAD.	Subjects performed 10 toe flexion repetitions with NIRS attached to the dorsum of their feet. Healthy subjects repeated the test with increased tight blood flow restriction. ABI and the area under the oxygenated hemoglobin curve were measured. Reliability was assessed by repeating the measurement in two trials, and validity was evaluated by finding the association among toe flex curve area, oxygen delivery, ABI, and ankle pressure.	Higher levels of blood flow restriction in healthy subjects resulted in larger O_2Hb deficit during toe flexion, as shown by a larger area under the curve (more negative). In patients with PAD, the most symptomatic legs showed significantly greater area under curve of O_2Hb compared with healthy legs, with a weak correlation with dorsal pedis artery pressure. Toe flexion is an effective test to evaluate foot perfusion and PAD even in the presence or absence of ABI measurements.
F Manfredini, et al. 2009 [46]	67 patients with PAD and 28 healthy subjects	Observational study	Assess if NIRS can determine calf muscle deoxygenation during treadmill walking in patients with PAD.	NIRS was attached to the calf muscle to measure the variation in oxygenation, deoxygenation, tHB and differential oxygenation. The test included 1 min warm-up, followed by treadmill walking at 1.5 km/h, increasing the speed every 10 min by 0.1 km/h. The test was stopped when the patients were unable to continue due to fatigue, dyspnea, or claudication.	The areas under curves for Hb, deoxygenation, and differential oxygenation were significantly differed in symptomatic and non-symptomatic legs. However, no significant differences in tHb were observed between symptomatic and non-symptomatic legs. Patients with PAD showed higher compensatory heart rate during exercise compared with healthy subjects. NIRS measurements were used to effectively quantify muscle metabolic response in PAD.

Table 4. *Cont.*

Article	Sample (n)	Study	Study Objective	Outcome Measurements	Results
DT Ubbink, et al. 2006 [81]	45 patients with different stages of leg ischemia and 20 healthy subjects	Prospective comparative study	Determine the reproducibility and clinical applicability of NIRS in patients with leg ischemia.	Reproductivity of various diagnostic tests, leg perfusion, and blood pressure were measured at rest, during exercise, and after changing posture. NIRS was attached to the calf muscle's lateral side. NIRS was used to measure StO_2 for 5 min while subjects walked on a treadmill at 3.1km/h speed and 8% incline.	NIRS could not detect resting StO_2 differences across various PAD stages or correlate with ABI. However, lower ABI after exercise was correlated with the StO_2 reduction measured by NIRS. Although ABI was able to detect leg ischemia at rest, NIRS could not detect it due to its inability to differentiate between the presence or absence of vascular disease. NIRS is a reliable measurement due to its ability to detect greater Hb desaturation during exercise in patients with PAD compared with controls. NIRS outcomes did not correlate with macro- and microcirculatory measurements.
Anthony J. Comerota, et al. 2003 [77]	14 patients with PAD and 35 healthy subjects	Prospective cross-sectional study	(1) Identify calf StO_2 and ABI correlation in patients with PAD. (2) Identify the sensitivity of muscle oxygenation to identify PAD. (3) Identify the relationship between StO_2 and claudication symptoms. (4) Assess the safety of NIRS in screening for PAD.	Patients rested before the progressive treadmill test. The ABI was measured before and at 5 min intervals following the test. NIRS was attached to the calf muscle to record StO_2 5 min before, during, and 20 min after the test. Outcomes included baseline StO_2, peak exercise StO_2, absolute percentage changes between baseline and peak exercise, StO_2 values at ICT and ACT, and StO_2 at 50% (T50) and 100% (T100) after stopping the exercise.	ABI was significantly different between PAD and healthy subjects, while no significant differences in StO_2 were observed. Patients with PAD showed significantly lower StO_2 at peak exercise, greater absolute difference between baseline and peak exercise, greater percentage changes from baseline to peak exercise, and longer recovery time at (T50) and (T100) compared with healthy subjects. A significant correlation was observed between T50 and ABI.
Anselm Egun, et al. 2002 [76]	16 patients with PAD, and 7 age-matched and 7 young healthy control subjects.	Comparative study	Determine exercise-induced calf muscle ischemia in patients with PAD using NIRS.	NIRS equipment was attached to the patients' most affected calf and the right calf of the healthy subjects. StO_2 was recorded 10 min before, during, and 10 min after treadmill walking. Subjects first walked for 1 min at 3.2 kph and 10° incline. After a 20 min rest, the maximum walking capacity was assessed at the same speed and incline. In this test, patients with PAD walked until pain forced them to stop, while healthy subjects walked for 7 min.	During treadmill walking, all subjects showed O_2Hb reduction. Patients showed greater HHb during exercise compared with healthy age-matched and young subjects; the differences were not significant. O_2Hb and tHb were lower during the maximum-exercise test in patients with PAD vs. healthy subjects. In recovery, patients showed significantly increased O_2Hb, tHb, and oxygen index, while healthy subjects showed no significant changes. ABI at rest was correlated with HHb but not with tHb or the oxygenated index during a maximum-walking test.
G.J. Kemp, et al. 2001 [82]	11 patients with PAD and 9 healthy subjects	Case–control study	Measure calf muscle oxygenation and adenosine triphosphate (ATP) in patients with PAD by using magnetic resonance spectroscopy (MRS) and NIRS.	NIRS and MRS measured calf muscle ATP level and StO_2 during isometric plantar flexion at 50% and 75% of maximum voluntary contraction for 2–4 min, following 5 min of recovery. Each subject repeated the plantar flexion test three times, and the results were averaged.	Compared with healthy subjects, patients with PAD showed faster and greater deoxygenation during exercise and slower reoxygenation after exercise.

Table 4. *Cont.*

Article	Sample (n)	Study	Study Objective	Outcome Measurements	Results
H. Miriam Kooijman, et al. 1997 [78]	11 patients with PAD and 15 healthy subjects	Experimental study	Evaluate the utility of NIRS to assess muscle oxygenation hemodynamics in patients with PAD compared with healthy subjects.	NIRS equipment was attached to the left calf of healthy subjects and the patients' most symptomatic calf muscle. Part 1: Venous occlusion was performed at rest using a cuff, followed by at least 30 min of rest. Part 2: Subjects performed standard treadmill walking for 4 min at 3.2 km/h speed and 6° incline. Subjects reported ICT and walked until pain forced them to stop. Part 3: The same walking protocol in part 1 was repeated to measure StO_2 during and after treadmill walking.	Patients with PAD showed significantly greater deoxygenation during walking compared to healthy subjects. Following the walking exercise, no significant difference was observed in blood flow between patients with PAD and healthy subjects. Patients with PAD showed significantly slower resaturation rates, longer recovery time measured by NIRS, and longer recovery time measured by ABI compared with healthy subjects.
Kevin K. McCully, et al. 1994 [83]	8 patients with PAD, 20 healthy older adult, and 6 healthy young subjects.	Comparative study	(1) Compare post-reoxygenation rate in PAD vs. healthy older adults. (2) Compare post-reoxygenation rate in healthy older vs. young adults. (3) Compare calf StO_2 depletion in PAD vs. healthy subjects.	ABI was measured before exercise. NIRS equipment was attached to the lateral soleus while subjects performed one-leg plantar flexion exercise every 5 s for one minute. Recovery time and StO_2 were recorded for 3–6 min after exercise (one leg in healthy subjects and both legs in patients with PAD). StO_2 was measured for 5 min in the standing position before and during the progressive treadmill test. During the treadmill test, ICT and ACT were recorded.	There was a significant difference in the rate of muscle oxygen saturation after plantar flexion exercise between the most symptomatic and less symptomatic legs of patients with PAD. Compared with healthy young and old subjects, patients with PAD showed greater and faster deoxygenation during walking and longer recovery after the walking test. The recovery time after exercise for the most symptomatic leg was longer compared with the less symptomatic leg.

NIRS was consistently identified as a valid and reliable technique for assessing muscle oxygenation during exercise. Validity outcomes included correlations with ankle-brachial index (ABI), ankle pressure, dorsalis pedis pressure, disease severity classification, and receiver operating characteristic analyses [80,81]. One study further assessed validity by comparing NIRS-derived recovery indices with 31P magnetic resonance spectroscopy recovery rates, demonstrating close agreement between the two methods [82]. Reliability was assessed using intra-class correlation coefficients, according to repeated measurement consistency during exercise, or by repeating the exercise recovery measurement using NIRS and ABI, as well as an intrasubject coefficient of variation, which demonstrated consistency in oxygen recovery between trials [78,80,82,83].

The calf muscle (gastrocnemius) was the most frequently monitored site (n = 9) [9,32,46,76–79,81,82]. One study assessed the lateral soleus during plantar flexion exercise, and the medial gastrocnemius during progressive treadmill testing [83], and another placed the NIRS sensor on the dorsum of the subjects' feet [80].

There was a variation in the timing of muscle oxygenation recording across studies. Comerota et al. recorded oxygenation for 5 min before exercise, throughout treadmill walking, and for 20 min during recovery [77]. Fuglestad et al. measured oxygenation for at least 3 min before exercise, during graded treadmill testing, and for 30 min post-exercise [32]. McCully et al. measured oxygenation during plantar flexion exercise and for 3–6 min afterward; however, pre-exercise recording duration and recovery timing after treadmill testing were not reported [83].

4. Discussion

This study systematically reviews the effects of exercise on lower-limb muscle oxygenation in patients with PAD, summarizing findings before, during, and after exercise. To our knowledge, this is the first systematic review to examine muscle oxygenation across all three phases of exercise. The results demonstrated that resting muscle oxygenation was similar between patients with PAD and healthy controls [9,32]. In contrast, patients with PAD showed a steeper, more rapid, and more pronounced decline in muscle oxygenation during walking, followed by markedly prolonged recovery to baseline, indicating substantial hypoxia in PAD muscles during ambulation [9,32,46,77–83]. Fuglestad et al. further reported that patients with PAD experienced a decline in StO_2 after an average of only 12 steps (range of 1–55 steps), indicating that calf muscle ischemia in patients with PAD occurs well before the onset of claudication symptoms and at unexpectedly short walking distances [32]. Park and colleagues also found greater StO_2 reduction after treadmill walking in patients with PAD compared with age-matched healthy individuals but a smaller difference in the minimum StO_2 [9]. These findings suggest that the exercise-evoked change in StO_2, rather than resting values or the nadir alone, may be the most sensitive and physiologically relevant biomarker of PAD-related muscle hypoxemia [20,77].

Fuglestad et al. proposed that the markedly altered StO_2 profiles and severe walking limitation in patients with claudication reflect the multiple interrelated pathological features of PAD [32]. The disease begins with the atherosclerotic narrowing of the large arteries (macrovascular disease), which restricts blood flow to the limbs [32]. In addition, patients exhibit microvascular abnormalities, including capillary basement membrane thickening, perivascular fibrosis, and impaired endothelial reactivity, which further limit oxygen and nutrient delivery [8,32,84–86]. Compounding these defects, the PAD muscle develops chronic ischemic myopathy marked by abnormal myofiber morphology, cytoskeletal disruption, mitochondrial dysfunction, oxidative damage, and fibrosis [14,87–94]. Together, these macrovascular, microvascular, and myopathic abnormalities converge to produce the characteristic StO_2 abnormalities and exercise intolerance of claudicating patients [95].

Several factors influence StO_2 dynamics during walking, including physical activity history and disease severity. Patients with a sedentary lifestyle showed faster time to reach the minimum StO_2 during treadmill walking, compared with patients with a light-to-moderate exercise history [96]. Intra-patient comparisons show higher muscle deoxygenation rates in PAD-affected versus unaffected legs [32,97]. Furthermore, those with severe PAD (ankle-brachial index < 0.50 and Fontaine classification III or IV) showed greater StO_2 reduction during walking [46], suggesting that the magnitude of exercise-induced StO_2 decline correlates with disease severity [32,98].

Evidence from plantar and toe flexion exercise further supports these findings. Kemp et al. reported greater reductions in muscle oxygenation during plantar flexion at both 50% and 75% of maximal voluntary contraction, along with slower recovery in patients with PAD compared with controls [82]. Recovery-phase muscle oxygenation findings were consistent with previous reports [23,83,99]. Additionally, McCully et al. reported a significantly prolonged recovery time constant (reflecting slower oxygen resaturation) following plantar flexion exercise in the PAD limb compared with the legs of both young and older controls, indicating impaired oxygen delivery and reduced microvascular perfusion in patients with PAD [83]. In contrast, recovery time constants did not differ between healthy young and older adults, indicating fast recovery after plantar flexion exercise in healthy populations [83]. Similarly, Manfredini et al. reported significantly greater StO_2 reductions during toe flexion exercise, quantified by the area under the oxygenation curve, in patients with PAD compared with healthy controls [80]. They attributed this finding to insufficient blood flow and oxygen delivery during toe flexion exercise [80]. Evidence related to toe

and plantar flexion exercise remains limited, highlighting the need for further studies to clarify physiological responses and potential rehabilitation implications in PAD.

In patients with claudication, recovery of StO_2 following treadmill walking exercises is slower than in healthy individuals, and this delayed recovery likely reflects impaired microvascular oxygen delivery capacity [9,32,46,76–78,83]. Park and colleagues suggested that microcirculatory dysfunction, characterized by reduced capillary recruitment, impaired endothelial-dependent vasodilation, and abnormal regulation of arteriolar tone, may limit the rapid restoration of oxygen supply once exercise ceases [9]. Although oxygen delivery through large vessels may be adequate at rest, the regulation of perfusion at the microvascular level is compromised [9]. This imbalance between oxygen resupply and muscle metabolic demand during recovery prolongs the StO_2 recovery slope, underscoring the contribution of microvascular pathology to exercise intolerance in PAD [9].

Regarding measurement accuracy, NIRS has been recognized as a reliable and valid tool for monitoring peripheral circulation during and after exercise [28,32,42,46,80,81]. NIRS is also a well-established research tool for monitoring changes in blood flow and muscle oxygenation and evaluating the effectiveness of exercise [28,32,42,46,80,81]. Fuglestad et al. reported the ability of NIRS to generate similar calf StO_2 measurements compared with other costly devices, supporting the feasibility of non-invasive measurement to assess muscle oxygenation [32]. Comerota et al. further reported a high correlation between recovery time, as measured by the ABI and NIRS, after exercise, indicating the effectiveness of NIRS in evaluating oxygen demand and delivery in muscles following exercise [77]. However, according to Kooijman et al., the recovery time measured by the ABI was faster than with NIRS. This difference arises because ABI recovery depends solely on blood flow restoration, whereas NIRS captures both blood flow and muscle metabolic recovery [78]. This distinction highlights an important advantage of NIRS over the ABI, as it provides a more comprehensive assessment of muscle recovery dynamics [78].

One particularly important aspect of the findings of NIRS studies is that although patients with PAD experience a much greater and earlier drop in StO_2 during exercise, which strongly correlates with walking impairment, resting muscle StO_2 (before exercise) does not differ significantly between patients with PAD and healthy subjects [32,79,100–102]. This finding is corroborated by several other methodologies. Specifically, contrast-enhanced ultrasound (CEU) demonstrates that resting microvascular blood volume and flow velocity are comparable between groups, but the ability to augment perfusion during exercise is blunted in PAD, reflecting impaired functional hyperemia [103–106]. Phosphorus magnetic resonance spectroscopy and BOLD MRI also confirm that resting muscle oxygenation and phosphocreatine recovery are similar, yet after exercise, PAD patients show slower phosphocreatine recovery and more pronounced hypoxia-triggered vasodilation, indicating reduced mitochondrial oxidative capacity and oxygen delivery under stress [107–109]. Collectively, these modalities reveal that the pathophysiological hallmark of PAD and claudication is an inability to increase muscle blood flow and oxygenation during exercise, while resting values remain largely preserved.

NIRS complements these modalities by providing a non-invasive, portable, and relatively inexpensive method for the continuous, real-time monitoring of superficial muscle oxygenation during rest, exercise, and recovery, without the need for contrast agents, radiation, or ultra-expensive imaging equipment [32,40,110,111]. NIRS is less operator-dependent than Doppler and ultrasound and is particularly well suited for repeated or longitudinal measurements, making it practical in both clinical and research settings [111,112]. However, its limitations include restriction to superficial muscle layers, sensitivity to adipose tissue thickness, an inability to directly quantify absolute blood flow, and lower spatial resolution than that of contrast-enhanced ultrasound or MRI [40]. By compari-

son, CEU provides higher spatial resolution and dynamic perfusion assessment, but it is operator-dependent and limited to superficial muscle groups and requires intravenous contrast, which may not be suitable for all patients, and a larger team to perform the test [113,114]. CEU image quality can be degraded by patient body habitus or motion, and quantitative perfusion parameters are not yet standardized across centers [115]. MRI enables comprehensive anatomical and functional evaluation of deeper muscle perfusion and microvascular flow, but it is expensive, time-consuming, less accessible, and sensitive to motion artifacts [116,117]. MRI may be contraindicated in patients with certain implants or severe renal dysfunction, and quantitative perfusion assessment is not routinely performed in clinical practice [117,118]. Doppler ultrasound (duplex) is widely available and reliable for macrovascular flow assessment, but it is highly operator-dependent and less accurate in the presence of heavy arterial calcification or multiple sequential lesions and cannot directly quantify microvascular or tissue-level perfusion [119,120]. In summary, NIRS is best positioned as a practical tool for non-invasive, dynamic assessment of superficial muscle oxygenation over long periods of time, while CEU, MRI, and Doppler ultrasound provide more detailed anatomic and perfusion data at substantially greater cost and complexity [112,121,122].

4.1. Methodological Heterogeneity Across Included Studies

An important consideration when interpreting these findings is the methodological heterogeneity across the 11 included studies. Exercise protocols varied widely: seven studies employed treadmill walking with differing speeds (1.5 to 3.2 km/h), inclines (0% to 10 degrees), and durations (symptom-limited vs. fixed time) [9,32,46,76,77,81,83], while the remaining used plantar flexion at 50–75% of maximal voluntary contraction [50,79,83] or toe flexion with progressive loading [80]. These protocol differences directly influence StO_2 kinetics and complicate cross-study comparisons [123,124]. The NIRS devices also differed, ranging from research-grade continuous-wave systems (e.g., NIRO, RunMan, and PortaMon) to low-cost wearable sensors (Moxy), each with distinct algorithms and interoptode distances that affect tissue sampling depth. Outcome variables were inconsistent, with some studies reporting StO_2 and others measuring O_2Hb, HHb, tHb, or derived indices (TOI, TSI, and area under the curve), limiting the quantitative pooling of results.

Patient populations also differed in disease severity (Fontaine stages II–IV), comorbidity profiles, and sample sizes (7 to 80 PAD patients per study). The anatomical site of NIRS measurement varied, with most studies monitoring the gastrocnemius but others targeting the soleus or foot dorsum—sites with distinct vascular supply and adipose tissue thickness. Despite this heterogeneity, the consistent finding across all studies that PAD patients exhibit greater exercise-induced deoxygenation and prolonged recovery strengthens the overall conclusion. Future studies should adopt standardized protocols, devices, and outcome reporting frameworks to enhance comparability.

4.2. Clinical Translation of NIRS Findings

While NIRS convincingly detects macro- and microvascular dysfunction during exercise in PAD [9,32,112], clinical translation requires further consideration. The ankle-brachial index (ABI), though widely used, has well-documented limitations: it can be falsely elevated with medial arterial calcification (common in diabetes and chronic kidney disease), provides no microvascular information, and does not assess dynamic exercise-induced ischemia [125–127]. NIRS overcomes these limitations by directly measuring tissue-level oxygenation during exercise. Several clinical applications emerge from this review: NIRS could serve as a point-of-care screening tool when combined with simple exercise protocols; NIRS parameters could objectively quantify disease severity given the observed correlations

with the ABI and walking capacity; NIRS monitoring could guide individualized exercise prescription by identifying critical ischemic thresholds; and serial NIRS measurements could monitor therapeutic response following revascularization or rehabilitation programs.

However, barriers remain before NIRS can be integrated into clinical workflows. There is no consensus on standardized measurement protocols, normative reference values, or clinically meaningful thresholds. Adipose tissue thickness affects signal quality, and NIRS is restricted to superficial muscle layers [112,128–130]. Multicenter validation studies with standardized protocols and prospective outcome data are needed to establish the diagnostic accuracy, prognostic value, and cost-effectiveness of NIRS-based assessment in PAD.

Study limitations included the inconsistent timing of baseline and recovery measurements, with only three studies reporting exact measurement intervals [32,77,83]. Comerota et al. measured muscle oxygenation for five minutes before and 20 min after exercise [73], while Fuglestad et al. reported three minutes of baseline recording and 30 min of post-exercise monitoring [32,97]. McCully et al. reported post-exercise measurements of 3–6 min but did not specify baseline recording duration [83]. Standardization of measurement protocols would improve comparability across studies. Furthermore, most included studies were observational, limiting the ability to assess causal effects. Future intervention-based and longitudinal studies are needed to better define the effects of specific exercise modalities and the long-term impact of exercise on muscle oxygenation in PAD.

5. Conclusions

In conclusion, this systematic review of 11 studies supports the use of NIRS-derived muscle oxygenation parameters during exercise as a sensitive and physiologically informative tool for characterizing PAD pathophysiology. Although resting muscle oxygenation does not differ between patients with PAD and healthy individuals, the dynamic response to exercise differs markedly. Patients with PAD consistently exhibit a faster and steeper decline in muscle oxygenation during exercise, followed by substantially delayed recovery. These exercise-induced oxygenation abnormalities reflect the convergence of macrovascular disease (atherosclerotic obstruction limiting bulk blood flow), microvascular dysfunction (impaired capillary recruitment, endothelial dysfunction, and perivascular fibrosis), and ischemic myopathy (mitochondrial dysfunction, oxidative damage, and muscle fiber degeneration), which together constitute the pathophysiological substrate of claudication.

From a clinical perspective, NIRS offers a non-invasive, portable, and relatively inexpensive method for assessing PAD at the tissue level, complementing ABI and imaging-based approaches. The observed relationship between NIRS-derived parameters and walking capacity suggests that these measures may serve as meaningful biomarkers of disease severity and functional limitation. In addition, the ability of NIRS to detect muscle deoxygenation early during exercise highlights its potential value for monitoring disease progression and therapeutic response.

These findings should be considered in the context of some limitations. The included studies were heterogeneous with respect to exercise protocols, NIRS devices, outcome measures, and patient populations, and most were observational with relatively small sample sizes. Standardized measurement protocols and larger prospective studies are needed to define normative values, establish clinically meaningful thresholds, and determine responsiveness to interventions such as revascularization, structured exercise therapy, and pharmacotherapy. Overall, NIRS appears well positioned as a practical and informative tool for assessing exercise-induced muscle oxygenation changes and for advancing the evaluation of disease severity and therapeutic response in PAD.

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Abbreviations

The following abbreviations are used in this manuscript:

PAD	Peripheral artery disease
StO_2	Tissue oxygen saturation
SmO_2	Muscle oxygen saturation
TOI	Tissue oxygenation index
Mb	Myoglobin
tHb	Total hemoglobin
O_2Hb	Oxyhemoglobin
Hb	Hemoglobin
HHb	Deoxyhemoglobin

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