

SYSTEMATIC REVIEW

The Use of Near Infrared Spectroscopy to Evaluate the Effect of Exercise on Peripheral Muscle Oxygenation in Patients with Lower Extremity Artery Disease: A Systematic Review

Nils Cornelis ^{a,*}, Panagiotis Chatzinikolaou ^{a,c,†}, Roselien Buys ^a, Inge Fourneau ^b, Jomme Claes ^a, Véronique Cornelissen ^a

^a Department of Rehabilitation sciences, KU Leuven, Leuven, Belgium

^b Department of Cardiovascular sciences, KU Leuven, Leuven, Belgium

^c Department of Physical Education and Sport Science at Serres, Aristotle University of Thessaloniki, Thessaloniki, Greece

WHAT THIS PAPER ADDS

This systematic review shows that exercise interventions seem to improve muscle de-oxygenation and re-oxygenation patterns, as measured using near infrared spectroscopy (NIRS). In addition, this study highlights the heterogeneity in NIRS application methods, outcome variables and analysis in the current literature. In summary, NIRS can become a valuable tool in the evaluation of improvements following exercise therapy in lower extremity artery disease, yet more robust randomised controlled trials should confirm these preliminary findings.

Objective: Near infrared spectroscopy (NIRS) has been suggested as a new diagnostic tool in patients with lower extremity artery disease (LEAD). The aim of this systematic review was to summarise the impact of exercise therapy on lower limb muscle oxygenation, evaluated by NIRS, in patients with LEAD, and to give an overview on NIRS instruments and methodology.

Data Sources: MEDLINE and Embase.

Review Methods: A systematic search was conducted in MEDLINE and Embase, from the earliest date available until 16 March 2020, to identify peer reviewed studies involving the use of NIRS in the evaluation of exercise training on muscle oxygenation in patients with LEAD. Primary outcomes were NIRS derived variables during treadmill exercise. Effect sizes were calculated as standardised mean differences. Assessment of methodological quality was done using a combined checklist from the Cochrane bias and the quality assessment tool for before and after studies without a control group.

Results: Eleven original trials were included involving 16 exercise groups and four control groups. Tissue saturation index (TSI) at rest remained unchanged following the exercise interventions. Exercise training increased time to minimum TSI during exercise (range effect sizes: +0.172 to +0.927). In addition, exercise training led to a faster recovery to half and full TSI rest values in most intervention groups (range effect sizes –0.046 to –0.558 and –0.269 to –0.665, respectively). Finally, NIRS data reproducibility and analytic methods were under reported in the included studies.

Conclusion: The available data suggest that exercise training improves de-oxygenation and re-oxygenation patterns, as measured with NIRS, in patients with LEAD. Whereas NIRS is a promising tool in the evaluation of LEAD, the low number of randomised controlled trials, as well as large heterogeneity in NIRS assessment methods, outcome measures, and instrumentation, warrants more research to better understand the role of muscle oxygenation associated with exercise induced improvements in walking capacity.

Keywords: Exercise therapy, Intermittent claudication, Lower extremity artery disease, Muscle oxygenation, Near-infrared spectroscopy, NIRS

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[†] Joint first authors.

* Corresponding author. KU Leuven, O&N4 Herestraat 49 – box 1510, 3000, Leuven, Belgium.

E-mail address: nilscornelis@kuleuven.be (Nils Cornelis).

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INTRODUCTION

Lower extremity artery disease (LEAD) is characterised by a gradual atherosclerotic narrowing in the lower limbs. Although this obstruction to blood flow is often asymptomatic, 10% – 35% of patients with LEAD present with

typical symptoms during daily activities.¹ The cramping like pain, referred to as intermittent claudication (IC), is the cardinal symptom of LEAD and results from the oxygen supply/demand mismatch in muscles distal to the obstructed vessel.² This mismatch is of great clinical interest, as the combination of an increased local anaerobic state combined with physical inactivity might result in an acquired myopathy.^{3,4} This peripheral myopathy is characterised by histological and metabolic changes, such as a muscle fibre type shift, reduced capillary density, higher lactate and acylcarnitine levels, and dysregulated mitochondrial capacity.^{2–5} Additionally, increased blood viscosity, and local endothelial and autonomic dysfunction further compromise optimal oxygen supply.^{2,5} Whether insufficient circulation is the main cause of peripheral myopathy is still debated,⁶ yet the cascade is undoubtedly detrimental.

Following this, different diagnostic techniques have been introduced to evaluate the underlying aetiology of LEAD and patients' responses to therapy. Well known evaluation methods vary in their ability to measure local haemodynamics (e.g., ankle brachial index [ABI] or imaging methods such as magnetic resonance imaging [MRI]), local metabolism, or tissue perfusion (e.g., muscle biopsies or transcutaneous oxygen pressure measurements). Yet, most methods are static or have limited penetration depth to study underlying changes in muscle perfusion during exercise.⁷ Therefore, non-invasive near infrared spectroscopy (NIRS) received considerable attention in vascular research starting from the early 1990s,⁸ with interest in it growing rapidly as new low cost and portable devices, with important clinical potential, become available.⁹ In short, NIRS uses near infrared light with different wavelengths (700 – 900 nm) to transmit photons to the muscle of interest non-invasively. As the absorption rate of the omitted photons is different for oxygenated and de-oxygenated chromophores, receiving photodetectors can differentiate between them.⁸ Notably, NIRS dynamically reflects oxygen supply and demand during exercise in healthy and diseased populations.¹⁰ In LEAD studies, NIRS can be used as a diagnostic tool as it is associated with clinical measures of disease severity (e.g., ABI and recovery kinetics), and can evaluate the effects of exercise interventions.^{11,12}

Although NIRS offers unique opportunities to gain insight into the pathophysiological state of patients with LEAD, it remains underused in today's clinical practice. Moreover, current reporting of NIRS methodology and derived outcome parameters is very heterogeneous and hinders widespread implementation. Therefore, a systematic review was conducted to summarise the literature to date on the effect of exercise therapy on NIRS derived outcomes in patients with LEAD. A further aim was to provide a detailed summary of NIRS instrumentation and assessment methods reported in current literature to guide future work in the field.

METHODOLOGY

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and the Synthesis Without Meta-

analysis (SWIM) guidelines were followed,^{13,14} and prospectively registered with PROSPERO, the International Prospective Register of Systematic reviews (registration number: CRD42020175401).

Search strategy

A comprehensive search was conducted in MEDLINE (Ovid) and Embase (Ovid), from their dates of inception until 16 March 2020, to identify relevant peer reviewed journal articles (Supplementary file 1). Reference lists from the eligible papers were manually searched for additional studies. No language restrictions were imposed on the search.

Inclusion and exclusion criteria

Eligibility criteria included (1) prospective cohort studies, and randomised and non-randomised controlled trials investigating the effect of an exercise intervention; (2) studies performed in people aged ≥ 18 years with LEAD and IC (classified as Rutherford 1–3 or Fontaine 2a, 2b); (3) those reporting mean and standard deviation (SD), standard error, or median and interquartile range (IQR) of at least one NIRS outcome parameter before and after the intervention; and (4) those published as a full length publication in a peer reviewed journal.

Study selection

The results from the initial search were imported into Rayyan software for systematic screening by two independent reviewers (N.C. and P.C.).¹⁵ After removal of duplicates, titles and abstracts were screened for eligibility. In a second phase, the full texts of potentially relevant articles were retrieved, which were then reviewed by both reviewers. Disagreements were resolved by consultation with a third reviewer (V.C.).

Data extraction

A standardised Access Database file (Microsoft, Redmond, WA, USA) was used by both reviewers to extract data independently from the individual studies, including publication details (year of publication, country of origin), study design, sample size, patient characteristics, exercise characteristics, NIRS instrumentation, and assessment methodology, as well as primary and secondary outcome measures.

Primary and secondary outcomes

The main focus was on NIRS derived parameters that could be assessed at rest, during a single bout of exercise, or during recovery from exercise (Fig. 1). For uniformity, tissue saturation index (TSI; $\text{oxygenated[haem]}/\text{total[haem]}$) is used as the reference term, which also includes muscle tissue oxygen saturation (StO₂) or tissue oxygenation index (TOI). Although NIRS cannot discriminate between chromophores (haemoglobin and myoglobin), outcomes are reported as published (e.g., oxygenated haemoglobin [O₂Hb], de-oxygenated haemoglobin [HHb], and total haemoglobin [tHb]) as

intracellular myoglobin tends to stay constant during exercise.^{8,10} Arterial or venous occlusion experiments are considered as a separate category. Secondary outcomes included pain free and maximum walking time or distance, six minute walking distance (6MWD), ABI, and peak oxygen consumption (VO_{2peak}). In the case of missing data, authors were contacted twice over a one month period to request data.

Risk of bias

Study methods. Owing to the different designs of the included studies, the Cochrane risk of bias tool and the quality assessment tool for before/after studies without a control group were combined to rate the methodological quality of the included articles.^{16,17} This combined checklist was used by two independent reviewers (N.C. and P.C.) rating the following 12 items (rating: yes and no): objective clearly stated; eligibility criteria; representative study sample; participants enrolment; random sequence generator; control group; description of the intervention and consistency; assessors blinded to intervention; follow up rate; statistical methods; complete outcome data; and non-selective reporting. Disagreements between reviewers were resolved by discussion with a third reviewer (V.C.). The overall score for each article was obtained by summing the number of “yes” answers.

Near infrared spectroscopy methodology. A separate analysis of the quality of the NIRS assessment methods was performed by rating the following six items: NIRS device characteristics; clear description of anatomical position; reproducibility of positioning; adipose tissue thickness (ATT)

measurement; description of the specified outcomes; analysis and reporting.

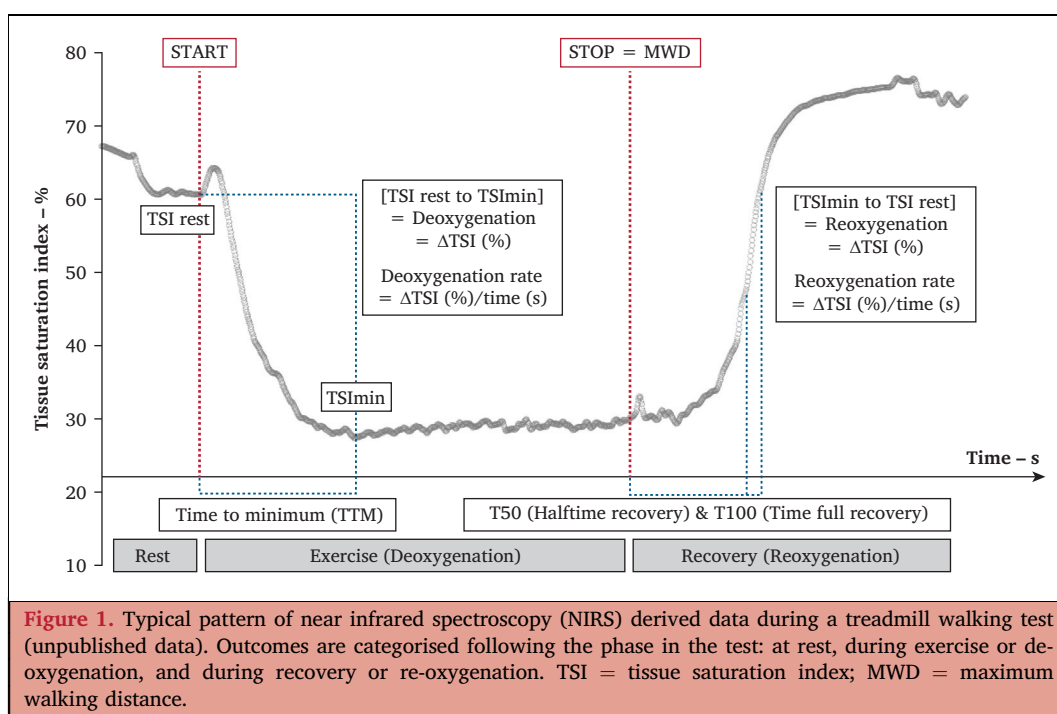
Statistics

Demographic data are presented as reported in the main article. The effect sizes of all included study groups were calculated by paired standardised difference of means using Comprehensive Meta-analysis version 2.2.064. Standardised difference of means can be interpreted following Cohen’s convention with the effect size being small (0.20), medium (0.50), or large (0.80).¹⁸ To calculate the standardised effect sizes, we assumed paired data to be correlated with an r value of 0.5. The decision to not perform a meta-analysis was based on the diversity of study designs and methods, with a limited number of studies including a matched control group. Therefore, the decision was made to summarise effect sizes, in order to discuss the range and distribution of the most common outcomes. Furthermore, effects sizes were presented visually to discuss both direction of effect and heterogeneity. A conversion tool was used to calculate the mean and SD for two studies that reported median and IQR.^{19–21} If data were only available in figures, means or SDs were extracted using Acrobat Reader (Adobe, San Jose, CA, USA).

RESULTS

Literature search

The original search yielded 440 studies. After removal of duplicates and exclusion of papers based on the eligibility criteria, 11 original studies involving 12 full text papers remained (Fig. 2). Two papers from Collins *et al.* were included. Both involved the same population sample, but



two different exercise test protocols were studied (i.e., constant and progressive work rate). Demographic data for Collins *et al.* were extracted from the original study.^{22,23} However, the NIRS substudy was selected for quantitative analysis, as it contained more information regarding the research question.²³ A request for missing data was sent to nine authors and six replied.^{23–28}

Study characteristics

Individual study characteristics are presented in Table 1. Four studies were randomised controlled trials (RCTs),^{20,24,26,27} three were randomised trials,^{22,23,29,30} two were non-RCTs,^{21,31} and two applied a pre-post design without a control group.^{25,28} Studies were published between 2009 and 2020. The majority ($n = 6$) were conducted in the USA,^{20,22–24,26,28,30} while the remainder were performed in UK,^{21,27} Italy,³¹ Brazil,²⁹ and Japan.²⁵ A total of 666 participants (73% men) participated in the studies. The mean age of the participants was 68.4 years, with study means ranging from 64.3 to 71.8 years. In total, 70 participants dropped out of the studies, leaving 596 available for analysis. All exercise intervention groups ($n = 16$) and control groups ($n = 4$) were analysed as individual study groups. One non-randomised control group consisted of patients that underwent angioplasty.²¹ Three other control groups received either best medical treatment,²⁰ advice on physical activity,²⁷ or attention control light resistance training.²⁶ Comparison groups of healthy participants ($n = 2$) were excluded from the analysis.^{30,31} Traditional treadmill walking was the most frequently prescribed exercise modality ($n = 7$).^{20,22,24,26,28–30} Three studies used alternative walking interventions with ankle loads,²⁹ NIRS guidance,³⁰ or pole striding.²² Two studies applied a home

based walking intervention involving two structured and one self paced walking programme.^{26,31} The remaining three studies used ergometer cycling,²⁵ arm cranking exercise,²⁷ or a circuit training programme.²¹ All exercise interventions had a duration of 12 weeks ($n = 10$), except for Manfredini *et al.*,³¹ who applied a 34 week intervention. Resting levels of TSI were reported in four studies,^{20,21,27,28} de-oxygenation parameters during exercise in eight,^{20,21,23,25–29} and recovery outcomes following exercise in six (Fig. 3).^{20,21,25,26,28,29}

Synthesis of results

Near infrared spectroscopy parameters at rest. In all studies resting TSI remained unchanged after the exercise interventions,^{20,21,27,28} usual care,²⁰ or angioplasty,²¹ with effect sizes ranging between -0.191 and 0.272 (Fig. 4A). Only Baker *et al.* reported a between group comparison and found no difference between the exercise and control group change scores.²⁰ Muscle oxygen consumption (mVO_2) at rest was assessed as HHb rate during venous occlusion,³¹ or by a combination of diffuse correlation spectroscopy and frequency domain NIRS measurements.²⁰ Two of three study groups observed a higher mVO_2 at rest after structured walking training.^{20,31} The increase in mVO_2 was statistically significantly higher after exercise training compared with usual care.²⁰ These effects were explained by a higher dynamic blood flow and oxygen extraction fraction vs. usual care,²⁰ or an increased mitochondrial capacity after exercise, as noted by Murrow *et al.*³⁰ The latter effect was more pronounced in the traditional group vs. a walking group receiving NIRS biofeedback (interaction effect: $p = .003$).³⁰ Two other studies evaluated O_2Hb recovery after arterial occlusion and found a significantly

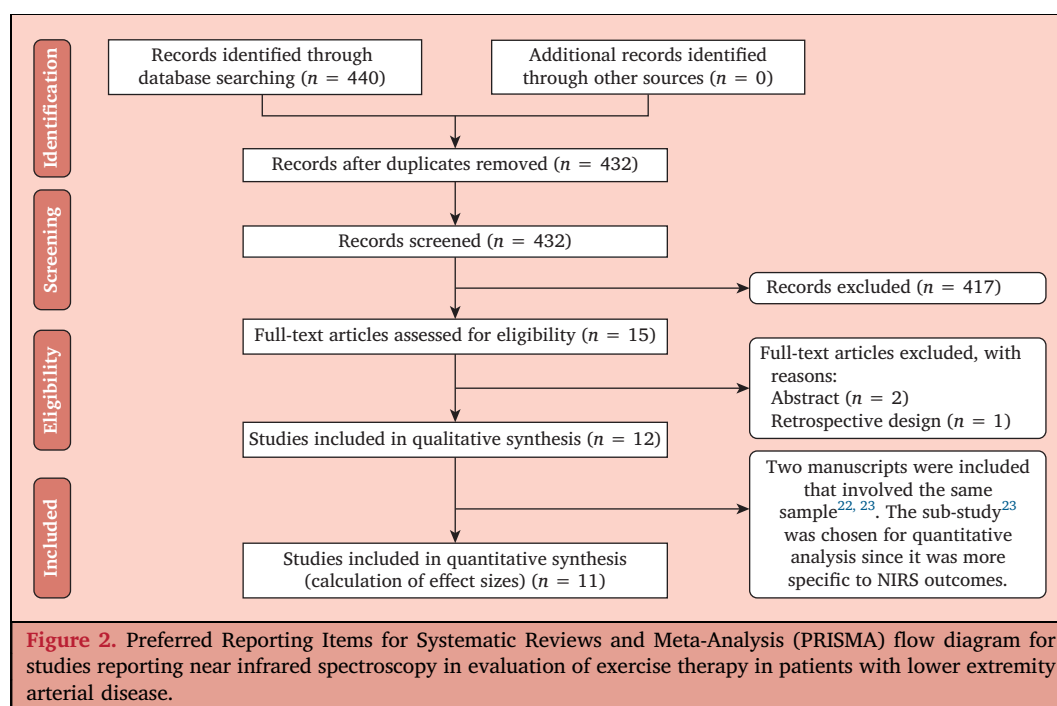


Table 1. Baseline characteristics of the included studies reporting near infrared spectroscopy (NIRS) in the evaluation of exercise therapy in patients with lower extremity arterial disease, detailed for exercise group (E), control group (C), and total sample (T)

Study	Design	Exercise group (E1)*	Comparison group(s)* of alternative exercise (E2) or control (C)	Sample size of included (analysed) –n	Age – y	ABI	Sex, M/F – n	Test methods
Baker <i>et al.</i> (2017), USA ²⁰	RCT	Fr: 3×/w I: mild–moderate pain T: 60 min, 12 w Ty: treadmill walking	BMT (C)	T: 64 (64) E: 29 (29) C: 35 (35)	T: 66.5 E: 66 C: 67	T: 0.63 E: 0.645 C: 0.65	41/23	Progressive treadmill test 3.2 km/h – 0% inclination + 2%/2 min
Beckett <i>et al.</i> (2012), UK ²¹	CT	Fr: 2×/w I: point of claudication T: 50 min, 12 w Ty: circuit training: step ups, toe walking, heel raises, wobble board, and resistance cycling	Angioplasty control (C)	T: 56 (56) E: 42 (42) C: 14 (14)	T: 66.5 E: 66 C: 68	T: 0.70 E: 0.69 C: 0.72	39/17	Constant work 2.5 km/h at 10% inclination Submaximal treadmill 100 s at submaximal intensity Arterial occlusion Acute hyperaemic response
Collins <i>et al.</i> (2012), USA ^{22,23,†}	RT	Fr: 3×/w I: low (25%–44% VO _{2peak}) to moderate (45%–59% VO _{2peak}) to high (60%–84% VO _{2peak}) intensity T: 30–60 min, 24 w Ty: walking without poles (treadmill and hospital corridors) (E1)	F: 3x/w I: low (25%–44% VO _{2peak}) to moderate (45%–59% VO _{2peak}) to high (60%–84% VO _{2peak}) intensity T: 30–60 min, 24 w Ty: walking with poles (outside and hospital corridors) (E2)	T: 103 (95) E: 52 (49) C: 51 (46)	T: 69.7 E: 68.0 C: 71.4	T: 0.63 E: 0.65 C: 0.62	96/7 [‡]	Constant work 2.9 km/h at 12% inclination ²² Progressive work (b) ²³ Small increases in inclination every 30 s; 6 min speed was increased every 3 min; starting speed was 2.9 km/h and inclination 0%: protocol was designed to have a 1 MET every 3 min
Figoni <i>et al.</i> (2009), USA ²⁸	Pre-post trial	Fr: 5×/w of which 3×/centre based and 2×/w home based I: maximum claudication pain T: 12 w Ty: (Treadmill) walking + calf exercises on ergometer	NA	T: 21 (15) E: 21 (15)	T: 68.8 [‡] E: 68.8 [‡]	T: 0.59 [‡] E: 0.59 [‡]	21/0	Progressive work 3.2 km/h – 0% inclination + 2%/2 min until a maximum inclination 14%
Gardner <i>et al.</i> (2014), USA ²⁶	RCT	Fr: 3×/w I: mild–moderate pain T: 20–45 min, 12 w T: 15–40 min, 12 w Ty: home based walking using a step monitor (E1) Ty: supervised treadmill walking (E2)	Attention–control group (C): light resistance training (3×/w)	T: 180 (180) ITT E1: 60 (60) E2: 60 (60) C: 60 (60)	T: 65.7 E1: 67 E2: 65 C: 65	T: 0.70 E1: 0.68 E2: 0.68 C: 0.74	96/84 [‡]	Progressive work 3.2 km/h – 0% inclination + 2%/2 min
Haga <i>et al.</i> (2020), Japan ²⁵	Pre-post trial	Fr: 3×/w I: 70% maximum load T: 40–60 min, 12 w Ty: ergometer cycling	NA	T: 19 (16) E: 19 (16)	T: 67 [‡] E: 67 [‡]	T: left 0.77; right 0.79 E: Left 0.77; right 0.79	13/3	Constant work Speed between 2.4 and 3.6 km/h, 0% inclination

Continued

Table 1-continued								
Study	Design	Exercise group (E1)*	Comparison group(s)* of alternative exercise (E2) or control (C)	Sample size of included (analysed) –n	Age – y	ABI	Sex, M/F – n	Test methods
Manfredini <i>et al.</i> (2012), Italy ³¹	Non-RCT	Fr: 6×/w I: speed 20%–30% lower than pain threshold (using metronome) T: 20 min, 34 w Ty: structured home based walking (E1) Healthy control group with unmodified active lifestyle (post-hoc) (C)	Fr: 6×/w I: self selected pace up to moderate pain T: 20–30 min, 34 w Ty: unstructured, free pace home based walking (E2)	T: 55 (45) E1: 36 (31) E2: 19 (14) C: 15 (15)	T: 71.3 E1: 71.9 [‡] E2: 70.3 [‡] C: 38.3 [‡]	T: 0.61 E1: 0.59 [‡] E2: 0.67 [‡] C: 1.09 [‡]	42/13	Progressive work (NIRS measurements) 1.5 km/h + 0.1 km/h/10 m, 0% inclination Venous occlusion Muscle oxygen consumption
Monteiro <i>et al.</i> (2019), Brazil ²⁹	RT	Fr: 3×/w I: maximum claudication T: 30 min, 12 w Ty: treadmill walking (E1)	Fr: 3×/w I: maximum claudication T: 30 min, 12 w Ty: modified treadmill walking using ankle weights (E2)	T: 40 (32) E1: 20 (16) E2: 20 (16)	T: 64.3 E1: 65.5 E2: 63.1	T: left 0.62; right 0.62 E1: left 0.61; right 0.62 E2: left 0.62; right 0.61	28/12 [‡]	Constant work (1 min warm-up with progressive increase to 3.2 km/h and 10% inclination, at moderate to maximum claudication 1–2 min active recovery at 2.0 km/h and 0% inclination) Arterial occlusion
Murrow <i>et al.</i> (2019), USA ³⁰	RT	Fr: 3×/w I: claudication pain ≥ 6/10 scale T: 40 min, 12 w Ty: treadmill walking (E1) Age matched control group (post-hoc)	Fr: 3×/w I: 15% reduction from TSI rest as a lower level threshold T: 40 min, 12 w Ty: NIRS guided treadmill walking (E2)	T: 36 (18) E1: 18 (10) E2: 18 (8) C: 20 (20)	T: 71.8 [‡] E1: 71.6 [‡] E2: 72.0 [‡] C: 61.0	T: 0.83 [‡] E1: 0.80 [‡] E2: 0.87 [‡] C:	14/4	Progressive work 3.2 km/h – 0% inclination + 2%/2 min Arterial occlusion Muscle oxygen consumption and muscle blood flow
Tew <i>et al.</i> (2009), UK ²⁷	RCT	Fr: 2×/w I: 60%–70% VO _{2peak} T: 20 min, 12 w Ty: arm cranking exercise	Control group with advice on PA (C)	T: 57 (51) E: 29 (27) C: 28 (24)	T: 69.5 [‡] E: 69 C: 70	T: 0.68 [‡] E: 0.68 C: 0.69	51/0	Progressive work 3.2 km/h – 0% +1% /min
Woessner <i>et al.</i> (2018), USA ²⁴	RCT	Fr: 3×/w I: mild–moderate pain T: at least 30 min, 12 w Ty: treadmill walking	Similar exercise group with nitrate supplementation	T: 35 (24) E: 18 (13) C: 17 (11)	T: 69.7 [‡] E: 71.5 [‡] C: 67.5 [‡]	T: 0.63 [‡] E: 0.70 [‡] C: 0.55 [‡]	15/9	Progressive work 3.2 km/h – 0% inclination + 2%/2 min

ABI = ankle brachial index; M = male; F = female; Fr = frequency; I = intensity; T = time; Ty = type; BMT = best medical treatment; CT = controlled trial; RT = randomised controlled trial; VO_{2peak} = peak oxygen consumption; MET = metabolic equivalent; NA = not available; RCT = randomised controlled trial; ITT = intention to treat; TSI = tissue saturation index; PA = physical activity.

* FITT principle.

[†] Same training characteristics except that intervention duration was 12 weeks. Sample size: T: 85(79), E1: 40(36), E2:45(35). Age: T: 69.4, E1: 66.8, E2: 71.7. ABI: T: 0.63, E1: 0.63, E2: 0.62. Sex (79 males/six females).

[‡] Data on analysed numbers of participants.

higher recovery rate in the angioplasty group but not in the exercise group.^{21,29} Furthermore, no interaction, time, or group effects were observed after training on TSI recovery time, delta HHb, and delta TSI following arterial occlusion at rest.²⁹

Near infrared spectroscopy parameters during exercise. In all studies time to minimum TSI (TTM) was increased after the exercise intervention, with five of seven exercise groups reaching statistical significance (range effect sizes: + 0.172

and + 0.927) (Fig. 4B). Two RCTs reported that changes in TTM were statistically significantly larger compared with the control group (*p* interaction .025 and < .001, respectively).^{26,27} Similarly, Tew *et al.* observed significantly higher TSI values at several time points during exercise after an arm cranking intervention.²⁷ Conversely, no changes in absolute de-oxygenation were noted following seven exercise interventions (range effect sizes for delta TSI: –0.127 and +0.350; and for TSI_{min}: – 0.286 and 0.000). Although the lowest TSI value was unchanged, patients could sustain

the low tissue oxygenation levels for a longer period after exercise training (time to resistance; time—effect $p < .001$).²⁹ Yet, a significant decrease in de-oxygenation, which translates to higher TSI values during exertion, was observed only after revascularisation and best medical treatment.^{20,21} Moreover, two studies reported the evolution of NIRS raw signals during exercise, and observed improved maintenance of O₂Hb during (sub)maximal exercise after walking training,^{24,31} without changes in de-oxygenation or tHb kinetics.^{24,31}

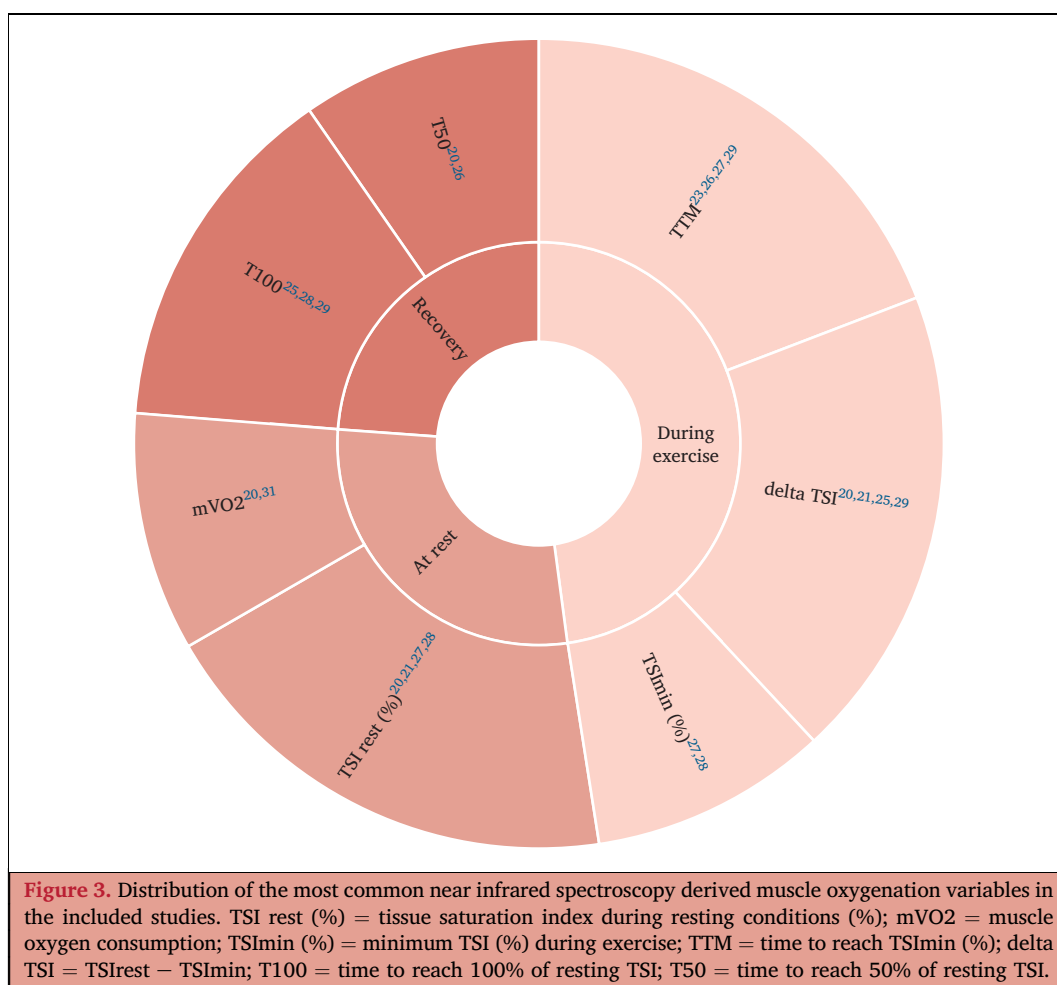
Near infrared spectroscopy parameters during recovery.

Two RCTs reported data on T50 (i.e., time to recover 50% of resting TSI),^{20,26} and three studies reported data for T100,^{25,28,29} defined as time to reach 100% of resting TSI, of which none included a control group (Fig. 4C). Contrary to Baker *et al.*,²⁰ Gardner *et al.* found a faster recovery (T50) following either supervised or home based exercise,²⁶ which was significantly different from the control group ($p = .020$). As the training interventions were similar for both studies, methodological differences most probably explain this discrepancy. That is, Baker *et al.* applied a frequency—domain technique to calculate half time oxygen extraction fraction, which resembled T50.²⁰ Although all studies showed a tendency towards an enhanced recovery following exercise training,^{25,28,29}

assessed as T100 (range effect sizes: -0.665 and -0.269), only the conventional training intervention group reached statistical significance.²⁹ Similarly, Beckitt *et al.* used T50 but defined it as half of the full recovery time.²¹ Following a circuit based exercise training, they found enhanced recovery after a submaximal test similar to the group that received angioplasty treatment. Yet, enhanced recovery after maximum exertion was only seen after revascularisation. Finally, relative re-oxygenation, defined as the time taken to reach 100% of resting TSI relative to test duration, was significantly improved following 12 weeks of walking, three times per week, with and without ankle weights.²⁹

Secondary outcomes

The majority of studies reported significant improvements in pain free (9/12 studies; 75%) and maximum walking capacity (14/16 studies; 87%), as well as 6MWD after the exercise interventions.^{24,26} Similarly, three studies applying an RCT design confirmed enhanced maximum walking capacity following walking and arm cranking exercise, respectively.^{20,26,27} However, a lack of improvement in maximum walking capacity during a progressive work rate test was noted after unstructured exercise (home based)³¹ and after a pole striding intervention.²³ Further, only one



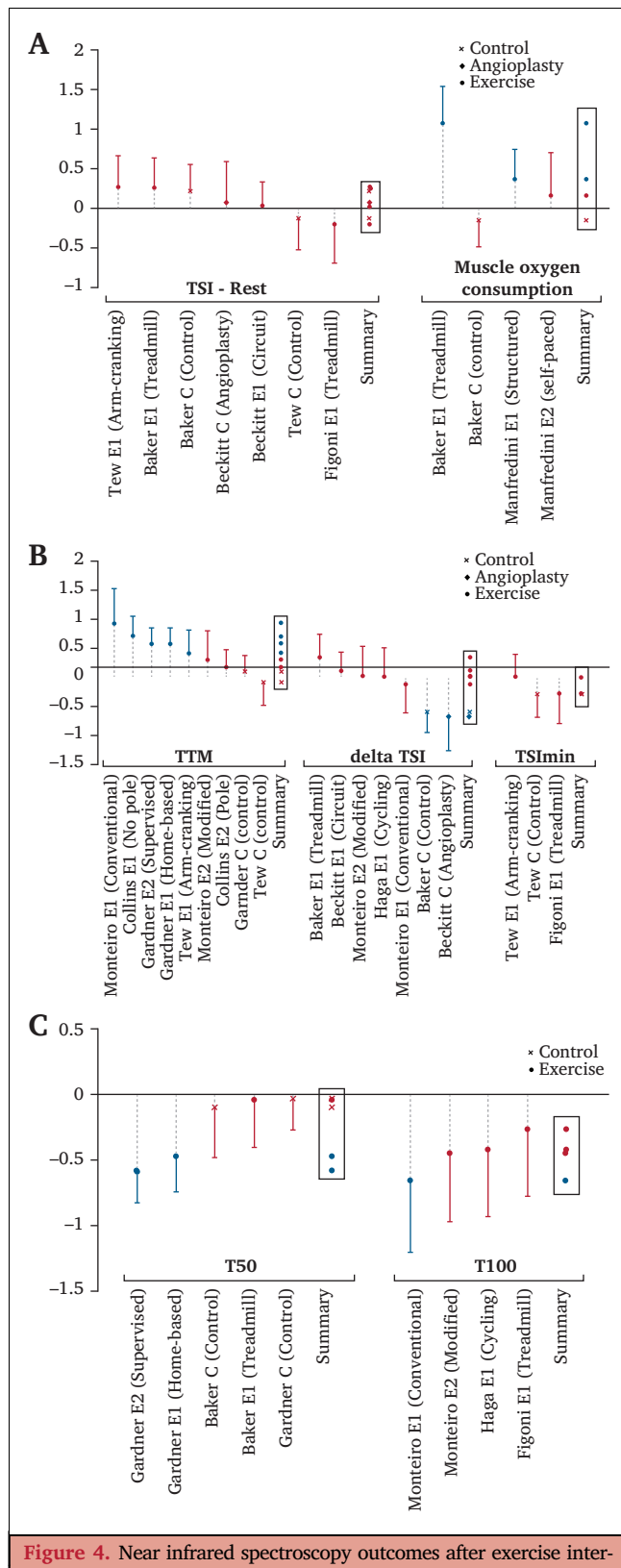


Figure 4. Near infrared spectroscopy outcomes after exercise intervention for lower extremity arterial disease at (A) rest, (B) exercise, and (C) recovery. (A) Effect sizes on tissue saturation index (TSI) and muscle oxygen consumption at rest. (B) Effect sizes on time to minimum TSI (TTM), delta TSI, and minimal TSI (TSImin) during exercise. (C) Effect sizes of halftime (T50) and total recovery time (T100) after an intervention. Results in red and blue reflect non-significant and significant ($p < .05$) effect sizes, respectively. Data on Collins are from Collins *et al.*²³

study assessed exercise capacity and found a statistically significantly improved VO_{2peak} following an arm cranking exercise compared with the control group.²⁷ Although nine studies evaluated ABI, only one reported an improvement in the affected leg after 34 weeks of a structured home based walking intervention.³¹

Detailed information on the effects of exercise training on individual study level can be found in [Supplementary files 2–4](#).

Risk of bias assessment. The median quality of the included studies was 8/12 (range 5 – 11) ([Supplementary file 5](#)). Specifically, the objective was clearly stated in nine articles, with two failing to provide a rationale and/or clear hypothesis for their study. All studies gave a clear description of eligibility criteria, with the sample being representative of the IC population in eight. However, only two studies enrolled all eligible participants. Only four studies reported random sequence generation methods and four included an attention control group. Regarding the methodology, interventions were described in detail and delivered consistently in 10 studies, but assessors were reported to be blinded in only two. Ten studies used adequate statistical methods to assess the significance of the changes in the outcomes, although four did not have sufficient participants at follow up (dropout rate $\geq 20\%$). No incomplete outcome data were found when comparing the results with the protocol; however, four studies failed to report all the prespecified outcomes.

Near infrared spectroscopy methodology assessment. Although all studies (except one) reported the NIRS device used,²⁵ almost all failed to report various device characteristics (e.g., wavelengths and sample frequency), which are important when comparing different studies ([Supplementary file 6](#)). To obtain valid and reliable results, a precise description of the anatomical placement is needed.⁸ Yet, only eight studies described probe position in detail, of which only four took appropriate measures to ascertain reproducibility. The remaining studies provided only a vague description regarding probe positioning (e.g., calf muscle). Two studies reported calf adipose tissue thickness (ATT) (measured with MRI and ultrasound, respectively),^{20,30} and only one excluded participants with a calf ATT of > 20 mm.³¹ The use of raw or filtered data for analysis was not reported in any of the included articles. Regarding NIRS parameters, nine studies described the reported variables in detail, and eight reported all the prespecified outcomes.

DISCUSSION

The aim of this review was to document systematically the effect of exercise interventions on muscle adaptations measured by NIRS after exercise interventions in patients with LEAD and to provide an overview of current NIRS methodology. Although earlier reviews have already addressed NIRS as a new method to evaluate and diagnose

Table 2. Common issues encountered in near infrared spectroscopy (NIRS) methodology and application as observed in current literature, and their potential solutions. For a more detailed list of recommendations, refer to the review written by Barstow⁸

Practical recommendations
Report the technology used and the specific device characteristics: i.e., sample frequency, number of optodes, interoptode distance, and wavelength.
Describe in detail the anatomical position of the probe placement and the methods undertaken for reproducibility for subsequent measurements and/or studies.
ATT should be measured at the site of interest and reported. Whenever possible, subject recruitment should be based on homogeneous ATT values or else a physiological calibration of the NIRS signals may be required.
Data from all raw NIRS signals (O ₂ Hb, HHb, tHb, diffHb) should be provided.
Outcome variables should be clearly defined. In case of experimental variables or analyses, variables should be described in detail to avoid confusion.
The software used and the methods to analyse the data should be reported in detail to ensure reproducibility and transparency.
Analyse and report changes from a timepoint of interest, amplitudes of responses, and slopes. These variables are more insensitive to confounding factors such as ATT or random noise in the signal.

ATT = adipose tissue thickness; O₂Hb = oxygenated haemoglobin; HHb = de-oxygenated haemoglobin; tHb = total haemoglobin; diffHb = difference of oxygenated and de-oxygenated haemoglobin.

patients with LEAD,^{11,12} this is the first comprehensive review to investigate the effect of exercise therapy on NIRS outcomes.

Impact of exercise on near infrared spectroscopy parameters

Rest. Earlier studies reported comparable resting TSI in patients with IC and healthy controls.^{9,12} Similarly, no change was found in resting TSI after training in patients with IC. Moreover, an angioplasty treatment and an exercise group reported similar resting TSI.²¹ This could suggest that resting blood flow is usually sufficient for proper muscle oxygenation, with the underlying supply demand mismatch occurring only during exercise and resembling the symptomatology of IC.

Exercise. A rapid maximum de-oxygenation in the beginning of exercise was previously specified as the hallmark NIRS pattern in patients with IC.^{9,10} Yet the results did not establish any improvements in absolute measures of de-oxygenation during treadmill testing. Whether de-oxygenation during exercise is related to blood flow, as evaluated by resting ABI, remains unclear, with studies reporting contrasting associations ($r = -.56, p = .002$; $r = .105, p > .05$).^{21,32} Yet, TTM substantially increased with training, meaning that patients could walk for longer before maximum de-oxygenation occurred. Similarly, O₂Hb was preserved during submaximal exercise without changes in tHb.^{24,31} Interestingly, early de-oxygenation is associated with maximum walking

capacity,^{32,33} as suggested earlier by Fuglestad *et al.*,⁹ who found a strong correlation between de-oxygenation one minute into exercise and maximum walking distance ($r = -.76$). In line with these findings, Gardner *et al.* found that the change in TTM correlated significantly with the change in maximum walking time ($r = .52, p < .001$ and $r = .43, p = .006$ for home based and supervised groups, respectively).²⁶ As TTM commonly appears prior to initial pain experience, these moderate correlations might be explained by the objective and subjective mismatch in pain perception and perseverance following an exercise programme.³⁴

Recovery. Concerning recovery, a tendency towards faster T50 and T100 following training interventions was noted. Faster re-oxygenation has previously shown clinical relevance for symptom resolution and is associated with better ambulatory outcomes.^{9,32,34} However, only one study achieved statistically significant results, whereas two others observed trends towards enhanced recovery after submaximal exercise intensity or recovery relative to total exercise time.^{21,29}

Underlying mechanisms of change using near infrared spectroscopy

Regarding resting muscle oxygen consumption, two studies showed increased values after an exercise intervention.^{20,31} Yet, muscle oxygen consumption is composed of blood flow and arteriovenous oxygen extraction, and therefore may involve various physiological adaptations.¹⁰ NIRS derived outcomes during exercise present local alterations that are expected after 12 weeks of exercise, such as improved capillarisation and microvascular haemodynamics,^{20,23,24,26,29} oxidative capacity,^{21,29,30} and oxygen extraction.²⁰ In line with local adaptations involved, a 2020 study from Gardner *et al.* reported associations between TTM and ambulatory function, independent of resting ABI and common health burdens.³³ Of note, Murrow *et al.* evaluated mitochondrial oxidative capacity at recovery using an exponential model to plot NIRS derived O₂Hb following repeated arterial occlusions after a bout of exercise.³⁰ They showed a trend towards improved mitochondrial capacity after an exercise intervention, which is similar to the improvement seen in other clinical populations with underlying mitochondrial dysfunction.^{30,35}

Still, this topic is part of a historical debate in which both muscle oxidative capacity and macrocirculation are opposed.⁶ Interestingly, the role of increased endothelial function and rheology has been suggested by the cross transfer effect of an arm cranking exercise,²⁷ with similar improvements in NIRS de-oxygenation and recovery patterns. On the contrary, ABI analyses in all but one of the included samples did not reveal an augmented resting blood supply,²⁰ which is in line with the available evidence.^{36,37} However, Manfredini *et al.* could discriminate two groups of responders after structured home based exercise.³¹ (1) 20 patients who had increased ABI had a blunted decrease of O₂Hb during submaximal exercise and a lower heart rate response; (2) 10 patients without a change in ABI increased their muscle oxygen consumption. These

findings were confirmed by the study of Baker *et al.*,²⁰ which reported both enhanced superficial blood flow and oxygen extraction levels during exercise. Collectively, redundancy of exercise responses and its physiological mechanisms may have an important role regarding increased walking capacity in patients with IC.³⁸

Study biases and methodology

Proper reporting of NIRS instrumentation, testing, and analysis is important as different technology and applied algorithms may affect the results and will hinder comparison among studies.⁸ In the included studies, the reproducibility of study protocols in a pre-post setting was often insufficient, with poor description of probe positioning,^{24,25,30} and without measures to ensure reproducibility for follow up assessments.^{21,23,26,31} The latter is of the utmost importance as reproducibility of the signals largely depends on a fixed probe location as oxygenation responses display large heterogeneity between different muscles, even within different regions of the same muscle.⁸ Additionally, the impact of adipose tissue thickness in the region of interest should be acknowledged when interpreting absolute concentrations of haemoglobin, as a thicker adipose layer can reduce the penetration depth of NIRS emitted wavelengths.⁸ However, the majority of included studies reported TSI outcomes, which are less prone to measurement error.⁸ Furthermore, a lack of uniformity of NIRS parameters reported across the different studies was noted, which makes comparisons among studies difficult. Therefore, it is recommended that researchers and clinicians should try to address these issues when performing NIRS measurements during exercise tests. Some examples of common issues and their potential solutions are presented in Table 2.

Limitations

The included studies had different methodologies and outcomes. To address this limitation, the sample effect sizes were calculated to present the direction of effect for most reported outcomes. The inclusion of non-randomised or non-controlled trials could introduce some bias yet was pre-specified and is in line with the exploratory nature of this review. In addition, it is becoming difficult to get ethical approval for controlled studies in LEAD as exercise is now a class IA recommendation in IC treatment.²¹ However, it should be acknowledged that these pre-post studies without a randomised control group risk regression to the mean. This phenomenon can be minimised by performing familiarisation and multiple measurements at baseline, which were only performed in two non-controlled studies.^{22,28}

Conclusions

Evidence to date seems to suggest that exercise interventions may improve de-oxygenation and re-oxygenation patterns in patients with IC, measured by NIRS applications during various exercise testing protocols. NIRS therefore appears to have potency as an evaluation

tool of peripheral muscle oxygenation following exercise interventions. Yet, given the scarcity of data, further research by means of larger, robust RCTs is needed. New trials should focus on better methodologies, with harmonised NIRS outcomes, and take into consideration transparency and reproducibility.

CONFLICTS OF INTEREST

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejvs.2021.02.008>.

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