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A Toe Flexion NIRS assisted Test for Rapid Assessment of Foot Perfusion in Peripheral Arterial Disease: Feasibility, Validity, and Diagnostic Accuracy

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WHAT THIS PAPER ADDS

The present study offers a new add on tool for non-invasive ambulatory screening and monitoring of peripheral arterial disease. The novelty of the test, assisted by near infrared spectroscopy, is its capacity to provide a rapid assessment of haemodynamics in tissues under natural conditions and to obtain a dynamic assessment of the foot, which makes possible exploration of its macro- and microvascular reserve. This discriminative capacity makes the present test of particular interest in diabetics, and in other pathological conditions when the ABI is not measurable or reliable.

Objectives: Feasibility, validity, and diagnostic accuracy of a non-invasive dynamic ambulatory test were assessed with near infrared spectroscopy (NIRS) evaluating foot perfusion in peripheral arterial disease (PAD).

Methods: This was a prospective observational study. Eighty PAD patients (63 males, 71 ± 9 years), including 41 patients with coexisting diabetes, participated. Thirteen healthy subjects (8 males, 26 ± 8 years) were also studied by echo colour Doppler providing 160 diseased and 26 non-diseased limbs. Under identical clinostatic conditions, participants performed a 10–repetition toe flexion tests with NIRS probes on the dorsum of each foot; the area under the curve of the oxygenated haemoglobin trace ("toflex area") was calculated and the ankle–brachial index (ABI) was measured. Time of execution, rate of wrong tests, and adverse reactions were recorded. Within session reliability was assessed by administering the test twice, with a 5 minute interval between tests. The validity was assessed determining whether the toflex area was (a) dependent on the oxygen delivery from the lower limb arteries simulating PAD conditions by a progressive blood flow restriction (40–120% of systolic pressure) in healthy subjects; (b) consistent with the degree of PAD ranked by ABI and correlated with ABI and ankle pressure values in PAD patients. The diagnostic accuracy in detecting PAD was compared with examination using echo colour Doppler ultrasound.

Results: All tests were rapidly, satisfactorily (<1% mistakes), and safely performed. Toflex area values, superimposable in the two sessions (intra-class correlation coefficient 0.92), were comparable to PAD values following blood flow restriction, consistent with PAD severity, correlated with dorsal pedis artery pressure ($r = .21$; $p = .007$) and ABI ($r = .65$; $p < .001$) in PAD, but not in the presence of diabetes. Toflex area was similar to echo colour Doppler for detecting PAD following receiver operating characteristic curve analysis (area = 0.987, $p < .001$; toflex area values ≤ -28 arbitrary units, sensitivity/specificity 95.6/100).

Conclusion: The toe flexion test enables ambulatory assessment of foot perfusion and PAD detection, even in the presence of non-measurable ABI or diseases affecting the microcirculation.

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INTRODUCTION

Non-invasive haemodynamic assessment of the lower limbs enables screening and monitoring of peripheral arterial disease (PAD), activities that are of particular importance in the presence of diabetes.[1] Validated tools are available, including the ankle–brachial index (ABI), toe brachial index, and echo colour Doppler, as well as techniques to assess tissue perfusion in the lower limbs such as the

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transcutaneous partial pressure of oxygen ($TcPO_2$).[2] However, these tools have limitations. They are static measures or selectively investigate the macrovascular circulation, or require post-exercise measurements; in addition, they may potentially be limited by calcification of blood vessels, or may represent a measure of skin perfusion.[1–9] A rapid non-invasive ambulatory assessment of the haemodynamic reserve of the foot under natural and dynamic conditions may provide an adjunctive method for the testing and monitoring of PAD patients, especially in the presence of medical conditions affecting both the larger vessels and the microcirculation. Near infrared spectroscopy (NIRS) non-invasively explores tissue microvascular haemodynamics,[4,5,10–12] monitoring the local balance between oxygen delivery and consumption. As it is suitable for dynamic and bedside measurements,[10,12] NIRS has been used for PAD assessment[4,13–15] to study perfusion of the foot,[16,17] or monitoring foot oxygenation in patients undergoing endovascular revascularisation[18] or intermittent pneumatic compression treatment.[19] On the basis of previous experience,[13,19–21] it was hypothesized that the oxygenation changes of the foot, when studied by the NIRS technique during a standardised task of toe flexion, might represent a measure of foot perfusion that is (a) both feasible and valid, (b) informative regarding the main arterial blood flow, and inclusive of the assessment of the peripheral microvascular blood flow when PAD is complicated by diabetes (c) with diagnostic capacity in detecting PAD.

MATERIALS AND METHODS

Study design and setting

This was a prospective observational study involving PAD patients and healthy subjects carried out at the Department of Rehabilitation Medicine, University Hospital of Ferrara. The local ethics committee approved this study (number: 04/2015).

Participants

From October 2015 to December 2016, eligible consecutive patients affected by PAD and referred to the program of Vascular Rehabilitation of the Department of Rehabilitation Medicine were invited to participate. Patients at Fontaine's stages II—III, without severe limitation of oxygen transport (severe anemia) and amputations or severe impairment of range of movement of the metatarsophalangeal joints were included in the study. Three skilled operators blinded to the new test at the Department of Vascular Surgery performed clinical examination and echo colour Doppler ultrasound. The abdominal aorta and iliac arteries, common, superficial, and deep femoral arteries, popliteal arteries, and both tibial axes were evaluated. High resolution imaging integrated with pulsed wave Doppler analysis and peak-flow velocity were used according to published standards.[22]

In addition, university students attending the laboratory and hospital personnel were approached to take part in the study as healthy volunteers. Written informed consent was obtained from all the participants. All healthy subjects aged $\geq$18 years underwent a clinical examination to exclude the presence of any chronic pathological condition.

Testing procedures

All the measurements necessary for the different phases of the study (Table 1) were carried out sequentially in a temperature controlled environment between 8:30 and 12:30 a.m. by the same expert operator within 15 days of the echo colour Doppler examination.

Ankle brachial index measurement. All participants underwent ABI measurement according to the standard[23] using a Doppler ultrasound device (Stereodop 448.S, Ultrasomed, Lavello, Italy) with a 9.3 MHz probe and a standard blood pressure cuff. PAD legs were ranked according to disease severity on the basis of the following ABI

Table 1. Phases of the study.

Aim	Action	Population (legs)	Method
Feasibility	Implementation and safety: time of completion including data analysis, rate of incorrect executions and/or adverse events	PAD, healthy (n = 186)	Descriptive statistics
Validity	Toe flexion test repeated two times on same day (consistency)	PAD, healthy (n = 186)	Intra-class correlation coefficient analysis
	Progressive external blood flow restriction (40—80—120% of systolic blood pressure) to simulate PAD	Healthy (n = 26)	One way analysis of variance
	Toflex area values ranked according to the ABI value only when measurable	PAD, healthy (n = 152)	One way analysis of variance
	Toflex- area correlation with the ABI value of: whole PAD population; D_{free}-PAD only; D-PAD only (discriminant)	PAD (n = 160)	Spearman's rho rank correlation
	Toflex area correlation with *posterior tibial* and *dorsal pedis* arteries pressure values	PAD (n = 160)	Spearman's rho rank correlation
Accuracy	Toflex area compared with Echo Colour Doppler for PAD detection	PAD, healthy (n = 186)	ROC curve analysis

Abbreviations: ABI, ankle brachial index; D_{free}-PAD, peripheral arterial disease patients without diabetes; D-PAD, peripheral arterial disease patients with diabetes; PAD, peripheral arterial disease; ROC, Receiver operating characteristic.

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