The severity of muscle ischemia during intermittent claudication

Anselm Egun, FRCS,[a] Vasim Farooq, MB, ChB,[a] Francesco Torella, FRCS,[a] Richard Cowley, BSc,[b] Maureen S. Thorniley, DPhil,[b] and **Charles N. McCollum, FRCS, MD,[a]** *Manchester, United Kingdom*

Purpose: **The degree of ischemia during intermittent claudication is difficult to quantify. We evaluated calf muscle ischemia during exercise in patients with claudication with near infrared spectroscopy.**

Methods: **A Critikon Cerebral Redox Model 2001 (Johnson & Johnson Medical, Newport, Gwent, United Kingdom) was used to measure calf muscle deoxygenated hemoglobin (HHb), oxygenated hemoglobin (O_2Hb), and total hemoglobin levels and oxygenation index (HbD; HbD = O_2Hb − HHb) in 16 patients with claudication and in 14 control subjects before, during, and after walking on a treadmill for 1 minute (submaximal exercise). These measures were repeated after a second maximal exercise in patients with claudication and after 7 minutes walking in control subjects. Near-infrared spectroscopy readings during maximal exercise were then compared with a model of total ischemia induced with tourniquet in 16 young control subjects.**

Results: **Total hemoglobin level changed little during exercise in both patients with claudication and control subjects. HHb levels rose, and O_2Hb level and HbD falls were more pronounced in patients with claudication than in control subjects after submaximal and maximal exercise. During maximal exercise, HbD fell markedly by a median (interquartile range) of 210.5 μmol/cm (108.2 to 337.0 μmol/cm) in patients with claudication compared with 66.0 μmol/cm (44.0 to 101.0 μmol/cm) in elderly control subjects and 41.0 μmol/cm (36.0 to 65.0 μmol/cm) in young control subjects ($P < .001$). This fall also was greater than the HbD fall induced with tourniquet ischemia at 90.8 μmol/cm (57.6 to 126.2 μmol/cm; $P = .006$).**

Conclusion: **Hemoglobin desaturation in exercising calf muscle is profound in patients with claudication, considerably greater even than that induced with three minutes of tourniquet occlusion. Further studies are necessary to investigate the relationship between the inflammatory response and near-infrared spectroscopy during exercise in patients with claudication. (J Vasc Surg 2002;36:89-93.)**

Intermittent claudication is a cramp-like pain in the leg muscles induced with exercise and is the most frequent chronic symptom of atherosclerosis, which affects more than 5% of men more than 50 years of age.[1] Most patients undergo conservative management and rarely need vascular surgery.[2] Few have progression to limb-threatening ischemia, but mortality rates from myocardial infarction and stroke are high, with 30% to 40% dying within 5 years of diagnosis.[3-6] Claudication appears to be associated with subsequent cardiovascular events, such as myocardial infarction and stroke.[7]

That repetitive low-grade ischemia reperfusion of leg muscles on walking leads to leukocyte and platelet activation and an inflammatory cascade involving free radicals, arachidonic acid metabolites, cytokines, adhesion molecules, and endothelial damage is known.[8-10] Although the mortality rate in patients with claudication is clearly related to the high prevalence of cardiac and cerebrovascular disease, the inflammatory response generated by exercise has been suggested to contribute to the poor prognosis.

The degree of ischemia induced with claudication is difficult to quantify. Nuclear magnetic resonance spectroscopy, which measures high energy metabolites in muscle, and near-infrared spectroscopy (NIRS), a noninvasive technique measuring tissue oxygenation and perfusion, have been proposed to assess metabolic changes as the result of intermittent claudication and to monitor the effect of medical therapy.[11-17] We used NIRS to investigate the severity of calf muscle ischemia induced with exercise in patients with claudication. We hypothesized that exercise would induce profound hemoglobin desaturation in the calf muscle of patients with claudication compared with exercise and short duration of ischemia in healthy individuals.

METHODS

Subjects. After ethical approval and informed consent, 16 patients with claudication were recruited. All had a typical clinical history of calf claudication, with cramp-like pain occurring after walking a fixed distance and resolving with rest. They were included in the study if the resting ankle brachial pressure index (ABPI) was less than 0.8. Patients with claudication were excluded for evidence of critical limb ischemia (rest pain, ulcer, or gangrene), cardiac failure, or impaired mobility from any cause. Patients with claudication and diabetes also were excluded because their ABPIs could not be measured reliably.

From the Academic Surgery Unit, South Manchester University Hospital,[a] and the Department of Instrumentation and Analytical Science, University of Manchester Institute of Science and Technology.[b]

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Reprint requests: Mr A. Egun, Academic Surgery Unit, South Manchester University Hospital, West Didsbury, Manchester, M20 2LR, United Kingdom (e-mail: aegun@fs1.with.man.ac.uk).

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Patients with claudication were compared with 14 healthy control subjects who comprised seven matched for gender and age (elderly control subjects) and seven aged between 20 and 30 years (young control subjects). All were required to have an ABPI of more than 1 with no fall on exercise. Sixteen young adults also were recruited to measure the severity of hypoxia and oxygen extraction during complete calf muscle ischemia.

Near-infrared spectroscopy. Reflectance NIRS is based on the Beer-Lambert law,[18] the relative transparency of biologic tissues to near infrared light and the characteristic absorption in the near infrared spectrum of hemoglobin, myoglobin, and cytochrome oxidase. Because the light-absorbing properties of these molecules vary with oxygenation, changes in their concentration can be measured. Myoglobin and cytochrome oxidase, however, are robust to large changes in oxygen supply. Hence, the variation in absorption detected with NIRS is, in most circumstances, the result of changes in hemoglobin oxidation and concentration. Changes in hemoglobin concentration (tHb) reflect variations in regional blood volume,[19] and changes in hemoglobin oxidation reflect the balance between oxygen supply and consumption.[20,21]

In vivo, near infrared light is scattered by the difference in refraction between tissue constituents, leading to an elongation of the path of the light beam. To measure absolute hemoglobin concentrations with NIRS, knowledge of the length of this path is necessary, with addition of a "pathlength factor" (specific to patient and tissues) to the Beer-Lambert law. Because pathlength is difficult to measure in vivo, only changes from an arbitrary baseline are usually measured, with NIRS as a trend monitor.

We used a Critikon Cerebral Redox Research Model 2001 (Johnson & Johnson Medical, Newport, Gwent, United Kingdom), a four wavelength spectroscope emitting light at 776, 819, 871, and 909 nm. This instrument was used with a sensor with a 3.5-cm distance between light source and detector. The Cerebral Redox Model provides a continuous output for changes in concentration of total (tHb), oxygenated (O_2Hb), and deoxygenated hemoglobin (HHb). The oxygenation index (HbD; HbD = $O_2Hb - HHb$), a previously validated parameter reflecting tissue oxygen use,[22] was calculated. HbD gives an indication of the net hemoglobin oxygenation status irrespective of blood volume changes and reflects the balance between oxygen supply and consumption and is affected by changes in perfusion pressure. Hemoglobin concentration changes were expressed as μmol/cm because tissue changes in absorption are related to the distance travelled by the light beam through the tissues.

Study plan. Patients with claudication and control subjects fasted for 8 hours and were asked to refrain from any physical activity on the morning of the study. On arrival to our unit, they were rested for 1 hour on a couch. The NIRS probe then was secured to the calf muscle with a self-adhesive bandage. In patients with claudication, the symptomatic leg was studied; if claudication was bilateral, the leg with most severe symptoms was chosen. The right leg was studied in control subjects. A general physical examination then was carried out and included measurement of systolic and diastolic brachial pressure in the right arm and ankle arterial pressures with a hand-held Doppler scan (Huntleigh Diagnostics, Cardiff, South Glamorgan, United Kingdom). The ABPI was calculated as the ratio between the highest pressure measured at the ankle (dorsalis pedis, posterior tibial, or peroneal artery) and the systolic brachial pressure.

Baseline NIRS recordings were taken during a 10 minute period. To evaluate the response of each group to submaximal exercise, a 1-minute walk on a treadmill then was performed at a speed of 3.2 kph and a gradient of 10 degrees. After a further 20-minute rest period on a couch, all subjects were asked to walk again at the same speed and inclination for 7 minutes or, for patients with claudication, until stopped with pain. This second test was to evaluate the response of patients with claudication to maximal exercise. NIRS measurements were taken every second during exercise and continued until values returned to their original resting levels (recovery period) with subjects lying on a couch.

In the model of complete ischemia, a tourniquet was inflated to twice the systolic blood pressure for 3 minutes around mid-thigh in 16 young healthy control subjects. A hand-held Doppler scan was used to confirm total cessation of blood flow in the superficial femoral artery. An ischemic time of 3 minutes was chosen to equate the median maximum walking time for patients with claudication during maximal exercise.

Data analysis. All results were entered on a purpose-designed database for further analysis. Data were analyzed with Excel 5.0 (Microsoft, Reno, Nev) and SPSS 9.0 (SPSS Inc, Chicago, Ill). Comparisons were made between patients with claudication and control subjects with changes in NIRS readings on exercise. Because NIRS data were skewed, a log transformation was attempted but did not produce a satisfactory fit to the normal distribution for all variables. The Kruskal-Wallis and Mann-Whitney *U* tests therefore were used to compare the groups, with the Spearman correlation test to explore associations between variables. Statistical significance was set at the standard .05 level.

RESULTS

Demographics, smoking habits, walking times, and ABPIs of the subjects studied are summarized in Table I.

Submaximal exercise (Table II). During the first exercise, a rise in HHb in all subjects was seen. This was more pronounced in patients with claudication, at a median (interquartile range) of 81 μmol/cm (21.9 to 180.5 μmol/cm), compared with elderly control subjects, at 25.1 μmol/cm (15.8 to 37.9 μmol/cm), and young control subjects, at 11.7 μmol/cm (3.8 to 46.8 μmol/cm; $P = .038$). A fall in O_2Hb in all subjects also was seen, especially in patients with claudication, but the difference was not statistically significant ($P = .11$), although tHb rose slightly in all subjects. The fall in HbD was much greater in patients with claudication, at 168.7 μmol/cm (46.7 to 297.3

Table I. Subjects

	Claudication (n = 16)	*Matched controls (n = 7)*	*Young controls (n = 7)*	*Tourniquet ischemia (n = 16)*
Mean age (range) (y)	63 (53-79)	62 (52-78)	24 (20-30)	29 (23-38)
Men/women	8/8	4/3	3/4	9/7
Smokers	3	1	2	3
Median MWT (range) (min)	3 (1-5)	Unlimited	Unlimited	Unlimited
Mean resting ABPI (range)	0.68 (0.44-0.8)	>1	>1	>1
Mean post-exercise ABPI (range)	0.52 (0.3-0.71)	>1	>1	>1

MWT, Maximum walking time on treadmill.

Table II. Changes in NIRS parameters (μmol/cm) in patients with claudication and in control subjects during and after submaximal exercise

	Patients with claudication	*Elderly controls*	*Young controls*
During exercise			
HHb	81.0 (21.9, 180.5)	25.1 (15.8, 37.9)	11.7 (3.8, 46.8)
O_2Hb	–64.8 (–162.3, –17.3)	–24.4 (–11.0, –30.6)	–23.3 (–21.9, –32.5)
tHb	19.3 (–47.2, 64.5)	9.5 (–20.1, 17.2)	18.0 (–25.4, 26.0)
HbD	–168.7 (–46.7, –297.3)	–40.5 (–24.8, –74.8)	–38.4 (–18.0, –45.6)
After exercise			
HHb	–0.8 (–23.5, 5.2)	–0.20 (–6.0, 8.8)	3.8 (–4.2, 8.3)
O_2Hb	20.8 (3.4, 59.2)	2.6 (–3.6, 17.9)	3.7 (–5.8, 18.9)
THb	38.0 (5.9, 56.1)	0.9 (–1.8, 26.6)	8.1 (2.4, 28.6)
HbD	21.4 (0.7, 79.1)	7.7 (–6.6, 12.5)	3.4 (–0.9, 20.6)

Values are median (interquartile range).

Table III. Changes in NIRS parameters (μmol/cm) in patients with claudication and in control subjects during and after maximal exercise

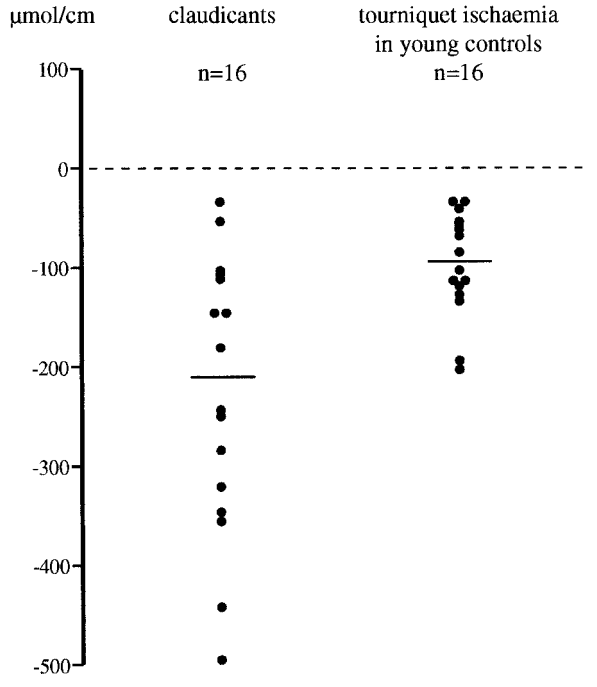
	Patients with claudication	*Elderly controls*	*Young controls*
During exercise			
HHb	86.5 (41.7, 193.0)	32.0 (11.0, 60.0)	21.0 (5.0, 45.0)
O_2Hb	–107.5 (–48.7, –178.7)	–41.0 (–69.0, 14.0)	–18.0 (–41.0, 16.0)
tHb	–12.5 (–55.7, 47.5)	–27.0 (–49.0, 21.0)	7.0 (–23.0, 20.0)
HbD	–210.5 (–108.2, –337.0)	–66.0 (–44.0, –101.0)	–41.0 (–36.0, –65.0)
After exercise			
HHb	–6.9 (–1.1, –22.2)	–2.7 (–5.8, 0.7)	–8.2 (–3.8, –17.4)
O_2Hb	24.2 (1.4, 47.7)	10.0 (2.6, 18.0)	9.2 (6.9, 28.3)
tHb	5.0 (–2.3, 40.1)	0.6 (–22.5, 15.5)	3.2 (–6.5, 18.2)
HbD	47.3 (–0.12, 76.0)	17.0 (10.0, 25.6)	26.5 (11.5, 38.8)

Values are median (interquartile range).

μmol/cm), compared with elderly control subjects, at 40.5 μmol/cm (24.8 to 74.8 μmol/cm), and young control subjects, at 38.4 μmol/cm (18 to 45.6 μmol/cm; $P = .007$). In the recovery period, patients with claudication showed a rise in O_2Hb, tHb, and HbD not seen in control subjects.

Maximal exercise (Table III). The median (range) time walked on the treadmill by patients with claudication was 3 minutes (1 to 5 minutes). All control subjects were able to walk for 7 minutes without pain. Similar qualitative changes in tissue oxygenation were found during maximal walking in patients with claudication and during 7 minutes of walking in control subjects. However, the rise in HHb ($P = .003$) and the falls in O_2Hb ($P = .001$) and HbD ($P < .001$) were significantly more pronounced in patients with claudication. During the recovery period, the rise in O_2Hb and HbD seen in patients with claudication was greater than those seen in control subjects. A significant correlation was found between resting ABPI and HHb rise in exercising patients with claudication ($r = -.45$; $P = .05$), but the correlation between resting ABPI and the fall in O_2Hb ($r = .10$; $P = .07$) and HbD ($r = .37$; $P = .15$) on exercise were poor. Also, no correlation was found between NIRS measurements and ABPI falls during exercise.

Tourniquet ischemia. Complete tourniquet-induced ischemia over 3 minutes in healthy control subjects resulted



Falls in HbD on maximum walking in patients with claudication and in healthy control subjects during tourniquet ischemia. Median (interquartile range) falls were 210.5 µmol/cm (108.2 to 333.7 µmol/cm) and 90.8 µmol/cm (57.6 to 126.2 µmol/cm), respectively ($P = .006$).

in a median (interquartile range) HHb rise of 35.0 µmol/cm (20.3 to 79.2 µmol/cm), and O_2Hb and HbD fell by 59.4 µmol/cm (28.0 to 73.8 µmol/cm) and 90.8 µmol/cm (57.6 to 126.2 µmol/cm), respectively, but tHb did not change. The fall in HbD during maximal walking in patients with claudication was 210.5 µmol/cm (108.2 to 337.0 µmol/cm), significantly greater than during tourniquet ischemia ($P = .006$; Fig).

DISCUSSION

According to our hypothesis, we showed profound hemoglobin desaturation in the calf muscles of patients with claudication during exercise. This desaturation was more marked than in elderly or young control subjects and, in accordance with previous reports,[23] was not accompanied by large changes in regional blood volume, measured with tHb. NIRS changes in patients with claudication during maximal exercise were similar but more pronounced than those seen during complete interruption of blood flow in healthy individuals, suggesting that walking induces severe ischemia in patients with peripheral vascular disease. In contrast with previous studies,[17,23] we did not find a strong correlation between NIRS and ABPIs. Our findings are consistent with the pathogenesis of claudication pain, because of the circulation failing to meet increased oxygen requirements during exercise. The rise in HHb and the falls in O_2Hb and HbD show increased oxygen extraction with muscles during walking compensating for insufficient oxygen delivery.

NIRS has been used previously to investigate tissue oxygenation in peripheral vascular disease[16] and grade the severity of intermittent claudication.[17,24-25] Recently, Komiyama et al,[26] evaluating NIRS in patients with claudication with diabetes, concluded that NIRS measured the hemodynamic severity of peripheral vascular disease more accurately than resting ABPI. NIRS has also been used to diagnose peripheral vascular disease in the elderly, for perioperative monitoring of vascular patients, and to assess the effect of hemodialysis in patients with peripheral vascular disease.[25-27] Although nuclear magnetic resonance spectroscopy also has been used to evaluate ischemia in patients with claudication, NIRS has significant advantages because it is cheaper, widely available, and easy to use. It is, however, reassuring that changes in saturation measured with NIRS and metabolic alterations measured with nuclear magnetic resonance spectroscopy show similar trends during muscular contraction.[28,29]

Although our data do not directly support an ischemia reperfusion injury, we confirmed that ischemia in the calf muscles of patients with claudication is severe. Future studies may investigate a potential correlation between the magnitude of the inflammatory response to exercise and NIRS changes in patients with claudication. If the degree of desaturation measured with NIRS could predict this response and if remote organ damage was shown to occur in response to inflammation, NIRS may become a useful tool not only to assess the severity of ischemia but also to identify patients with claudication with poor prognosis.

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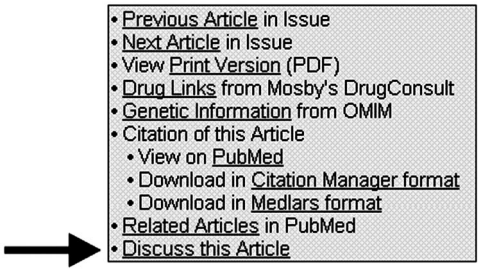

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