

Noninvasive quantification of muscle oxygen in subjects with and without claudication

Bok Y. Lee, MD; Lee E. Ostrander, PhD; Milon Karmakar, MD; Lubo Frenkel; Burton Herz, MD

Department of Surgery, VA Medical Center, Castle Point, NY 12511; New Rochelle Hospital Medical Center, New Rochelle, NY 10801

Abstract—The disabling pain of intermittent claudication (IC) arises from oxygen deprivation in the lower limbs during walking. Measurement of the oxygen deficiency within the limb tissue now appears possible with recently expanded understanding of the photon transport through tissue for photons in the visible and near infrared range. Noninvasive measurement consists of preferentially measuring photons that have traveled more deeply into limb tissues and that, therefore, may reach locations of ischemic tissue. Oxygen measurements appear to be possible up to a depth approaching 1.5 cm beneath the surface of the skin. The present study reports on data acquired from the limbs of 11 subjects with IC and 12 subjects without IC. The subjects with IC are patients with clinical findings of claudication based upon segmental Doppler pressure profiles and subjective reports by the patient of pain during exercise. The subjects without IC are individuals with no prior history of ischemic vascular disease. The results consist of photon reflectance measurements at red and infrared wavelengths (approximately 660 nm and 880 nm respectively) taken before, during, and after exercise. Infrared reflectance indices are plotted as well as oxygenation indices generated from combining red and infrared reflectances. A compilation of exercise data shows responses that are generally consistent with the expected physiological responses to mild exercise in subjects with and without IC. We anticipate that the findings of this study may lead to an objective noninvasive testing procedure for measuring the ischemic and exercise-induced changes in muscle oxygenation in the presence of claudication. If the testing of ischemic hypoxia continues to show consistency and accuracy

in determining the disability of the subjects with IC, future studies can more effectively test modes of conservative management, such as cessation of smoking, alternative exercise regimens, weight loss, and alternative pharmacological agents.

Key words: *claudication, ischemic vascular disease, oxygen consumption, tissue oxygen.*

INTRODUCTION

Claudication is a manifestation of ischemic vascular disease and is characterized by severe ischemic pain during walking (1). A study of 18,388 subjects (London civil servants) reported that intermittent claudication (IC) was associated with a twofold increase in age-specific risk for death and a loss of 10 years of life expectancy (2). In men over 60 years of age, the incidence of IC is two to three times that of diabetes mellitus (3).

The obstructed vascular system of the person with IC cannot compensate effectively for the increased metabolic demands of ambulation. In the absence of compensation, a drop in tissue oxygenation occurs, and the resulting pain from the IC is disabling to the patient (4).

Diagnosis of the severity of IC is not easily accomplished. Ideally, one could measure the oxygen levels within the muscle, in order to assess the balance between oxygen supply and consumption, and thereby evaluate vascular insufficiency. However, noninvasive testing does not permit direct measurement. Conventional noninvasive methods measure variables, such as blood flow and oxygen supply. However, in a cross section of ani-

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Address all correspondence and requests for reprints to: B-Y Lee, MD, Chief, Surgical Service, VA Medical Center, Castle Point, NY 12511.

mals, it was found that the partial pressure of oxygen in tissues does not correlate with these variables (5).

Measurement of oxygen at locations one or more cm into tissue now appears to be possible as a result of the recently expanded understanding of the transport of light through light-scattering media. Such methods are now being applied to biological tissue and they are reported to be capable in some instances of measuring tissue oxygenation in the brain through the skull (6). The possibility of using similar methods to elucidate the vascular problems of persons with IC is the subject of this study.

In the study described in this article, the photon reflectance provides a measure of oxygen saturation, identified as diffusive reflectance oxygen saturation ($S_{dr}O_2$). Parameters directly related to $S_{dr}O_2$ are determined noninvasively. Similarities within and differences between the groups with and without IC are examined.

Light Reflectance Methods

Light reflectance methods were described as far back as 1912, when a light torch was used to illuminate tissue (diaphanography) so as to visualize breast lesions (7). The present study uses a form of reflectance spectrophotometry. Photons propagating within a diffusive medium, such as biological tissue, are randomly scattered and absorbed. Some of the photons that enter the tissue survive to find their path out of the tissue and, therefore, become reflected photons. The results of experimental studies and modeling by researchers have demonstrated that the depth (6) to which photons travel and the amount of light reflected are related to the optical properties of the biological medium.

The optical properties of blood are wavelength-dependent and vary with the oxygenation of the hemoglobin and, to a lesser extent, with other tissue components, such as myoglobin. The use of two or more photon wavelengths (usually red and infrared) provides selective evaluation of oxygen saturation from the measured photon attenuation within the tissue. Distance between source and detector is related to the distribution of depths to which the photons have traveled during their residence within the tissue. The further the distance of the light-emitting diodes (LEDs) from the detectors, the larger the fraction of photons that have penetrated to any selected depth before being reflected back to reach the photodetectors. Reflectance of light through the skin for two or more different source-detection separations are contrasted to accentuate the reflectance from the deeper layers (8). Measurements of reflectance appear to be possible

that incorporate photons that have reached a depth approaching 1.5 cm beneath the surface of the skin.

Muscle Oxygen During Exercise

Within the muscle and other body tissues, tissue oxygen is determined by a balance between the rate of oxygen transport to the tissues in the blood and the rate at which the oxygen is utilized by the tissues. The oxygenated arterial blood arriving in the tissues transports across vessel walls into the interstitial fluids and bathes the cells of the tissue with oxygen. In the interstitial fluid, the PO_2 averages approximately 40 mmHg, while in the capillaries, it is 95 mmHg. The venous blood leaving the tissue capillaries contains O_2 at approximately the same pressure as that in the interstitial fluid surrounding the capillaries (9). Since venous blood is a large percentage by volume of blood in tissue, reflectance data are heavily influenced by venous blood changes.

During exercise, the muscle blood vessels are generally expected to dilate and blood flow to increase. With the increase of the blood flow, oxygen is transported into the tissues at a greater rate. If the metabolic rate remained constant (e.g., no exercise or constant exercise) while

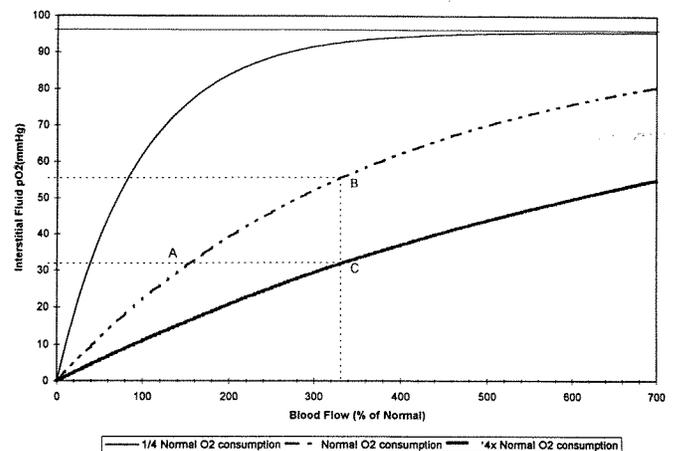


Figure 1. Effect of blood flow and oxygen consumption on tissue PO_2 .

flow increased, the tissue oxygen would increase. This is illustrated in **Figure 1**, by the middle curve labeled (A)-(B). Increased metabolism, as shown in this figure, upon moving to point (C) has the counter-effect of decreasing interstitial fluid PO_2 (10).

During exercise, the cells utilize more oxygen for metabolism than under resting conditions. As illustrated in **Figure 1**, an increase in tissue oxygen consumption shifts the tissue PO_2 from the curve labeled B to the curve labeled C, and reduces interstitial PO_2 . A decrease in hemoglobin concentration decreases the oxygen carrying capacity and has the same effect on interstitial fluid PO_2 as does a decrease in the blood flow.

Functioning of the Muscle Oxygen Device

The oxygen device is a reflectance oximeter. The device probe shines a "pencil beam" of photons (either infrared or red light approximately 660 nm or 880 nm, respectively) on the skin surface and simultaneously detects and quantitates the intensity of reflected light at multiple distances from the photon source. Red light at 660 nm responds markedly to the color changes of hemoglobin in blood with oxygen saturation. The red reflectance is also heavily influenced by blood volume (or more precisely, by hemoglobin concentration). The infrared light reflectance focuses upon blood volume, since infrared reflectance has an oxygen sensitivity of only about 10 percent that of red light. That is, the infrared reflectance depends primarily on the regional blood volume and is relatively independent of the level of oxygenation of the blood.

Data are acquired at multiple source-detector separations at each wavelength. The system incorporates measurements at source-detector separations of 1, 2, 3, and 4 cm, and at red (660 nm) and infrared (880 nm) wavelengths. The interface unit provides switching among different separations, as well as modulation of the light sources, to allow discrimination against ambient light. However, there is a limitation to the source-detector separation as the reflectance becomes increasingly attenuated with greater source-detector separations. The physical arrangement of the embedded LEDs and detectors in the probe is, therefore, crucial to the function of the instrument. The probe for the oxygen device consists of four parallel rows of embedded LEDs and a photodetector row (**Figure 2**). Photons from each LED enter the biological medium. Of those that exit, some impinge upon the sensitive area of a photodetector and contribute to an electrical signal produced by the photodetector. Within the probe, the LEDs are optically isolated from the detectors such that placement of the probe on an opaque surface inhibits all detectable transfer of photons from sources to detectors. Each row of LEDs has a red (R) LED and an infrared (IR) LED.

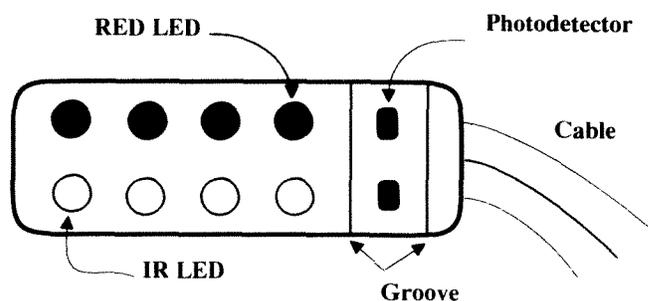


Figure 2.

Diagram showing the probe head and physical arrangement of the R-red and IR-infrared LEDs and the photodetectors.

System Components for the Oxygen Device

The muscle oxygen device consists of up to three probes of which one was used for the present study, an interface electronics unit and a laboratory computer with data input-output board. The interface unit has connections on the front panel for the test probes and has two connections on the rear panel for a power supply and the input/output data board. The interface unit also includes a receiver to collect and amplify the detected photon signals. The input/output data board controls the interface switching as well as converting the detected signals to digital form. The computer stores and analyzes the acquired data, as well as providing a time record of the acquired data. The system software provides an interface between instrument function and the operator, and allows for calibrating the device.

METHODS

The procedure is explained to the test subjects in advance and informed written consent for the procedure is obtained. The study included 11 patients experiencing IC and 12 subjects without clinical evidence or history of IC. The present research was a preliminary study in which only one probe was used, with the probe applied to the lateral side of the calf over the gastrocnemius muscle of the leg. Test subjects were asked to go through a series of activities that included initial rest, standing in place, exercise, and post-exercise rest.

During calibration, the probes are zeroed by covering them so as to block all external light and to minimize the light transfer from sources to detectors within the probes. Once the zeroing is completed, a measuring site

is selected. A non-uniform site (e.g., a site near a large blood vessel) can produce large changes in reading with the probe displacements of body movement that occur during exercise. To test for this, the probe is manually subjected to lateral mechanical movement while observing reflectance readings. If a large fluctuation in readings does occur with motion, the probe is relocated and the reflectances observed again. Once a test location is chosen, the probe is secured against the skin surface of the calf with foam straps. The next step is to calibrate the probe so as to bring all calibrated reflectances to a baseline value of unity. Finally, the exercise phase is undertaken with continuous measurements and data collection takes place. Minor protocol differences applied to the subjects. In general, the subjects without IC were calibrated in the supine position and exercise consisted of heel lifts. The patients with IC began in the sitting position, as an easier position for instrumentation, and exercised with walking in place.

In these preliminary studies, acquired data were examined for consistency with expected physiological responses, and for general similarities and differences between the patients with IC and the subjects without it. The logarithm of infrared reflectance was plotted against time as an index of the regional blood volume. The log difference of red reflectance from infrared reflectance was plotted as an index of blood oxygen saturation (i.e., oxygenation index). Except where blood concentration is low, the signals from the 4 cm source-detector separation (largest separation) of the device being used were overwhelmed by noise. Therefore, the results that follow show source-detector separations to 3 cm.

PRELIMINARY RESULTS

Example graphs of the reflectance data for a test subject without IC are shown in **Figures 3** and **4**. Curves labeled IR1, IR2, and IR3 are infrared reflectance data at source-detector separations of 1 cm, 2 cm, and 3 cm, respectively. Similarly curves labeled OI1, OI2, and OI3 are oxygenation index data at separations of 1 cm, 2 cm, and 3 cm, respectively.

Reflectances were in a steady state during baseline recording, as evidenced by constant readings (other than measurement noise and small "physiological" variations). In the subject without IC, a decreased infrared reflectance is observed with a change from supine to standing position. The decrease can be explained as an

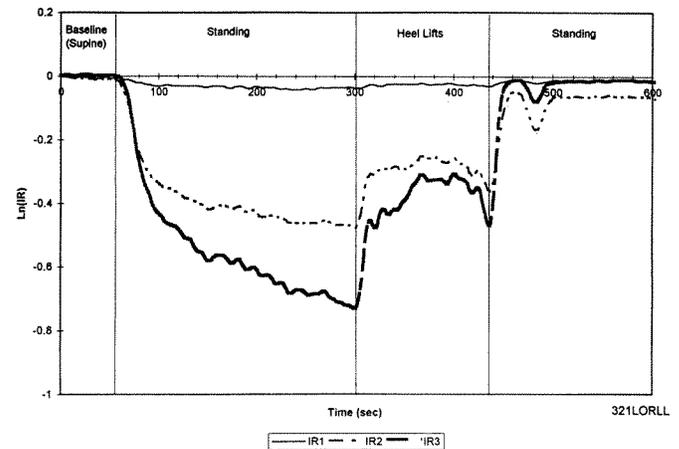


Figure 3.
Infrared reflectance for a subject without claudication.

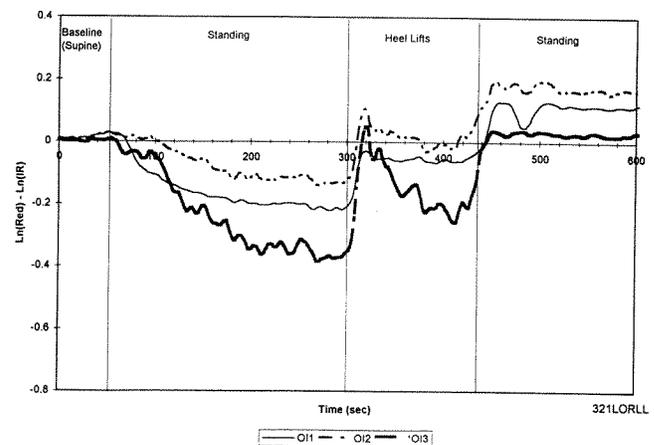


Figure 4.
Oxygenation index for a subject without intermittent claudication.

increase of the regional volume in the lower limbs upon standing, due to the effects of gravity as body position is changed. The greater drop in IR3 and IR2 as compared with IR1 suggests that the photons traveling more deeply (seen in IR3 and IR2) have a greater increase in blood volume than may have occurred in the shallower layers of the tissue. **Figure 4** presents corresponding results for the oxygenation index. With continued standing, a continuing drop in OI3, as well as OI1 and OI2, is seen. This drop can be explained as an increase in the amount of deoxygenated blood. For the oxygenation index to decrease, the rate of fall in red reflectance exceeded that of infrared reflectance.

During exercise, a nondisabled individual has an increased heart rate. The individual also has vasodilation in the peripheral vascular system due to local mediators as well as ejection of blood by active pumping of the contracting muscles (11). The reduced blood volume in the sensor vicinity is seen as an increased infrared reflectance (Figure 3). The abrupt increase in OI reflectance suggests an in-rush of oxygenated blood (Figure 4).

With an increase in blood flow, greater quantities of oxygen are transported to the lower limbs over a given period of time. This would contribute to the increase in tissue PO_2 . The oxygen consumption, however, also increases. The magnitude of this increase would be influenced by the overall muscle mass, athletic features of the patient, and the amount of energy spent, as well as the inflow of oxygenated and outflow of deoxygenated blood during the exercise. In Figure 4, with the subject exercising (toe lifts), the OI reflectance decreased, and this change is consistent with an increase in deoxygenated blood.

On completion of the exercise protocol in individuals without IC, the infrared reflectance returned immediately to baseline level. This change would be expected when the blood concentration in the tissue returns immediately to baseline levels. In Figure 4, the OI reflectance is elevated, consistent with oxygen levels above baseline in a hyperemic response.

Results of the Experiments: A Subject with IC

The subject for whom data are provided in Figures 5 and 6 showed bilateral femoral-popliteal occlusive disease. The segmental Doppler systolic pressure profile indicated bilateral occlusive disease with ischemic indices in the claudication range. Graphs of reflectance data for this patient are shown in Figures 5 and 6. In Figure 5, the IR reflectance remains relatively constant at the calibration level in the baseline period while the patient is seated. We see a decrease in infrared reflectance at the largest source-detector separation (IR3) as the patient stands, associated with an increase in lower limb blood volume. The oxygenation index increases, suggesting that the blood entering the limb contains more oxygen than was present with the subject sitting. Exercise consisted of walking in place. For patients with IC, the expected response is a decrease in oxygenated blood flow, and the pumping action of the muscles may also cause a decrease in blood volume (Figure 5). The observed drop in IR reflectance is consistent with a decrease in blood volume. The drop in OI2 and OI3 (Figure 6) is also consistent with a decrease in oxygenated blood. The patient with IC showed an elevation in

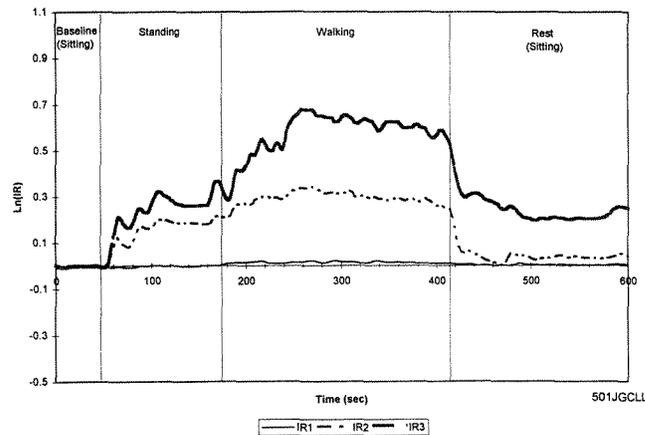


Figure 5. Infrared reflectance for a patient with intermittent claudication.

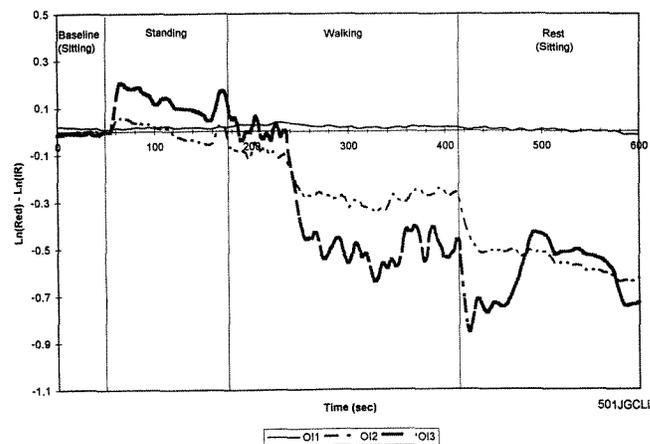


Figure 6. Oxygenation index for a patient with claudication.

oxygenation index during the final rest period and a large drop was seen in infrared reflectance consistent with pooling of blood in the limb postexercise, at an oxygen concentration better than that during exercise.

Results of Tests for 12 Subjects without IC and for 11 Subjects with IC

All of the subjects without IC showed a gradual decrease in oxygenation index with standing, presumably associated with pooling of blood in the limbs after changing from a supine position. During toe lifts, 10 of the 12 subjects without IC showed a steady level of oxygenation index. Two subjects without IC showed a gradual

decrease. During walking in place, three patients with IC (four limbs) showed steady oxygenation index levels during exercise, while the remaining six patients with IC showed changes: two limbs with a rapid decrease, one limb with a gradual increase, and the remaining four limbs with a gradual decrease.

During the postexercise recover period, all but one of the subjects without IC showed an increase in oxygenation index. In the patients with IC, the oxygenation index in three limbs decreased in the immediate postexercise recovery period, while it increased slowly in six limbs and rapidly in two limbs.

DISCUSSION

Caution should be exercised in interpreting data by comparing subjects with and without IC, due to the previously described differences in calibration and exercise protocol. Nonetheless, in periods after the baseline calibration period, the responses within each group were consistent with expected physiological responses, as previously described.

Clinical Applications

This study provides an assessment of a noninvasive method of measuring oxygen level at depths up to 1 cm or more beneath the surface of the skin in patients with IC. By assessing oxygen levels in the limb at one or more sites of ischemia in claudication, a more direct and relevant evaluation of the true state of ischemia at depth within tissues is anticipated. Noninvasive vascular instrumentation currently used to evaluate limb ischemia is limited in the ability to reflect the state of oxygenation in the tissue. The study suggests that $S_{dr}O_2$ may be an objective noninvasive testing variable for measuring the ischemic and exercise-induced changes in muscle oxygenation. If information acquired by reflectance methods continues to show consistency and accuracy in determining physiologic changes with exercise of the subject with IC, future studies can more effectively assess disability and test the effects of conservative management of claudication, such as cessation of smoking, various exercise regimens, weight loss effects, and medications.

Immediate Possible Clinical Applications

The following list shows potential applications for a reliable, noninvasive method of measuring ischemic oxygen changes in the limb:

1. *Objective assessment of IC.* This will aid in the diagnosis of vascular disease and in monitoring the disease status and the effects of surgical and medical management.
2. *Evaluation of rest pain.* The diagnostic challenge lies in the differentiation of claudication from neuropathic pain associated with diabetes mellitus, especially in limbs with concomitant arterial obstruction. While measurement of $tcPO_2$ levels by the modified Clark polarographic electrodes may be diagnostic for rest pain (12–14), $tcPO_2$ has limitations in that it evaluates oxygen levels in the skin. It has been noted that these measurements tend to be unreliable when sympathetic tone is increased, when cellulitis is present, and when the area under study is hyperkeratotic, as well as in obese or edematous patients. The age of patients also tends to affect $tcPO_2$ levels showing a drop in oxygen tension with advancing age (15). By directly evaluating the amount of oxygen at the muscular level, the diffuse reflectance test could be of great value in evaluating this special group of patients.
3. *Evaluation of ischemic ulcers and gangrene.* There is no absolute definition of what constitutes an ischemic ankle pressure. It is well established that the use of ankle/brachial indices (ABI) may be erroneous, especially in patients with high systemic pressure and in patients with calcified vessels. Digital plethysmography is used to determine the degree of ischemia in limbs with normal or abnormal ankle pressures but “not ischemic” ankle pressure (16). It is hoped that in these situations direct measurement of oxygen levels at the site of ulcers and ischemia will better guide management decisions.
4. *Evaluating the effects of indicated sympathectomies.* Uhrenholdt (17), Thulesius et al. (18), and Yao and Bergan (19) have all documented critical levels of skin pressure below which sympathectomy is not effective and indeed may even be harmful. By quantifying oxygen levels before and after sympathectomies, both in the skin and in deeper muscle, we anticipate improved evaluation of procedures that continue to be done. The quantification of direct oxygen levels can help clarify the role of sympathectomy, if any, in the management of limbs with ischemia.
5. *Establishing criteria to predict healing of foot lesions.* Ankle pressures tend to be poorly predictive in evaluating perfusion of the foot. Noncompressible foot arteries and pedal arterial obstruction in the absence of above-ankle disease, especially in diabetics, have greatly limited evaluation of healing potentials in these patients. We anticipate that by directly measuring the oxygen levels deeper in the muscle, at or near the site of foot ulcers, a better prediction of healing and determi-

nation of appropriate clinical management may be possible.

6. *Establishing the appropriate level of major amputations.* Using blood pressure values and analyzing pulse volume waveforms have a limited role in predicting the level of amputation (20,21). tcPO₂ measurements are not always reliable predictors (22–25). The use of a critical PO₂ index defined as the calf-brachial tcPO₂, by Kram et al. (26), provides a better predictive accuracy. They noted that all patients with an index less than 0.20 failed to heal and 97 percent of patients with an index greater than 0.20 healed successfully. We anticipate that by better quantifying the oxygen levels deep within the muscle and by developing an appropriate index value, we will be able to offer surgeons direct relevant, objective criteria for selecting amputation levels.

7. *Measurement of tissue oxygen levels in myocutaneous flaps.* Tissue oxygen tension can be used as a sensitive indicator of acute impairment of the blood supplying pedicle in island flaps and in monitoring free tissue transfers (27) and as a useful indicator in monitoring cutaneous flaps (5).

8. *Direct measurement of oxygen levels in deep tissue may be useful in predicting the success of various operations.* Preoperative ABIs and pulse volume recordings are only roughly correlated with infrainguinal graft survival. Many grafts remain patent in limbs in which no ankle pressure or pulse is detected. Direct measurement of muscle oxygen may provide objective evaluation postoperatively.

9. *Postoperative monitoring.* Doppler flowmetry is now the most versatile noninvasive method in assessing graft patency in the immediate postoperative period. In those patients in whom ankle pressure or pulse volume recordings cannot be obtained, direct measurement of deep tissue oxygen levels in addition to the above will augment evaluation.

10. *Follow-up studies.* In the postoperative period, neither the absolute value of ABI nor the pulse volume recording amplitudes have any predictive value in early bypass graft failure (28,29). It has been documented that even when Doppler studies indicate ischemic indices some limbs continue to survive without tissue loss, most likely due to the development of collateral circulation. Direct measurement of deep oxygen levels will be an invaluable adjunct in the follow-up of these patients.

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