Noninvasive Detection of Skeletal Muscle Underperfusion With Near-Infrared Spectroscopy in Patients With Heart Failure

John R. Wilson, MD, Donna M. Mancini, MD, Kevin McCully, PhD,
Nancy Ferraro, RN, Vita Lanoce, MS, and Britton Chance, PhD

The present study was undertaken to determine whether near-infrared spectroscopy can be used to noninvasively assess skeletal muscle oxygenation in patients with heart failure. The difference between light absorption at 760 and 800 nm was used to assess hemoglobin-myoglobin oxygenation. Initial studies conducted in isolated canine gracilis muscle demonstrated that 760–800-nm absorption correlated closely \((r = -0.97 \pm 0.01)\) with venous hemoglobin \(O_2\) saturation when the muscle was stimulated to contract at 0.25–5.0 Hz. In normal subjects \((n=6)\) and patients with heart failure \((n=8)\), 760–800-nm absorption changes from the vastus lateralis muscle were monitored at rest, during progressive maximal bicycle exercise, and during thigh cuff inflation to suprasystolic pressure, an intervention designed to assess minimal hemoglobin-myoglobin oxygenation. Absorption changes were expressed relative to the full physiologic range noted from rest to thigh cuff inflation. During exercise, normal subjects exhibited an initial increase in hemoglobin-myoglobin oxygenation followed by a progressive decrease in oxygenation to 27±13\% of the physiologic range at the peak exercise workload of 140±9 W. In contrast, patients exhibited an initial decrease in hemoglobin-myoglobin oxygenation with the first workload, followed by a progressive further decrease to 26±13\% of the physiologic range at a peak exercise workload of 60±8 W, less than half the peak workload noted in the normal subjects. At all exercise loads, hemoglobin-myoglobin oxygenation was significantly less in the patients than in the normal subjects. These data suggest that near-infrared spectroscopy can detect impaired skeletal muscle \(O_2\) delivery in patients with heart failure. This technique could provide a valuable method of assessing muscle \(O_2\) delivery in patients, particularly before and after therapeutic interventions. (Circulation 1989;80:1668–1674)

Patients with heart failure are frequently limited by muscular fatigue due at least in part to skeletal muscle underperfusion.\(^1\)\(^2\) Therefore, one of the major objectives in such patients is to improve blood flow to skeletal muscle. To accomplish this end, a method of assessing skeletal muscle perfusion is required. However, such a method is presently not available. The two most commonly used techniques to estimate muscle flow are measurement of total leg flow with a thermodilution femoral venous catheter and venous plethysmography. The catheter technique is invasive and does not distinguish between flow to working muscle, flow to nonworking muscle, or flow to nonmuscular tissue. The plethysmography technique does not distinguish between muscular and nonmuscular limb flow and cannot be used to assess leg flow during upright exercise. The xenon-133 technique has also been used to measure muscle flow but is imprecise.\(^3\)

In the present study, we evaluated a new, noninvasive method of assessing \(O_2\) delivery to skeletal muscle: near-infrared \((NIR)\) spectroscopy. Use of propagated light to study skeletal muscle was pioneered by Chance and Weber\(^4\) and Chance and Jobsis\(^5\); light was used to study cytochromes in the sartorius muscle. Butler and Norris\(^6\) showed at the same time that NIR light propagates through very thick objects. Jobsis-Vander Vliet and colleagues subsequently applied this technology to the study of neonate brains and human skeletal muscle (Jobsis,\(^7\) Piantadosi and Jobsis-Vander Vliet,\(^8\) Wiensperger et al,\(^9\) Hampson et al,\(^10\) and Hampson and Piantadosi\(^11\)).
NIR spectroscopy exploits the difference in optical absorption spectra between the oxygenated and deoxygenated states of myoglobin and hemoglobin. At a wavelength of 800 nm, the oxygenated and deoxygenated forms of myoglobin and hemoglobin exhibit similar absorption coefficients. Therefore, absorption of light at this wavelength is proportional to the total amount of myoglobin and hemoglobin in the muscle under examination. At a wavelength of 760 nm, absorption is primarily by the deoxygenation forms. Therefore, changes in light absorption at 760 nm provide assessment of changes in deoxygenated hemoglobin-myoglobin. The difference between absorption at 760 and 800 nm provides an index of hemoglobin-myoglobin deoxygenation normalized for changes in total hemoglobin and myoglobin.

In this study, we examined the relation between NIR absorption and O₂ availability in the working dog gracilis muscle. We then used this technique to assess skeletal muscle oxygenation in patients with heart failure. Light absorption at 800 and 760 nm was measured on vastus lateralis muscle of patients and normal subjects performing upright maximal bicycle exercise. We reasoned that if patients develop muscle underperfusion during exercise, they would exhibit a greater level of hemoglobin-myoglobin deoxygenation than the normal subjects.

**Methods**

**Canine Gracilis Muscle**

We studied five dogs to determine whether NIR spectroscopy provides reliable information about skeletal muscle O₂ availability. Muscle hemoglobin-myoglobin deoxygenation was assessed using the dual-wave spectrometer schematically illustrated in Figure 1. A 75-W tungsten-iodine light source was filtered at 760 and 800 nm by a 60-Hz rotating wheel that allowed time-sharing of the source. Light was transmitted to the tissue via a fiber-optic light guide. Reflected light was delivered via a second fiber-optic light guide to two photomultipliers. Changes in absorption at 760 and 800 nm were used to assess changes in deoxygenated hemoglobin-myoglobin and total hemoglobin-myoglobin concentration, respectively. The difference in absorption between 760 and 800 nm was used to assess deoxygenated hemoglobin-myoglobin, normalized for changes in total hemoglobin-myoglobin concentration.

To examine the relation between muscle O₂ availability and NIR spectral information, the venous outflow of the right gracilis muscle was isolated in four of the dogs. All veins draining into the right femoral vein between the inguinal ligament and the distal caudal femoral vessels were ligated except for those vessels draining the gracilis muscle. The proximal femoral vein was then cannulated, and its flow was directed via tubing to the left femoral vein. The distal caudal femoral and popliteal veins were ligated so that blood draining from the femoral vein was exclusively from the gracilis muscle. Fiber-optic light guides were placed on the skin over the muscle. The hemoglobin O₂ saturation of gracilis venous effluent and gracilis NIR absorption were then simultaneously measured at rest and during muscle exercise at 0.25, 0.5, 1, 2, 3, 4, and 5 Hz induced by stimulating the obturator nerve with supramaximal 0.5-msec pulses.

To clarify the contribution of myoglobin to NIR absorption changes, one dog was studied. The gracilis muscle venous bed was isolated, as described. In addition, the arterial inflow was isolated. All vessels from the femoral artery were ligated except for those perfusing the gracilis muscle. The distal femoral artery was ligated, and the proximal femoral artery cannulated. The contralateral femoral artery was cannulated, and blood from this artery was delivered to the other femoral artery via polyethylene tubing. This tubing was then clamped, and the muscle exercised at 6 Hz for 2 minutes to produce maximal hemoglobin and myoglobin O₂.

**Figure 1. Schematic illustration of the near-infrared spectrometer.**
desaturation. The muscle was then perfused for 20 minutes with oxygenated Krebs solution containing 0.35 mM ethyl hydrogen peroxide at 20 ml/min to convert myoglobin to the ferryl form and thereby prevent myoglobin desaturation.\textsuperscript{12,13} The muscle was then reperfused with blood and ischemic exercise repeated.

**Evaluation in Humans**

Eleven patients with heart failure (mean age, 55±5 years old) and six normal age-matched subjects (mean age, 49±3 years old) were studied. All of the patients had left ventricular ejection fractions of less than 35\% (mean, 22±2\%). Heart failure was attributed to coronary diseases in six patients and to idiopathic cardiomyopathy in five. All patients were receiving digoxin and diuretics, and six of 11 were receiving vasodilator agents. Patients with peripheral vascular disease were excluded from the study. All subjects gave written informed consent to the study.

Subjects were studied in a fasting condition. After arrival in the laboratory, the subject sat on an upright Monarch exercise bicycle. Two fiber-optic light guides spaced 1.5 cm apart were positioned over the right vastus lateralis muscle 10–12 cm from the knee. A thigh cuff was positioned around the upper thigh. A mouthpiece was placed in the subject’s mouth; expired gas was delivered to a SensorMedics Metabolic Cart for respiratory gas analysis. Blood pressure was measured on the upper arm by cuff sphygmomanometer. The electrocardiogram was monitored continuously.

After a 3-minute rest period, subjects performed maximal symptom-limited bicycle exercise. Exercise was started at a workload of 20 W. The workload was increased by 20 W every 2 minutes. Cuff blood pressure was measured at the end of each workload. Immediately after termination of exercise, the thigh cuff was inflated to 250 mm Hg by a rapid cuff inflator. After plateauing of the 760–800 nm signal, the cuff was deflated and the recovery curve recorded.

The path length of the NIR light in the muscle is unknown for continuous light, although work by Chance et al\textsuperscript{14} suggests that the average path length in human skeletal muscle is approximately 2.6 cm. Consequently, NIR signals monitored in this study do not yield absolute levels of hemoglobin-myoglobin deoxygenation. Changes in deoxygenation were expressed relative to the overall change in the signal noted from rest to the signal noted after thigh cuff inflation. The signal after thigh cuff inflation was presumed to represent near-maximal hemoglobin-myoglobin deoxygenation. The resting signal was presumed to reflect a similar level of hemoglobin and myoglobin oxygenation in both normal subjects and patients with heart failure.

**Statistical Analysis**

Results are expressed as mean±SEM. Comparison between control and heart failure subjects was performed with unpaired t testing. Relations between variables were analyzed with linear regression analysis. A p value of less than 0.05 was considered statistically significant.

**Results**

**Canine Gracilis Muscle**

At rest, gracilis muscle blood flow averaged 11.2±1.6 ml/min. Venous hemoglobin O\textsubscript{2} saturation averaged 73.3±4.3\%, arterial hemoglobin O\textsubscript{2} saturation averaged 93.4±1.1\%, and hemoglobin averaged 14.5±1.1 g/dl. Exercise (0.25–5 Hz) increased blood flow to 36±6 ml/min and decreased venous hemoglobin O\textsubscript{2} saturation to 20.8±5.8\% but did not change arterial O\textsubscript{2} saturation.

The relation between changes in NIR absorption and venous hemoglobin O\textsubscript{2} saturation are illustrated in Figure 2. In all four dogs, a close linear relation was observed between these variables with correlation coefficients of \(-0.97±0.01\) (range, \(-0.97\) to \(-0.98\)). There was no evidence for a biphasic curve, as might be expected if myoglobin contributed substantially to the signal. A representative NIR tracing obtained from one experiment is shown in Figure 3.

To further clarify the contribution of myoglobin to the NIR signal, one additional dog was studied. The muscle was exercised at 6 Hz with no flow. The muscle was then perfused for 20 minutes with oxygenated Krebs solution containing 0.35 mM ethyl hydrogen peroxide at 20 ml/min to convert myoglobin to the ferryl ion and thereby prevent myoglobin desaturation.\textsuperscript{12,13} The muscle was reperfused with blood and ischemic exercise repeated. Before ethyl hydrogen peroxide treatment, exercise decreased absorption by 52 arbitrary units. After treatment, NIR absorption decreased by 49 units. The similarity between the two exercise responses suggests that exercise-induced changes in 760–800 nm absorption is primarily produced by changes in hemoglobin O\textsubscript{2} saturation.
Stimulation of the muscle directly beneath the gracilis muscle (approximately 2–2.5 cm deep) resulted in no measurable NIR absorption change, indicating that the system was primarily detecting changes occurring in superficial muscle.

**Patients With Heart Failure**

At rest, the patients with heart failure and the normal control subjects exhibited comparable heart rates, blood pressure, \( \overline{V}_{O_2} \), and respiratory gas exchange ratios (Table 1). At peak exercise, patients exhibited slightly reduced heart rates and mean arterial blood pressure. Peak exercise \( \overline{V}_{O_2} \) was only \( 14.3 \pm 1.9 \text{ ml/min/kg} \) in the patients versus \( 30.2 \pm 1.4 \text{ ml/min/kg} \) in the normal subjects \((p<0.001)\). However, the respiratory gas exchange ratio at peak exercise was comparable in both groups.

Changes in 760–800-nm absorption (i.e., oxygenated-hemoglobin-myoglobin) were analyzed by assigning the resting absorption a value of 100% and the absorption noted during cuff inflation a value of 0%. Changes in \( \overline{V}_{O_2} \) and NIR absorption are illustrated in Figure 4. Normal subjects exhibited a slight increase in oxygenated hemoglobin-myoglobin at 20 W followed by a progressive decrease to a level of 27±5% at maximal exercise. A representative tracing in a normal subject is shown in Figure 5.

In the patients with heart failure, two patients exhibited no change in NIR absorption during exercise. Both of these patients were obese with body weights of 121% and 164% of ideal body weight for their heights\(^{15}\); all other patients and normal subjects had body weights less than 120% of ideal body weight, with mean weight being 102±3% of ideal body weight. In the two patients, the failure of NIR absorption to change was attributed to a failure of the light to reach skeletal muscle due to the thickness of the thigh fat and skin layers.

All of the remaining nine patients exhibited progressive reductions in hemoglobin-myoglobin oxygenation. One of the patients had a normal peak exercise \( \overline{V}_{O_2} \) of 31.6 ml/min/kg and exhibited changes in hemoglobin-myoglobin oxygenation similar to that observed in the normal subjects. Changes in hemoglobin-myoglobin oxygenation in the remaining eight patients with reduced peak exercise \( \overline{V}_{O_2} \) levels (8.5–17.5 ml/min/kg) are illustrated in Figure 4. With the onset of exercise, hemoglobin-myoglobin oxygenation decreased in contrast to the increase noted in the normal subjects. Oxygenation decreases were significantly greater in the patients than in the normal subjects at all workloads, consistent with reduced skeletal muscle perfusion. However, at peak exercise, patients achieved hemoglobin-myoglobin oxy-
genation levels (26±4%) comparable to those noted in the normal subjects, although the levels were achieved at workloads markedly less than in the normal subjects (normal subjects, 140±9 W; patients with heart failure, 60±8 W; p<0.001). An example of hemoglobin-myoglobin oxygenation changes in a patient with heart failure is provided in Figure 6.

Five of the patients underwent repeat exercise testing 2–3 weeks after their initial exercise test. Hemoglobin-myoglobin oxygen levels were comparable during both tests (20 W: run 1, 81±15% vs. run 2, 89±14%; 40 W: run 1, 55±13% vs. run 2; 58±23%; 60 W: run 1, 49±16% vs. run 2, 53±27%).

To ensure that the different hemoglobin-myoglobin oxygenation responses in the normal subjects and patients with heart failure were not simply due to a lesser degree of absorption change in the patients with heart failure, the total change in 760–800-nm absorp-

![Figure 5](image)

**Figure 5.** Near-infrared absorption changes at rest and during exercise in normal subjects performing maximal bicycle exercise. Curve labels are the same as in Figure 3.

![Figure 6](image)

**Figure 6.** Near-infrared absorption changes at rest and during exercise in a patient with heart failure performing maximal bicycle exercise. HbO₂+MbO₂ decrease, 760–800-nm absorption. The resting absorption was assigned a value of 100% and the absorption level noted with cuff inflation, a value of 0%. Blood volume decrease, 800-nm absorption. At this wavelength, the oxygenated and deoxygenated forms of myoglobin and hemoglobin exhibit similar absorption coefficients.

![Figure 7](image)

**Figure 7.** Relation between the slope of the absorption-systemic VO₂ relation and peak exercise VO₂. HF, patients with heart failure.

tion from rest to peak exercise was compared in the two groups. Data were obtained with the same gain setting. The total absorption change was 26±6 arbitrary units in the normal subjects versus 29±3 absorption units in the patients (p=NS).

To investigate whether the recovery of muscle oxygenation was delayed in patients with heart failure, the time taken for hemoglobin-myoglobin oxygenation to achieve 50% of the resting level after thigh cuff release was calculated. This time was comparable in the normal subjects (45±11 seconds) and in the patients with heart failure (52±8 seconds) (p=NS).

The adequacy of skeletal muscle blood flow should be proportional to the change in hemoglobin-myoglobin oxygenation. To investigate whether peak exercise VO₂ is determined by muscle flow, the slope of the relation between 760 and 800-nm absorption expressed as a percentage, and systemic VO₂ was calculated. Patients with heart failure exhibited inverse slopes nearly threefold greater (−0.121 ±0.015%/ml/min) than that of normal subjects (−0.042±0.004%/ml/min) (p<0.001), consistent with impaired muscle O₂ delivery in the patient. When the slope of the absorption-VO₂ relation was correlated with peak exercise VO₂, a relatively close linear relation was noted (Figure 7).

**Discussion**

During incremental exercise, blood flow to working skeletal muscle increases progressively accom-
panied by a progressive decrease in capillary and venous hemoglobin O\textsubscript{2} saturation and in myoglobin O\textsubscript{2} saturation\textsuperscript{1,2,16-19}. In patients with heart failure, the cardiac output response to exercise is attenuated, accompanied by reduced skeletal muscle blood flow\textsuperscript{1,2}. A compensatory increase in O\textsubscript{2} extraction occurs to maintain O\textsubscript{2} uptake. This increased O\textsubscript{2} extraction decreases capillary and venous hemoglobin O\textsubscript{2} saturation and presumably also reduces myoglobin O\textsubscript{2} saturation.

The present study was undertaken to determine whether NIR spectroscopy can be used to detect these flow-related changes in hemoglobin and myoglobin O\textsubscript{2} saturation. It has been shown that this technology can detect changes in tissue oxygenation in the brain and skeletal muscle of experimental animals\textsuperscript{7-10}. This technique has also recently been used to detect changes in normal human forearm muscle oxygenation during ischemia and to assess brain oxygenation in children\textsuperscript{11,20}. The present study represents the first application of NIR spectroscopy to the assessment of circulatory disease in humans.

To ensure that NIR spectroscopy could be used to detect changes in working skeletal muscle and to investigate the relative contribution of hemoglobin versus myoglobin to NIR absorption changes, we initially studied canine gracilis muscle. Myoglobin oxygenation has previously been evaluated in this muscle by Gayeski et al\textsuperscript{18} and Connett et al\textsuperscript{19}. Muscles were frozen and then examined for the state of myoglobin oxygenation by low-temperature spectroscopy. Our results demonstrate that 760–800-nm absorption closely parallels changes in venous hemoglobin O\textsubscript{2} saturation. The relation between venous O\textsubscript{2} saturation and 760–800-nm absorption was linear, suggesting that changes in hemoglobin O\textsubscript{2} saturation were primarily responsible for the absorption changes. Myoglobin desaturation does not occur until intracellular P\textsubscript{o}2 drops below 20 mm Hg. If myoglobin was contributing substantially to the signal, one might expect a biphasic change in absorption, the initial phase reflecting hemoglobin deoxygenation and the secondary phase reflecting myoglobin deoxygenation. It should be noted, however, that hemoglobin and myoglobin desaturation could be so closely coupled that a linear relation occurs.

To further investigate the contribution of myoglobin versus hemoglobin to NIR absorption changes, we examined 760–800-nm absorption changes before and after muscle treatment with ethyl hydrogen peroxide. Ethyl hydrogen peroxide converts myoglobin to the ferrous form that no longer undergoes desaturation\textsuperscript{12,13}. Thus, such a treatment should remove the contribution of myoglobin from the 760–800-nm signal. Ethyl hydrogen peroxide treatment did not substantially influence 760–800-nm absorption changes with exercise, further supporting the conclusion that absorption changes are principally due to hemoglobin desaturation. Seiyama et al have arrived at similar conclusions in rat skeletal muscle\textsuperscript{21}, although the relevance of such findings to dog and human skeletal muscle is uncertain because human and canine muscle have a more than 10-fold greater concentration of myoglobin than rat muscle\textsuperscript{22}. However, this study and that of Seiyama et al do not totally exclude the possibility that myoglobin contributes somewhat to 760–800-nm absorption changes. Millikan\textsuperscript{23}, for example, observed the absorption spectrum of hemoglobin and myoglobin in the intact sartorius muscle of the cat and concluded that a majority of the absorption originated from myoglobin rather than hemoglobin. Therefore, in this study, changes in 760–800-nm absorption are interpreted as reflecting changes in hemoglobin and myoglobin oxygenation rather than only in hemoglobin oxygenation.

Having established the relation of NIR absorption to venous hemoglobin oxygenation saturation changes in the dog, we sought to use NIR spectroscopy to monitor muscle hemoglobin-myoglobin oxygenation during bicycle exercise in patients with heart failure. The NIR light guides were placed over the vastus lateralis, a muscle activated during bicycle exercise. Based on our findings in the dog, we anticipated detection of changes from muscle up to 3 cm deep. Consistent with this presumption, we were unable to detect any change in 760–800-nm absorption in our two most obese subjects, presumably due to their having thick skin and fat layers over the vastus lateralis.

With exercise in the normal subjects, we observed an initially slight increase in hemoglobin-myoglobin oxygenation. This probably reflected an increase in arterial blood flow to the muscle, a change that would be expected to increase the overall hemoglobin oxygenation. With higher levels of exercise, progressive hemoglobin-myoglobin deoxygenation occurred. At peak exercise, the desaturation plateaued, consistent with achievement of maximal O\textsubscript{2} extraction.

In the patients with heart failure, the initial workload resulted in a decrease in hemoglobin-myoglobin oxygenation in contrast to the increase observed in the normal subjects, probably due to flow impairment in the patients. Throughout exercise, hemoglobin-myoglobin oxygenation decreased more than in the normal subjects, further supporting impaired O\textsubscript{2} delivery to working muscle. Interestingly, at peak exercise, the patients exhibited hemoglobin-myoglobin oxygenation levels comparable to those noted in the normal subjects, supporting achievement of similar levels of maximal O\textsubscript{2} extraction in both groups.

To investigate whether patients’ exercise capacity was influenced by O\textsubscript{2} delivery, we examined the relation between peak exercise \textit{V}O\textsubscript{2} and the slope of the line relating 760–800-nm absorption changes to \textit{V}O\textsubscript{2}. A direct linear relation was noted, consistent with the presumption that maximal exercise capacity in patients with heart failure is deter-
mined by the capacity of the circulation to deliver O₂ to working muscle.

The principal limitation of NIR spectroscopy is that the path length taken by the reflected NIR light is not known. Therefore, NIR signals cannot be converted into absolute levels of O₂ saturation but can only be viewed in relative terms. To permit comparison of patients with normal subjects, we expressed NIR changes within a range defined by the resting absorption level and the level noted at peak exercise after cuff occlusion. We assumed that patients would exhibit equal or greater hemoglobin–myoglobin deoxygenation at rest than the normal subjects. At peak exercise with the cuff inflated, both groups should exhibit comparable levels of hemoglobin–myoglobin deoxygenation. Therefore, the full range in the patients with heart failure should be similar to or less than in the normal subjects; reduction in the range would make it more difficult to detect inadequate muscle oxygenation.

Supporting the presence of similar ranges in the two groups, the full change in 760–800-nm absorption from rest to maximal deoxygenation was comparable in the two groups. An alternative method of calibration is to use a range defined by the resting absorption change and the change noted after cuff release. This was not used because patients with heart failure exhibit a substantially blunted reactive hyperemic response to ischemia.²⁴

In summary, the present study suggests that NIR spectroscopy provides a useful, noninvasive method of monitoring skeletal muscle O₂ delivery in patients with heart failure. This approach should be useful in assessing the severity of flow impairment in patients. Perhaps of greater importance, NIR spectroscopy could also be used to assess the effect of therapeutic interventions on skeletal muscle in patients with heart failure. Because NIR spectroscopy can be repeatedly performed without discomfort or risk to patients, it should be possible to serially evaluate changes in hemoglobin–myoglobin oxygenation before and after a therapeutic intervention. Improved muscle perfusion should be accompanied by a reduction in the degree of hemoglobin–myoglobin deoxygenation noted during exercise.

Acknowledgment

We thank Franz Orishimo for his technical assistance in this study.

References


Key Words • spectrometry • muscle, skeletal
Noninvasive detection of skeletal muscle underperfusion with near-infrared spectroscopy in patients with heart failure.
J R Wilson, D M Mancini, K McCully, N Ferraro, V Lanoce and B Chance

Circulation. 1989;80:1668-1674
doi: 10.1161/01.CIR.80.6.1668

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/80/6/1668

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/