APPLICATION OF NEAR INFRARED SPECTROSCOPY TO THE EVALUATION OF EXERCISE PERFORMANCE AND LIMITATIONS IN PATIENTS WITH HEART FAILURE

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ABSTRACT

Exercise performance in patients with heart failure is limited primarily due to a reduction in cardiac output. This results in skeletal muscle hypo-perfusion. Near infrared spectroscopy provides a simple noninvasive method for assessing skeletal muscle oxygenation during exercise. In this paper we review the application of this technique to patients with heart failure and describe excessive limb and respiratory muscle oxygenation as compared to normal subjects. The potential of this technology for monitoring clinical improvement and therapeutic efficacy also is discussed.

Keywords near infrared spectroscopy; heart failure; magnetic resonance spectroscopy.

1 INTRODUCTION

Exertional fatigue is a common limiting symptom in patients with chronic congestive heart failure. This has been traditionally attributed to underperfusion of skeletal muscle, with resultant ischemia.[1,2] Many studies have demonstrated reduced skeletal muscle perfusion at rest and during exercise in these patients. Thermodilution catheters, measurement of venous saturations, and nuclear techniques such as xenon washout have been used to measure skeletal muscle perfusion.[1,3,4] All of these methodologies are invasive and frequently are technically difficult. The development of an easily applicable, reproducible noninvasive technology would greatly assist in the investigation of muscle oxygenation and perfusion. This technology could assist in grading the severity of the disease as well as in assessing responses to different therapies. This is true not only for congestive heart failure but other disease states such as peripheral vascular disease, where skeletal muscle ischemia is prominent. Near infrared spectroscopy (NIRS) is a new technology that encompasses many of the abovementioned elements and may provide a noninvasive, easily applicable means to monitor muscle oxygenation.[5–7] In this brief review we provide a summary of the current available near-infrared technology, its validation in man, and recent clinical uses.

2 NEAR INFRARED SPECTROSCOPY

Near infrared spectroscopy provides a noninvasive technology to investigate skeletal muscle oxygenation during exercise.[5–7] Near infrared spectrometers are commercially available, portable, and user-friendly devices. One device manufactured by NIM, Inc. (Philadelphia, Pennsylvania) is described in greater detail later in this review. Near infrared technology is based on the optical properties of hemoglobin. Near infrared light can propagate through tissues and, at particular wavelengths, is differentially absorbed by the oxygenated and the deoxygenated forms of hemoglobin and myoglobin.[5–7] Both oxygenated and deoxygenated forms absorb light at 800 nm whereas at 760 nm absorption is primarily by the deoxygenated forms. Thus the illumination of intact tissue with selective wavelengths of near infrared light allows the qualitative assessment of changes in the tissue concentration of these molecules.

Optical physiological monitoring is not a new technique but dates back to 1935 when Millikan,[8] using a primitive optical scheme, was able to demonstrate deoxygenation of stimulated muscle. The near infrared spectrometer we used was designed by Dr. Britton Chance. Measurements are made using a dual-wave system. We initially used a device that consisted of a 75-W tungsten-iodine light source that was filtered at 760 and 800 nm by a 60-Hz rotating wheel that allowed time sharing of the source.[7] Light was transmitted to the tissue via one fiber optic light guide. Reflected light was delivered via a second fiber optic light guide to a photomultiplier. We currently use a commercially

available device (Runman, NIM, Inc.) which uses a flexible plastic probe. Two tungsten lamps are inserted at both ends of this probe and two photodetectors are situated between the lights. The tungsten lamps emit white light at a user-modifiable frequency, i.e., the strobe rate can be set at fast, slow, and medium frequencies. Current optical techniques differ by the number and value of wavelengths employed. Our system uses two wavelengths on either side of the oxy/deoxyhemoglobin isobestic point. A broad range of wavelengths is radiated by the tungsten filament lamps in the probe. All wavelengths other than 760 and 850 nm are filtered out. The probe has been engineered for a photon depth penetration of 2 to 3 cm.[9] The actual photon path length is usually much greater than this, with the average path length between 5 and 10 cm. Recent measurements indicate that with the Runman device, the average path length of the NIR light is approximately 70 to 80 mm, with an average penetration depth of 25 to 30 mm. This depth reaches the muscle layer and thus provides an estimate of muscle oxygenation.[10]

Near infrared absorption changes in the muscle reflect changes in the oxygenation of the microvasculature, i.e., tissue oxygenation at the level of small blood vessels, capillaries, and intracellular sites of oxygen uptake. Differences in absorption changes between large and small blood vessels are unlikely to be observed primarily due to Beers law because photons are unlikely to emerge from arteries and veins. Given an approximately 8 m*M* blood concentration with an extinction coefficient of 1 mM^{-1} cm^{-1}, in a 1-mm diameter vessel, absorbance would be 0.8. Thus, only 10% of the light photons impinging upon a 1-mm artery would survive absorption. Similarly, small reflectance values would be obtained. In contrast, photon transit through a single blood cell in tissue would absorb only a few percent per red blood cell and thus many passages through the capillary, arteriolar, and venous bed are possible. Therefore, successful photon pathways in muscle will proceed through minimum absorbers, i.e., arterioles, capillaries, and venules. Near-infrared absorption changes therefore reflect primarily these small blood vessels.[10]

2.1 VALIDATION

Several studies have been performed to validate the use of this technology in both animal and human experiments. In animal studies it has been shown that the differential absorption between 760 and 800 nm of light (760 to 800 nm absorption) measured from the surface of the exercising canine gracilis muscle was correlated with venous hemoglobin oxygen saturation.[7] Other investigators have demonstrated that near infrared parameters measured from intact feline hindlimb muscle change rapidly in response to progressive oxygen deprivation and correlate with changes in blood flow and oxygen consumption of the hindlimb.[11] Linear relationships with 760 to 800-nm absorption with venous hemoglobin saturation of the sagittal sinus of the brain have also been demonstrated.[12] Finally, a strong linear relationship between 760 to 850-nm absorption and deep vein oxygen saturation of the forearm during exercise has been shown in man.[10]

In a recent study Costes[13] compared near infrared spectroscopy of the vastus lateralis muscle during steady-state bicycle exercise and femoral venous oxygen saturation in 6 normal subjects. During steady-state testing in the normoxic state at 80% of maximum VO_2, no change in near-infrared absorption occurred despite a marked decrease in femoral venous oxygenation. During the first part of the steady-state exercise, a transitory decline in near-infrared muscle oxygenation was observed. These same investigators did observe a progressive fall in near infrared muscle oxygenation during incremental bicycle exercise. The explanation for these findings is unclear. Though the authors stress that great care was taken in placing the probe, variability in probe placement, and/or adipose thickness may have contributed to the variability of their findings.

During both incremental maximal and steady-state exercise under hypoxic conditions, near-infrared muscle oxygenation decreased progressively. Femoral venous oxygen saturation was correlated with near infrared muscle oxygenation during hypoxia. The authors speculate that changes in myoglobin desaturation may be contributing to the near infrared absorption changes observed in the hypoxic versus normoxic exercise.

The contribution of skin blood flow to the 760 to 850-nm absorption changes has also been investigated in normal subjects by simultaneous measurement using laser flow Doppler and near infrared spectroscopic recordings. Skin blood flow was enhanced by immersion in hot water. Changes in skin blood flow but not 760 to 850 nm absorption were noted in all subjects.[10] Similarly, Hampson[14] obtained simultaneous near infrared recordings of skin folds and muscle in an ischemic forearm. The overlying skin signal contributed minimally to the near infrared muscle signals in that study. These results probably reflect the small volume of skin relative to muscle being sampled by the optical light guides.

Changes in near infrared absorbency changes during pharmacological interventions at rest and during forearm exercise in man have also been studied.[10] Forearm blood flow measurements were quantitated using venous plethysmography. Intraarterial infusions of nitroprusside and norepinephrine were selected as potent vasodilator and vasoconstrictor agents by which to acutely alter muscle perfusion. Absorption changes of 760 to 850 nm paralleled alterations in limb perfusion both at rest and with exercise. The percent oxygenation increased with nitroprusside (NP) and decreased with norepinephrine both at rest and with exercise.

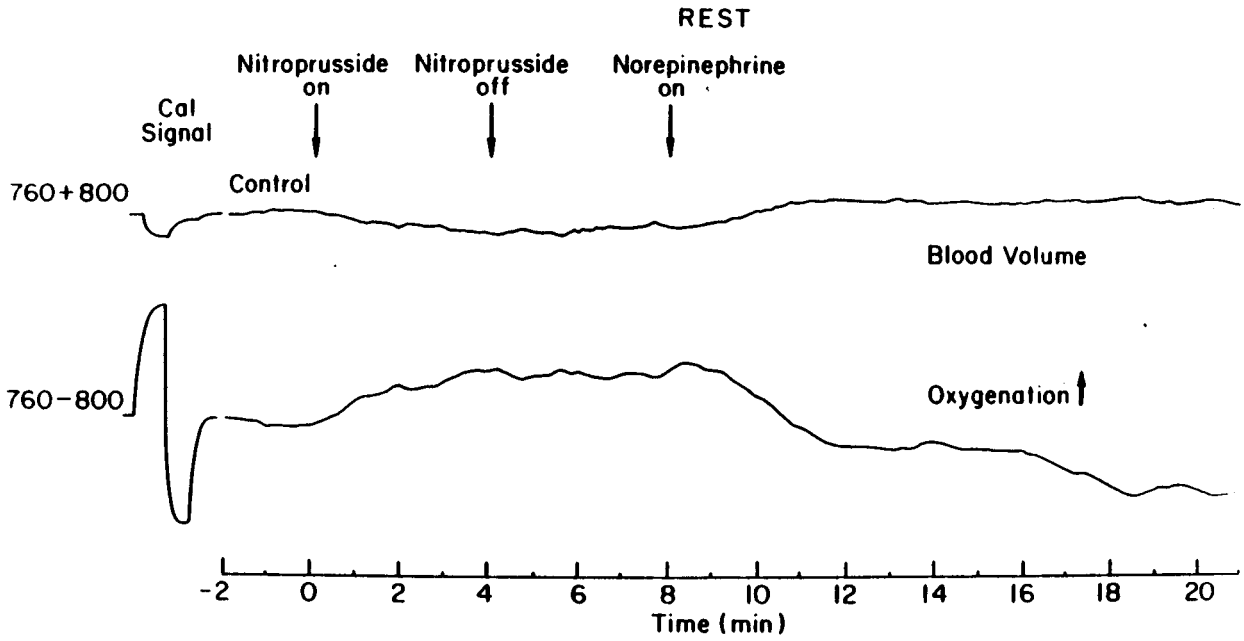

Fig. 1 Near-infrared tracings at rest in the control state and during nitroprusside and norepinephrine infusions. The lower curve depicts the difference signal (760 to 800 nm) and muscle oxygenation. With the nitroprusside infusion, hyperoxygenation is observed and with the norepinephrine infusion deoxygenation is seen (NP, nitroprusside; NE, norepinephrine). (From Ref. 10 with permission.)

Figure 1 illustrates the near infrared absorption changes during these infusions. Limb perfusion assessed by venous plethysmography at rest and with exercise tended to increase with nitroprusside and to decrease with norepinephrine. Absorption changes of 760 to 850 nm provided more consistent changes than did venous plethysmography. As venous plethysmography assesses total limb blood

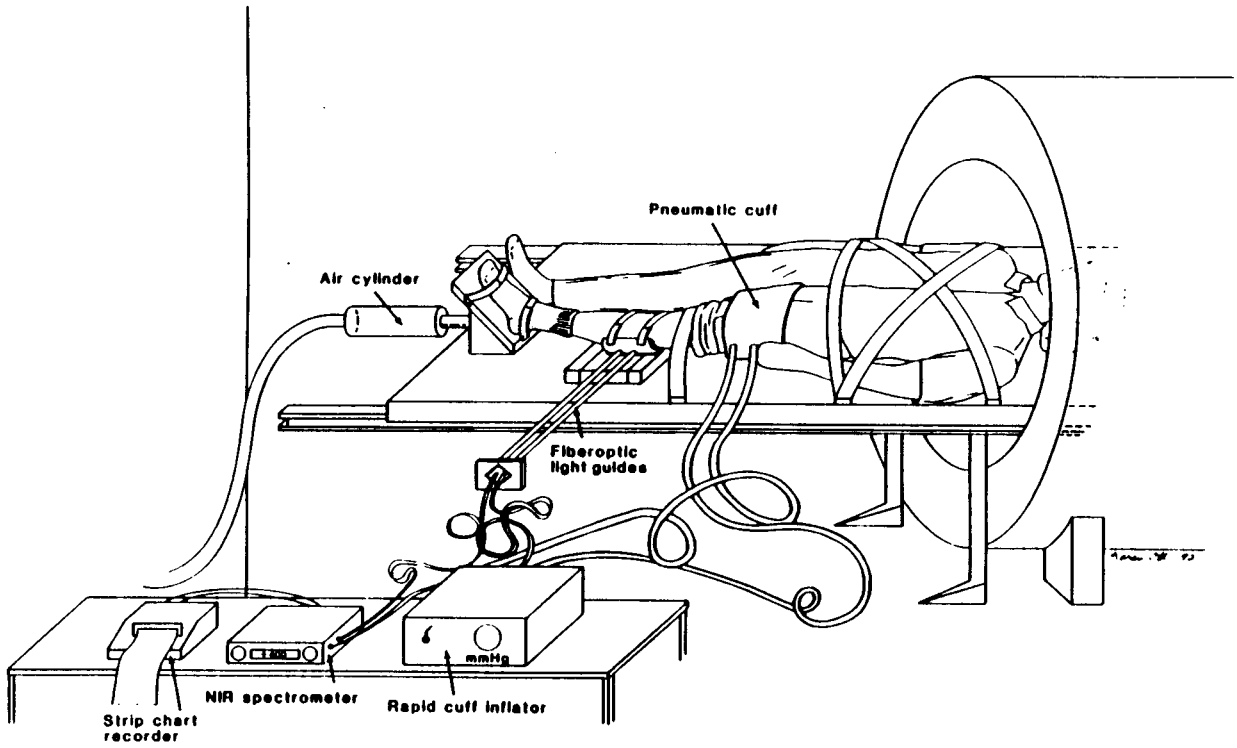

Fig. 2 Simplified schematic of ^{1}H magnetic resonance spectroscopy apparatus interfaced with specially designed nonmagnetic fiber optic light guides of the near-infrared spectrometer. (From Ref. 18 with permission.)

flow, including skin blood flow, near infrared spectroscopy has the advantage of providing localized data for skeletal muscle oxygenation and, indirectly, blood flow.

Edwards[15] varied inspired oxygen concentrations to calculate hemoglobin flow through an organ by NIRS by using the Fick principle. Resting forearm blood flow was measured by venous occlusion plethysmography. Values of hemoglobin flow derived by near infrared spectrometry and resting forearm blood flow measured by plethysmography were closely correlated.

Finally, the contribution of myoglobin to the 760 to 800-nm absorption was assessed using ^{1}H magnetic resonance spectroscopy to detect deoxygenated myoglobin signals at rest and during calf exercise in four subjects. In early work, it was thought that myoglobin as well as hemoglobin contributed significantly to muscle near-infrared light absorption. However, animal studies from this laboratory[7] and by Seiyama, Hazeki, and Tamura[16] suggest that almost all of the absorption is from hemoglobin. In an isolated canine gracilis muscle preparation, we monitored near-infrared absorption during progressive pacing before and after treatment with ethyl hydrogen peroxide. Treatment with this chemical converts myoglobin to its ferrous form, which does not undergo desaturation. Ethyl hydrogen peroxide treatment did not affect the tissue–venous blood relationship.[7]

^{1}H proton spectroscopy has been used to monitor the formation of deoxymyoglobin in man. Proton resonances from oxygenated myoglobin are usually concealed under the water peak. However, with deoxygenation the electron spin of the ferrous ion changes from a low to a high spin state. A paramagnetic shift occurs, making protons from deoxygenated myoglobin visible at approximately 70 ppm from the water peak.[10,17,18] Thus, *in vivo* monitoring of deoxymyoglobin is possible. Previous studies have demonstrated the detection of deoxygenated myoglobin in the resting ischemic human forearm muscle, as well as a signal from standard deoxymyoglobin solutions that approximate normal human tissue levels.[17] We interfaced near infrared spectroscopy with the nuclear with the nuclear magnetic system, enabling simultaneous monitoring of hemoglobin and myoglobin deoxygenation as well as 3′P metabolism. Figure 2 illustrates the experimental design. We were able to demonstrate a high degree of hemoglobin deoxygenation without any concomitant myoglobin deoxygenation during exercise in the majority of subjects who performed maximal calf plantarflexion. The major signal from NIR spectroscopy in these subjects appeared to be derived primarily from hemoglobin (Figure 3).[10] In a larger study we again demonstrated that near infrared absorption changes are derived in the majority of subjects from hemoglobin deoxygenation though in some subjects a contribution from myoglobin deoxygenation could not be excluded (Figure 4).[18]

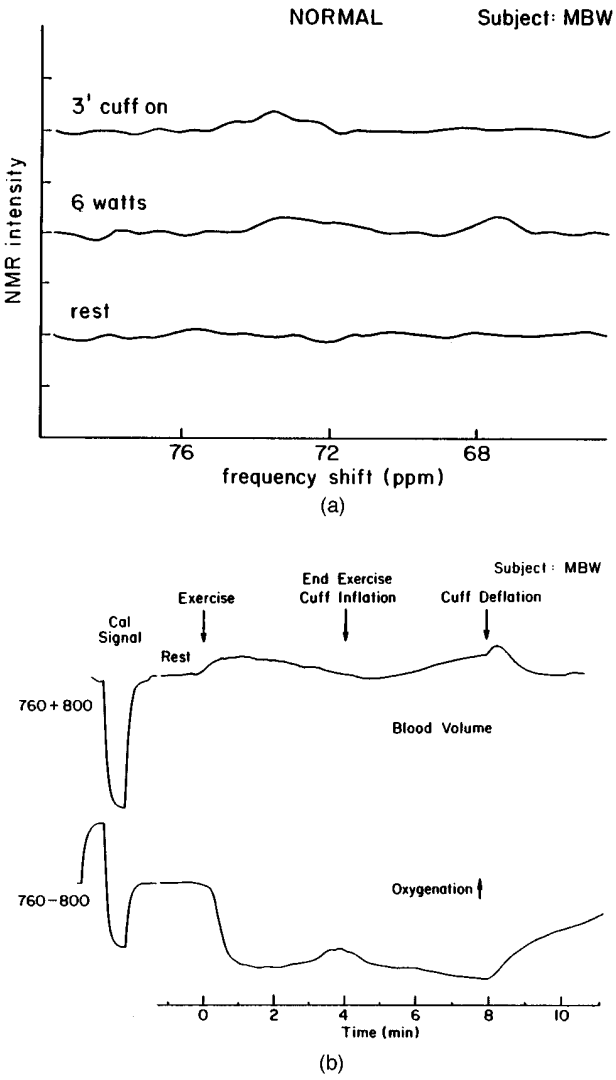

Fig. 3 Deoxymyoglobin proton signals from a calf at rest, during exercise, and with cuff ischemia is shown with simultaneous near-infrared tracing. In subject MBW, no deoxymyoglobin signal is detected. This indicates that the deoxygenation observed from the near-infrared is derived exclusively from deoxygenated hemoglobin. (From Ref. 10 with permission.)

2.2 CLINICAL APPLICATION

We previously measured 760 to 800-nm absorption changes from the vastus lateralis muscle in normal subjects and patients with heart failure during progressive bicycle exercise.[7] To assess maximal muscle deoxygenation at end exercise, we inflated a thigh cuff to suprasystolic pressure. Absorption changes were expressed relative to the full physiologic range noted from rest to the end of thigh cuff inflation. Skeletal muscle oxygenation at the end of exercise was 27 and 26% of the physiologic range in normal and heart failure patients, respectively (Figure 5). At comparable workloads, skeletal muscle

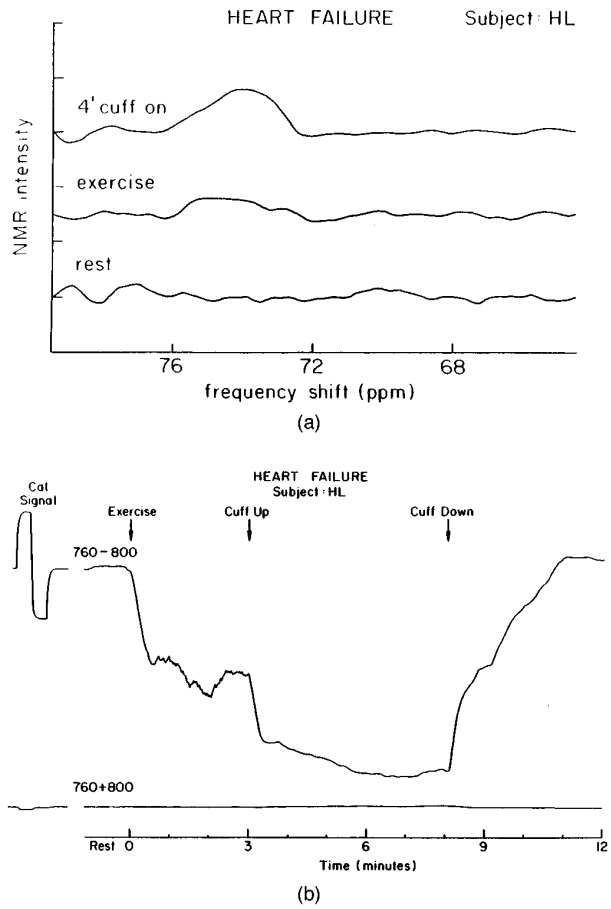

Fig. 4 In subject HL, a deoxymyoglobin signal is observed with cuff ischemia. At the end of exercise, a small-intensity signal is also visible which may represent deoxymyoglobin. With cuff ischemia, the near-infrared absorption further increases; this may represent a contribution from deoxymyoglobin though the majority of the absorption is derived from deoxygenated hemoglobin.

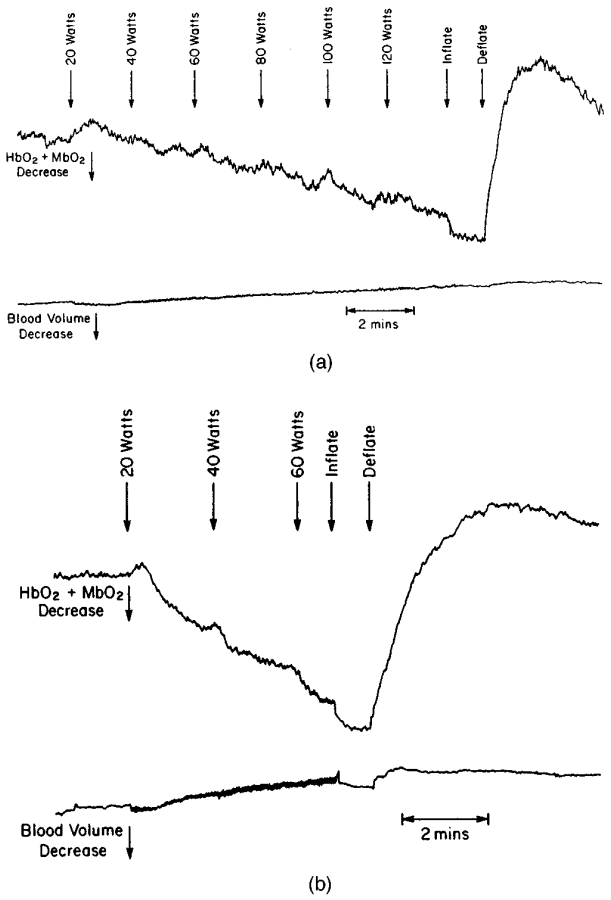

Fig. 5 Near-infrared absorption changes during maximum bicycle exercise in a normal (a) and a heart failure (b) subject. Inflate indicates point of cuff inflation. Deflate indicates point of release. HbO_2+MbO_2 represent the difference signal (760 to 850 nm). (From Ref. 7 with permission.)

oxygenation was significantly less in patients with heart failure, suggesting impaired oxygen delivery in these patients.

In a recent larger study of 65 patients with heart failure, vastus lateralis oxygenation during bicycle exercise was again measured using the commercially available NIR spectrometer (Runman).[19] In 13 of the 65 patients, adequate spectra were not obtained due to technical limitations. Skeletal muscle oxygenation at the end of exercise averaged 35 ±18%. There was significant variability in the skeletal muscle oxygenation data. Other investigators studying normal subjects have noted variability with this device at low workloads. Wasserman used this device to study vastus lateralis muscle oxygenation in 11 healthy subjects during bicycle exercise.[20] He observed a slow decrease in muscle oxygenation during low work rates followed by a more rapid decrease in the range of the anaerobic threshold. A minimum saturation was observed at 80% of maximum VO_2. Wasserman did not use thigh cuff ischemia to achieve a minimal oxygenation, therefore his data cannot be directly compared with our findings. The reproducibility of his findings was assessed in one patient who performed bicycle exercise four times in a 1-month period. NIR absorption changes were very similar at moderate to high workloads but there was much variability at the lower workloads. Our heart failure patients generally achieve only modest work levels; the variability we observed is consistent with his findings.

We have also used near infrared spectroscopy to assess the effect of acute therapeutic interventions on oxygenation of leg skeletal muscle.[21] We examined supine calf plantarflexion before and during dobutamine infusion to determine any improvement in muscle oxygenation. No acute change was observed, which was consistent with our failure to observe any acute muscle metabolic benefit[1,20] as well as with prior reports that demonstrated no acute improvement in overall exercise capacity despite central hemodynamic benefits.[7]

Other investigators have used the near infrared spectrometer to study oxygenation of several differ-

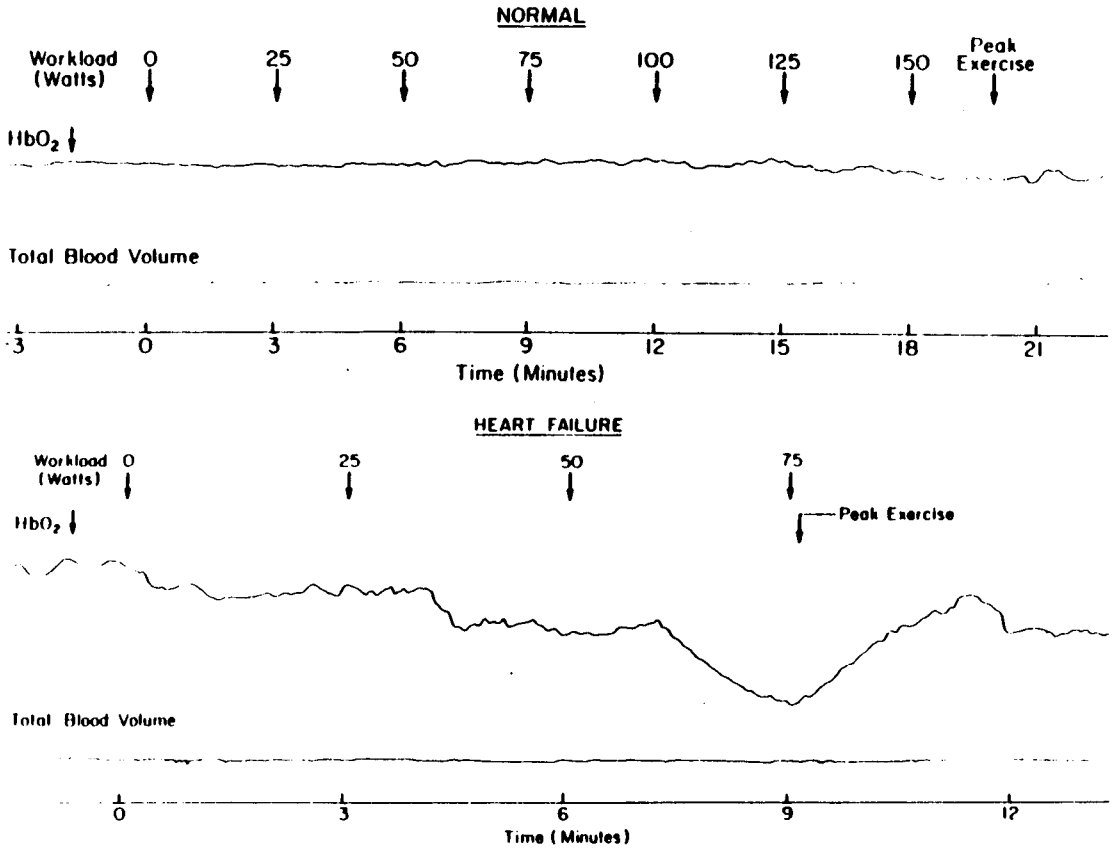

Fig. 6 Accessory respiratory muscle oxygenation during bicycle exercise in normal and heart failure subjects. No deoxygenation occurs in the normal subject whereas progressive deoxygenation is observed in the heart failure subject. (From Ref. 39 with permission.)

ent muscles in patients with different disease states. McCully investigated soleus and gastronemicus muscle oxygenation during plantarflexion and treadmill exercise in healthy elderly patients and those with severe peripheral vascular disease (PVD).[24] McCully focused on the time constant of recovery of oxygen saturation, i.e., the time in seconds required for the NIR absorption to return to baseline levels. He observed a significant prolongation in recovery in the diseased limb rather than in either the normal limb from the patient with PVD or the older normal subject.

Exertional dyspnea as well as fatigue is a prominent symptom in patients with heart failure. Though these are two very different sensations, both dyspnea and fatigue may originate from changes in the skeletal muscle.[25] The work of the ventilatory muscles is significantly increased in patients with heart failure and the ability to adequately perfuse these muscles is decreased. Assessment of respiratory muscle oxygenation has required catherization, with sampling of the drainage from the diaphragmatic veins. This is highly invasive and technically complex.[25] Accessory oxygenation of respiratory muscle during bicycle exercise in normal, chronic heart failure, and mitral stenosis patients has been studied noninvasively using near infrared spectroscopy.[26,27] Progressive deoxygenation of accessory respiratory muscle was observed in heart failure and mitral stenosis patients; no significant absorption changes were observed in the same accessory respiratory muscles of normal subjects (Figure 6). In the patients with mitral stenosis, serial assessment of both accessory respiratory and vastus lateralis oxygenation during bicycle exercise was performed before and 48 h following mitral valvuloplasty.[27] A diminution of respiratory muscle deoxygenation during bicycle exercise was noted in patients 48 h following mitral valvuloplasty and was presumably due to both a decrease in the work of breathing as well as an increase in the ability to increase cardiac output. Simultaneous monitoring of vastus lateralis oxygenation did not demonstrate an acute improvement in muscle oxygenation with valvuloplasty. These findings suggest that the acute therapeutic response from this form of treatment is achieved through increases in respiratory perfusion rather than an increase in leg blood flow.

Following cardiac transplantation, improved oxygenation of respiratory muscle during bicycle exercise has been noted despite the lack of alteration of the tension time index of the diaphragm, i.e., the mechanical work of breathing.[28] Since the sensation

of dyspnea is greatly relieved following cardiac transplantation, the alleviation of this symptom appears to be related to improved respiratory muscle perfusion rather than a reduction in the work of breathing.

2.3 COUPLING OF NEAR INFRARED TO MAGNETIC RESONANCE SPECTROSCOPY

We have coupled ^{31}P magnetic resonance spectroscopy (MRS) to near infrared spectroscopy to provide simultaneous monitoring of cellular metabolism and oxygenation in man. Metabolic abnormalities during exercise have been described in patients with heart failure using ^{31}P MRS, a technology that permits noninvasive monitoring of phosphocreatine, inorganic phosphate, adenosine triphosphate (ATP), and pH in working muscle. During exercise, adenosine diphosphate (ADP) is a key stimulant of mitochrondrial oxidative phosphorylation. The inorganic phosphorus to phosphocreatine (Pi/PCr) ratio correlates closely with ADP concentration. By monitoring changes in the Pi/PCr ratio at different work levels, alterations in the control of oxidative phosphorylation can be detected.[29,30] Exercise also activates glycolysis, producing an increase in intracellular lactate concentration and a decrease in intracellular pH. By monitoring changes in muscle pH during exercise, changes in glycolytic activity can be detected.[31] The metabolic behavior of both the forearm and calf muscle during exercise in patients with heart failure has been examined. Abnormal skeletal muscle metabolism, i.e., reduced oxidative metabolism with an earlier shift to glycolytic metabolism, has been demonstrated in patients with heart failure.[32–38] Specifically, patients with heart failure have a more pronounced increase in the Pi/PCr ratio and a more rapid drop in local pH than normal subjects performing comparable workloads. Recovery analysis of phosphocreatine also demonstrates prolonged recovery times in these patients, again suggesting an abnormality of oxidative metabolism. These abnormalities appear to be independent of total limb perfusion,[33,37,38] histochemical changes,[35] and muscle mass.[36] Whether these metabolic changes result from severe tissue hypoxia due to a maldistribution of blood flow or inability to use available O_2 stores during exercise remains unclear.

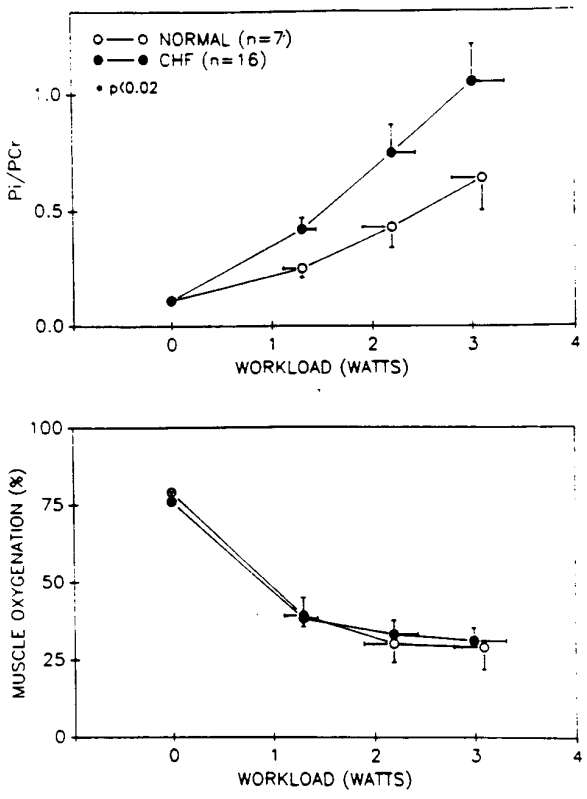

Fig. 7 (a) Correlation of P_i/PCr ratio and workload in normal and heart failure subjects (P<0.02); (b) correlation of muscle oxygenation assessed from 760 to 850-nm absorption with work in normal and heart failure subjects in the (P=NS). All data expressed as mean ±SEM. (From Ref. 10 with permission.)

Simultaneous application of phosphorus (^{31}P), proton (^{1}H), and near infrared spectroscopy provided a unique opportunity to examine muscle metabolism and oxygenation in man. Calf exercise was performed by normal subjects and patients with heart failure.[18] Using this combined approach, we were able to demonstrate that during exercise with minimal cardiovascular stress the metabolic abnormalities observed in patients with heart failure occur despite what appears to be adequate muscle oxygenation (Figure 7). As shown in Figure 7, metabolic abnormalities are present in the heart failure subjects despite similar tissue oxygenation levels. The absence of deoxymyoglobin signal during exercise of the small muscle mass and the normal muscle oxygenation throughout exercise further indicated that the ^{31}P metabolic abnormalities in these patients do not result from inadequate O_2 availability. Prior studies using venous plethysmography had demonstrated similar tissue perfusion between normal and heart failure subjects. However, whether maldistribution of blood flow occurred, resulting in ischemia to exercising muscle, remained unclear. This study excluded this hypothesis and demonstrated that the metabolic changes are not caused by severe tissue hypoxia during exercise of small muscle mass.

Simultaneous application of ^{1}H spectroscopy with near infrared recordings permitted analysis of the differential rates of deoxygenation of hemoglobin and myoglobin. In those subjects who exhibited deoxymyoglobin during calf exercise, hemoglobin and myoglobin oxygenation during exercise was compared. Hemoglobin deoxygenation preceded myoglobin deoxygenation in all subjects. No deoxymyoglobin signal was detected until hemoglobin was at least 70% deoxygenated.[18]

3 CONCLUSIONS

Near infrared spectroscopy is a very promising technique both from a research and a clinical perspective. In both animal and human studies it has been demonstrated to provide a qualitative index of changes in tissue oxygenation. In exercise physiology studies, it provides useful information on regional tissue oxygenation and indirectly on perfusion. Future clinical studies are needed to evaluate if near infrared spectroscopy will be a valuable tool in the assessment of new therapeutic interventions. Additional modifications of the device are needed to provide greater reproducibility of data, flexibility in the penetration depth, and quantitation.

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