Respiratory Muscle Deoxygenation During Exercise in Patients With Heart Failure Demonstrated With Near-Infrared Spectroscopy

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Exertional dyspnea in patients with heart failure may be due, in part, to respiratory muscle underperfusion. Near-infrared spectroscopy is a new technique that permits noninvasive assessment of skeletal muscle oxygenation by monitoring changes in near-infrared light absorption. With use of near-infrared spectroscopy, serratus anterior muscle oxygenation during maximal bicycle exercise was compared in 10 patients with heart failure (ejection fraction $16 \pm 5\%$) and 7 age-matched normal subjects. Oxygen consumption ($\dot{V}O_2$), minute ventilation ($\dot{V}_E$) and arterial saturation were also measured. Changes in difference in absorption between 760 and 800 nm, expressed in arbitrary units, were used to detect muscle deoxygenation.

Minimal change in this difference in absorption occurred in normal subjects during exercise, whereas patients with heart failure exhibited progressive changes throughout exercise consis-

tent with respiratory muscle deoxygenation (peak exercise: normal 3 ± 6, heart failure 12 ± 4 near-infrared arbitrary units, $p < 0.001$). At comparable work loads patients with heart failure had significantly greater minute ventilation and respiratory rate but similar tidal volume when contrasted with normal subjects. However, at peak exercise normal subjects achieved significantly greater minute ventilation and tidal volume with a comparable respiratory rate. No significant arterial desaturation occurred during exercise in either group.

These findings indicate that respiratory muscle deoxygenation occurs in patients with heart failure during exercise. This deoxygenation may contribute to the exertional dyspnea experienced by such patients.

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The mechanism underlying exertional dyspnea remains unclear. One hypothesis is that respiratory muscle underperfusion occurs. Specifically, it has been suggested that the reduced cardiac output that limits blood flow to the limb during exercise also results in respiratory muscle ischemia and, ultimately, respiratory muscle fatigue (1,2). This hypothesis has yet to be tested because no technique has been available to assess respiratory muscle perfusion in humans.

Near-infrared spectroscopy is a new technique originally pioneered in 1959 (3,4) that permits noninvasive assessment of skeletal muscle oxygenation (5–9). This technique relies on the optical properties of hemoglobin. Both oxygenated and deoxygenated hemoglobin absorb light at 800 nm, whereas primarily deoxygenated hemoglobin absorbs light at 760 nm. Therefore, by monitoring the difference in absorption noted at these two wavelengths, it is possible to assess changes in hemoglobin oxygenation normalized for changes in total hemoglobin. The principal limitation of near-infrared spectroscopy is that absolute levels of deoxygenated hemoglobin cannot be determined because the path length of the

reflected light is unknown. Therefore, near-infrared spectroscopy at present can only assess directional changes in muscle oxygenation.

The purpose of the present study was to investigate whether respiratory muscle deoxygenation occurs during exercise in heart failure by using near-infrared spectroscopy. Therefore, we monitored the difference in absorption at 800 and 760 nm over the serratus anterior muscle during maximal bicycle exercise in patients with heart failure and in a group of age-matched control subjects.
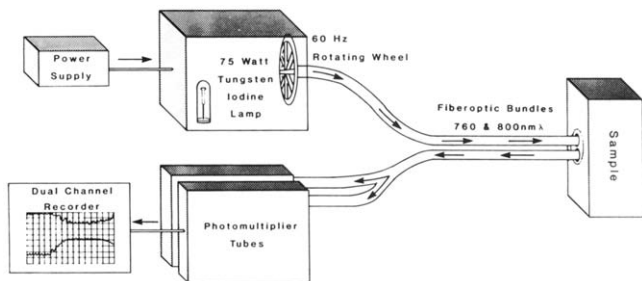
Methods

Study patients. Ten patients with heart failure were studied. All patients were receiving digoxin and diuretic agents, nine were receiving angiotensin-converting enzyme inhibitors and one was also receiving an investigational phosphodiesterase inhibitor. All patients were nonsmokers with no history of lung disease, kyphoscoliosis or recent respiratory infection; those limited by angina or claudication were excluded from the study. Average age ($\pm$ SD) was 57 ± 10 years. The etiology of heart failure was coronary artery disease in six patients and dilated cardiomyopathy in the remaining four. Ejection fraction averaged $16 \pm 5\%$ and peak exercise oxygen consumption ($\dot{V}O_2$) was 13.4 ± 3.4 ml/kg per min.

Seven age-matched (49 ± 6 years) control subjects were

also studied. Peak exercise VO_2 of this group averaged 30.0 ± 3.9 ml/kg per min. All control subjects were nonsmokers with no known medical problems.

The protocol was approved by the Committee on Studies Involving Human Beings at the University of Pennsylvania in January 1989. Written informed consent was obtained from all subjects.

Near-infrared spectral analysis. The near-infrared spectrometer comprises a light source, 60-Hz rotating wheel, fiber-optic bundles and photomultiplier tubes (Fig. 1). A 75-W tungsten iodine light provides a light source that is filtered at 760 and 800 nm with use of a 60-Hz rotating wheel that allows time sharing of the light source. The 60-Hz rotating wheel generates a decoding signal for dividing the photomultiplier tube output between the 760 and 800 nm amplifier channels. Light is transmitted to the tissue through a fiber-optic light guide. Reflected light is delivered with a second fiber-optic light guide to a photomultiplier tube. The maximal photon path length is approximately 2.6 cm [10]. Sampling volume is somewhat variable because the light pulse propagates in multiple elliptic trajectories. The depth of the penetration of the light is $\leq 50\%$ of the distance between the light probes [10]. For the current apparatus this would represent a depth of 8 to 10 mm.

Changes in absorption at 800 nm are used to assess changes in total hemoglobin concentration and thus in vivo blood volume. The difference in absorption between 800 and 760 nm is used to assess hemoglobin oxygen saturation. Myoglobin also absorbs light at these wavelengths. However, previous studies from this [9] and other [11] laboratories suggest that the predominant signal is from hemoglobin. We have previously validated this system in the gracilis muscle of the dog. The difference in light absorption at 760 versus 800 nm correlated closely with venous hemoglobin oxygen saturation when the isolated canine gracilis muscle was stimulated to contract at 0.25 to 5 Hz. Absorbency changes were unchanged with the spectroscopy probe adherent to the overlying skin or directly opposed to the muscle [9]. We subsequently used this technique to monitor

vastus lateralis muscle oxygenation during upright bicycle exercise in normal subjects and patients with heart failure [9].

All studies were performed with use of the same gain settings on the spectrometer. Absorption changes were then expressed as arbitrary units of deviation from a stable baseline. Each arbitrary unit represents a 2 mm deflection on the recorder tracings. The higher the arbitrary unit, the greater the muscle deoxygenation. A negative value represents hyperoxygenation. The 800-nm absorption curve was used to assess total hemoglobin concentration and thus blood volume.

Protocol. Standard pulmonary function tests were obtained in the patients with heart failure on a day separate from the exercise study. All exercise was performed in the fasting state. On the patients' arrival in the exercise laboratory, near-infrared fiber-optic light guides were placed on the sixth intercostal space, anterior axillary line over the serratus anterior muscle. This superficial muscle originates from the anterior medial aspect of the first eight ribs and inserts into the entire medial border of the scapula. One of its functions is to serve as an accessory inspiratory muscle to further elevate the ribs during marked respiratory distress.

The subjects were then positioned upright on a Monarch exercise bicycle and connected with a three-way Hans Rudolph valve to a SensorMedics metabolic cart for respiratory gas analysis. Arterial saturation was monitored using an Ohmeda ear oximeter. Blood pressure was measured by cuff sphygmomanometer. The electrocardiogram (ECG) was monitored continuously. After a 3-min rest period, subjects performed maximal symptom-limited bicycle exercise. Exercise was begun at a work load of 20 W that was increased by 20-W increments every 2 min to a symptom-limited maximum. Cuff blood pressure was measured at the end of

Table 1. Pulmonary Function Tests in Nine Patients With
Heart Failure

	Actual Value	Predicted
Forced vital capacity (liters)	3.5 ± 0.8	87 ± 19%*
FEV1 (liters)	2.6 ± 0.5	83 ± 14%*
FEV1/FVC	76 ± 8%	
Maximal voluntary ventilation (liters)	109 ± 27	
Maximal inspiratory pressure (torr)	46 ± 22	>56 ± 4
Maximal expiratory pressure (torr)	95 ± 33	>95 ± 11

*These values indicate percent of the predicted values. FEV1 = forced
expiratory volume in 1 s; FVC = forced vital capacity.

each work load. Respiratory gases, arterial saturation, heart
rate and near-infrared spectra were monitored throughout
exercise.

In five patients with heart failure, hyperventilation was
performed for 30 s and near-infrared absorbency changes
were recorded. To determine if the latter changes noted over
the serratus muscle during exercise were due to generalized
vasoconstriction, on a separate day two normal subjects and
three patients with heart failure underwent maximal bicycle
exercise with the near-infrared light probe placed over an
immobilized forearm muscle (brachioradialis).

Statistical analysis. Data from patients with heart failure
and normal subjects at rest and during exercise were com-
pared with Student's nonpaired t test. The relations between
variables were examined by linear regression analysis. A
p value < 0.05 was considered significant. All data are
expressed as mean values ± SD.

Results

Pulmonary function tests (Table 1). Because results of
pulmonary function tests are dependent on age, gender and
race, mean predicted value or percent, or both, is included in
Table 1 along with a normal range. Lung volumes (that is,
forced vital capacity [FVC], expiratory flow rates (forced
expiratory volume in 1 s [FEV1]), the ratio FEV1/FVC and
maximal voluntary ventilation were normal. Maximal in-
spiratory pressure measured as maximal mouth pressure
generated during forced inspiration against a pressure gauge
tended to be low.

Table 2. Rest and Peak Exercise Response in 7 Normal Subjects
and 10 Patients With Heart Failure

	Rest		Exercise	
	Normal	HF	Normal	HF
Heart rate (beats/min)	79 ± 6	93 ± 11*	156 ± 11	131 ± 16*
Mean blood pressure (mm Hg)	93 ± 8	87 ± 5	133 ± 5	111 ± 15*
VO₂ (ml/kg per min)	4.6 ± 0.8	4.3 ± 0.7	30.0 ± 3.9	13.4 ± 3.4*
Respiratory quotient	0.8 ± 0.1	0.8 ± 0.1	1.2 ± 0.1	1.2 ± 0.2
Arterial saturation (%)	97 ± 1	96 ± 2	94 ± 2	93 ± 6

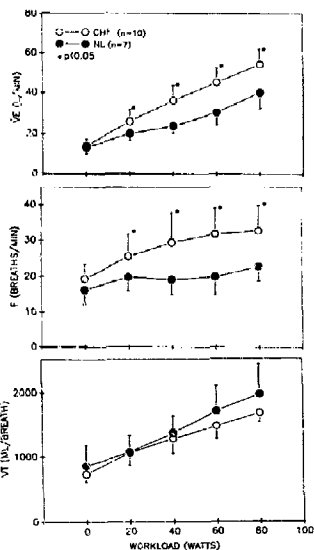*p < 0.001, normal subjects versus patients with heart failure (HF).

Figure 2. Ventilatory response at rest and during exercise in pa-
tients with congestive heart failure (CHF) and in normal subjects
(NL). F = respiratory rate; V_E = minute ventilation; VT = tidal
volume. *p < 0.05, normal subjects versus patients with heart
failure.

Exercise response (Table 2, Fig. 2 and 3) At rest, patients
with heart failure had a significantly higher heart rate but
values for mean arterial blood pressure, oxygen consump-
tion, respiratory quotient and arterial saturation were com-
parable with those of the normal subjects. At peak exercise,
heart rate, mean arterial blood pressure and oxygen con-
sumption were significantly reduced in patients with heart
failure as compared with normal subjects. Both groups
achieved a comparable respiratory quotient, with average
values of 1.20, consistent with maximal or near-maximal
exertion. Arterial saturation at peak exercise was also com-
parable in both groups; neither group demonstrated signifi-
cant arterial desaturation from rest to peak exercise.

At rest, minute ventilation, respiratory rate and tidal
volume were not significantly different in the two groups
(Fig. 2 and 3). At comparable exercise work loads, minute
ventilation and respiratory rate were significantly greater in
patients with heart failure. However, this difference was
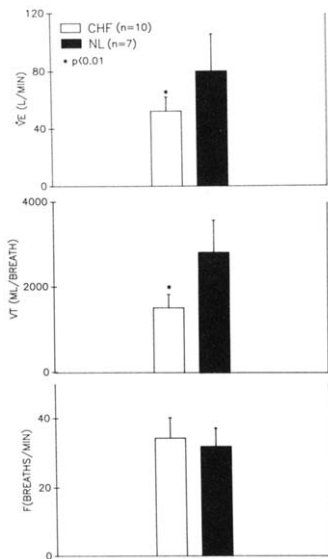primarily due to an increase in respiratory rate because

Figure 3. Maximal ventilatory response. *p < 0.05, normal subjects versus patients with heart failure. Abbreviations as in Figure 2.

values for tidal volume of the groups at each work load were comparable (Fig. 2). At peak exercise normal subjects achieved significantly greater minute ventilation and tidal volume with a similar respiratory rate (Fig. 3).

Near-infrared spectral changes (Fig. 4 to 6). In the normal subjects, the difference in absorption at 760 and 800 nm did not change significantly until peak exercise when a small increase in absorption was noted, consistent with muscle deoxygenation (Fig. 4). In Figure 5 the upper curve corresponds to the difference in absorption at 760 and 800 nm; a fall in this curve represents a decrease in oxygenation. In this normal subject only minimal respiratory muscle deoxygenation was noted at peak exercise. The lower curve corresponds to 800 nm absorption. At this wavelength the oxygenated and deoxygenated forms of hemoglobin exhibit similar absorption coefficients. Therefore, absorption of light at this wavelength is proportional to the total amount of hemoglobin. In this example the blood volume remains constant throughout exercise.

In the patients with heart failure, progressive changes in the difference in absorption at 760 and 800 nm were noted (Fig. 4). At all exercise loads and at peak exercise, absorp-
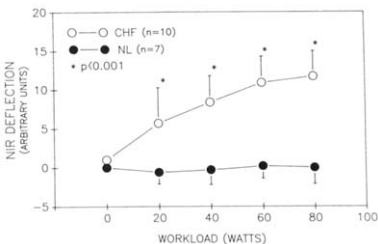

Figure 4. Changes in the difference between absorption at 760 and 800 nm (NIR deflection) during exercise in heart failure and normal subjects. *p < 0.001, normal subjects versus patients with heart failure. NIR = near-infrared spectroscopy; other abbreviations as in Figure 2.

tion changes were significantly greater than in the normal subjects (peak exercise: normal 3 ± 6; heart failure 12 ± 4 near-infrared arbitrary units; p < 0.001). With the onset of exercise (Fig. 6), this patient with heart failure developed a progressive decrease in the difference between absorption at 760 and 800 nm peaking at maximal exercise and recovering slowly after cessation of exercise; absorption at 800 nm, that is, total blood volume, remained constant at rest and throughout exercise.

Only two patients were limited by dyspnea during exercise. Both patients exhibited a rapid marked decrease in the difference between absorption at 760 and 800 nm. However, other patients limited primarily by leg fatigue displayed similar levels of deoxygenation. Only one normal subject was limited by dyspnea; he exhibited the most marked deoxygenation of the normal group.

After maximal exercise and return of the curve of the difference between absorption at 760 and 800 nm to baseline, five patients with heart failure hyperventilated for 30 s with the near-infrared light guides over the serratus muscle. Ventilation averaged 62 ± 14 liters/min. No deoxygenation was associated with the difference between absorption at 760 and 800 nm, with −1 ± 1 arbitrary unit deflection at the end of hyperventilation. In two normal subjects and three patients with heart failure, no significant deoxygenation of the immobilized brachioradialis muscle was noted at maximal exercise (normal subjects −0.5 ± 3; patients with heart failure 0.3 ± 1 near-infrared arbitrary units; p = NS).

Relation of near-infrared spectral changes and ventilatory variables. No significant correlations in patients with heart failure could be drawn between the maximal change in difference between absorption at 760 and 800 nm and peak minute ventilation, respiratory rate, peak tidal volume, maximal inspiratory pressure or peak VO_2 (all r < 0.6; p = NS). Thus, the level of respiratory muscle deoxygenation did not appear to be a simple function of respiratory muscle strength or respiratory rate.
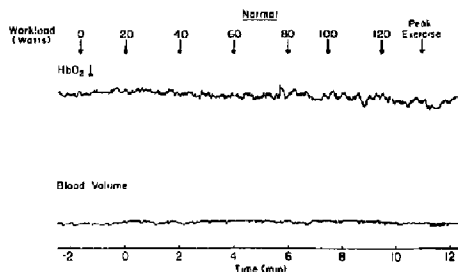
Figure 5. Near-infrared absorption changes of the serratus anterior muscle at rest and during exercise in a normal subject. Upper curve = difference in absorption at 760 and 800 nm; lower curve = absorption at 800 nm; NIR = near-infrared spectroscopy; HbO₂ = oxygenated hemoglobin; ↓ = decrease.

For all subjects a weak negative correlation was observed between maximal 760 to 800 nm absorption and peak $\dot{V}O_2$ (r = −0.5, p < 0.05). This was probably artifactual because the data for patients with heart failure and normal subjects were clustered at opposite extremes.

Discussion

Mechanisms of exertional dyspnea. Exertional dyspnea is a frequent symptom in patients with heart failure, but the mechanism responsible for it is uncertain. One hypothesis is that dyspnea is caused by a heightened central neurologic drive due to stimulation of pulmonary receptors by a rapid rise in pulmonary capillary wedge pressure (12). However, several studies (13–16) in patients with chronic heart failure have failed to demonstrate a direct relation between dyspnea and pulmonary capillary wedge pressure both at rest and with exercise. Moreover, breathlessness persists after vagal blockade (16) and heart-lung transplantation, indicating that neural input from the lung parenchyma is not necessary for the sensation of dyspnea to be experienced.

An alternative mechanism for exertional dyspnea in heart failure is respiratory muscle underperfusion (1,2). During exercise, patients with heart failure exhibit a reduced cardiac output and hypoperfusion of the exercising limb muscles. Concurrently, such patients also demonstrate an excessive ventilatory response (13–16,17), decreased lung compliance (18–21) and increased airflow resistance. These factors increase the work of breathing. A limited ability to increase perfusion of the respiratory muscles during exercise, coupled with the higher work of breathing, may result in respiratory muscle ischemia with consequent respiratory muscle fatigue and dyspnea.

This hypothesis has not yet been investigated in humans because it has not been possible to monitor respiratory muscle perfusion. However, respiratory muscle fatigue presumably for ischemia has been noted (1) in an experimental model of cardiogenic shock produced by tamponade. In this canine model, diaphragmatic muscle performance and perfusion were monitored during mechanical ventilation and spontaneous breathing. Death occurred in spontaneously breathing dogs as a result of respiratory muscle failure
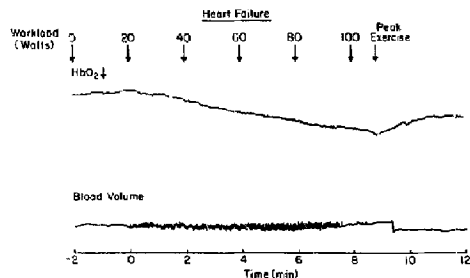

Figure 6. Near-infrared absorption changes of the serratus anterior muscle at rest and during exercise in a patient with heart failure. Abbreviations as in Figure 5. There is motion artifact in the lower curve during recovery.

followed by cardiac arrest. Preterminal increased neural excitation to the diaphragm occurred, implying an impairment of the contractile process. Septic (22) and hemorrhagic shock (23) also produce progressive respiratory muscle fatigue. In humans, evidence that respiratory muscle fatigue from underperfusion can occur is suggested by observations that peripheral venous lactate increases during exhaustive progressive incremental resistive breathing (24) and during asthmatic attacks (25).

Deoxygenation of respiratory muscles during exercise. In this study we sought to determine if deoxygenation of respiratory muscles during exercise occurs in patients with heart failure by applying a new technology, that is, near-infrared spectroscopy (5). This technique relies on the optical properties of hemoglobin. The principal limitation of near-infrared spectroscopy is that the path length of the reflected light is unknown. Therefore, near-infrared spectroscopy can only provide qualitative data.

To characterize respiratory muscle oxygenation, we monitored serratus anterior muscle oxygenation. This muscle serves as an accessory inspiratory muscle to elevate the ribs during marked respiratory effort. Our choice of the serratus anterior muscle was mandated by technical restraints. Ideally, diaphragmatic oxygenation should be measured because the diaphragm is the primary muscle of respiration. At present, assessment of diaphragmatic blood flow is technically impossible. Nevertheless, we believed that evaluation of the serratus anterior muscle deoxygenation would be useful because fatigue of the diaphragm and accessory respiratory muscles occurs simultaneously during incremental resistive breathing in humans, as assessed with transcutaneous electromyelograms (26).

Before performing exercise studies, we obtained pulmonary function tests on all of the patients to exclude intrinsic lung disease. Lung volumes and expiratory flow rates were normal. Sullivan et al. (15) reported similar findings in patients with chronic heart failure. However, a mild reduction in maximal static inspiratory pressure was noted, suggesting reduced respiratory muscle strength. Previous investigations (27) in patients with mitral valve disease have also demonstrated a reduction in maximal static inspiratory pressure. Reduction in maximal inspiratory pressure has been correlated with the perceived intensity of dyspnea during exercise (16).

Ventilatory abnormalities versus respiratory muscle deoxygenation. Despite the relatively minimal ventilatory abnormalities at rest, we noted marked abnormalities of ventilation during exercise, which are consistent with findings of previous investigators (13-15,17). These changes included significantly greater minute ventilation and respiratory rate but similar tidal volume in patients with heart failure at comparable exercise work loads when contrasted with normal subjects. These ventilatory abnormalities were associated with respiratory muscle deoxygenation, as evidenced by near-infrared absorbance changes. During submaximal exercise, control subjects displayed virtually no change in

the difference between absorption at 760 and 800 nm; at peak exercise only a small change in absorption occurred. In contrast, patients with heart failure exhibited a progressive increase in difference between absorption at 760 and 800 nm, consistent with an increasing quantity of deoxygenated hemoglobin in the muscle.

There are several possible explanations for these findings. The most likely hypothesis is that perfusion of the respiratory muscles is reduced in patients with heart failure consistent with prior observations that blood flow to working limb muscles is impaired (9). With hyperventilation, patients with heart failure achieved minute ventilation comparable with that at peak exercise. However, serratus anterior deoxygenation did not occur during hyperventilation. This finding suggests that during maximal exercise, it is the inability to increase cardiac output to the respiratory muscles coupled with the increased work of breathing that underlie the observed absorbency changes.

Differences in recruitment of the serratus anterior muscle may have accounted for the different near-infrared absorbency patterns observed. In normal subjects accessory muscles are generally not recruited until minute ventilation exceeds 50 liters/min (28). Our normal subjects achieved a peak minute ventilation of 80 liters/min, suggesting that accessory muscle recruitment did occur. However, in our patients an immediate deoxygenation of the serratus anterior muscle was noted. This may reflect an early recruitment of this accessory muscle to assist in the higher work of breathing, an alternate respiratory pattern, or both. In patients with chronic asthma, an increased inspiratory activity of the serratus anterior muscle during both quiet and forced breathing has been observed in electromyograms (29). Despite possible differences in muscle recruitment, the dramatic difference between the study groups in respiratory muscle deoxygenation at peak exercise implies hypoperfusion. Alternatively, our findings may be a manifestation of generalized vasoconstriction that occurs during exercise. This hypothesis is unlikely because application of the near-infrared probe over immobilized forearm muscle during graded bicycle exercise in both normal subjects and patients with heart failure revealed no significant deoxygenation at this gain setting.

Clinical implications. To what extent respiratory muscle deoxygenation contributes to exertional dyspnea in heart failure cannot be established from this descriptive study. Future studies are warranted to define the relation of respiratory muscle deoxygenation to muscle fatigue and dyspnea. Nevertheless, our observations suggest that such deoxygenation may play an important role. The serratus anterior muscle is a relatively minor accessory respiratory muscle that is normally activated only at high ventilatory levels. Major increases in serratus anterior deoxygenation were observed in patients even at low ventilatory levels. Such a finding suggests that deoxygenation of the diaphragm is likely to be more intense because this muscle is activated more extensively during exercise and therefore requires

substantially greater blood flow than the serratus anterior muscle.

Application of near-infrared spectroscopy to the respiratory muscles has far-reaching research and clinical implications. This technique provides the first tool to study respiratory muscle perfusion in humans. Near-infrared spectroscopy could be used to evaluate the efficacy of mechanical ventilation, drug therapy, or both. Pharmacologic interventions designed to improve respiratory muscle perfusion may ameliorate respiratory muscle deoxygenation and fatigue. In patients with pulmonary disease, aminophylline has been demonstrated to improve perfusion, contractility and endurance of the diaphragm (30–32). The subjective improvement without evidence of bronchodilation in asthmatic patients taking methylxanthines may result from the effects of these agents on diaphragmatic function. Analogously, amrinone has been shown to increase diaphragmatic blood flow (33). Drugs such as amrinone may derive therapeutic efficacy in patients with heart failure not only through vasodilation and cardiac inotropic activity, but also through improved perfusion of respiratory muscles.

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