# Severe Exercise-Induced Hypoxemia

Chris Garvey FNP MSN MPA, Brian Tiep MD, Rick Carter PhD MBA, Mary Barnett RN,
Mary Hart RRT FAARC, and Richard Casaburi PhD MD



**Exercise training is an essential component of pulmonary rehabilitation and is associated with improved function and other important outcomes in persons with chronic lung disease. A subset of pulmonary rehabilitation patients experience hypoxemia that may occur or worsen with exercise. For the purpose of this review, severe exercise-induced hypoxemia is defined as an $S_{pO_2}$ of < 89% during exercise, despite use of supplemental oxygen delivered at up to 6 L/min. There is a paucity of evidence and clinical guidelines that address assessment and management of this important manifestation of chronic lung disease. This review presents background of this topic and suggests strategies for assessment, management, and safety measures for patients with severe exercise-induced hypoxemia.** *Key words: severe exercise-induced hypoxemia; pulmonary rehabilitation; exercise.*
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## Introduction

Exercise training is an essential component of pulmonary rehabilitation (PR) and is associated with improved function and other important outcomes in persons with

Ms Garvey is affiliated with the Pulmonary Rehabilitation Program, Seton Medical Center, Daly City, California, and with the Sleep Disorders Center, University of California–San Francisco, San Francisco, California. Dr Tiep is affiliated with the Pulmonary Rehabilitation Program, City of Hope National Medical Center, Duarte, California. Dr Carter is affiliated with the Integrative Physiology Laboratory, Lamar University, Beaumont, Texas. Ms Barnett is affiliated with the Respiratory Disease Management Institute, Pomona, California. Ms Hart is affiliated with the Martha Foster Lung Care Center, Baylor University Medical Center, Dallas, Texas. Dr Casaburi is affiliated with the Los Angeles Biomedical Research Institute, Harbor-University of California–Los Angeles Medical Center, Torrance, California.

Ms Garvey has disclosed relationships with Boehringer Ingelheim, Pfizer, and Breathe Technologies. Dr Tiep has disclosed relationships with Chad Therapeutics/Inovo, Nonin Medical, Hill Rom, Air Sep, Invacare, and Rotech. Ms Hart has disclosed relationships with GlaxoSmithKline and Monaghan Medical. Dr Casaburi has disclosed relationships with Forest, Novartis, Breathe Technologies, Theratech General, Boehringer-Ingelheim, Medtronics, Respironics, Actelion, Pfizer, Astra Zeneca, and Inogen. The other authors have disclosed no conflicts of interest.

Correspondence: Chris Garvey FNP MSN MPA, Pulmonary Rehabilitation, Seton Medical Center, 1900 Sullivan Avenue, Daly City CA 94015. E-mail: chrisgarvey@dochs.org.

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chronic lung disease. A subset of PR patients experience hypoxemia that may occur or worsen with exercise. For the purpose of this review, severe exercise-induced hypoxemia (SEIH) is defined as an $S_{pO_2}$ of $< 89\%$ during exercise, despite use of supplemental oxygen delivered at up to 6 L/min. The definition includes this level of desaturation being sustained for a minimum of one minute, regardless of the patient's baseline $S_{pO_2}$. Previous definitions have been similar; Dempsey and Wagner describe mild exercise-induced hypoxemia as an arterial oxygen saturation of 93–95% (or 3–4% less than at rest), moderate exercise-induced hypoxemia as 88–93%, and SEIH as $< 88\%$.[1] There is a paucity of evidence and clinical guidelines that address assessment and management of this important manifestation of chronic lung disease. This review presents background of this topic and suggests strategies for assessment, management, and safety measures for patients with SEIH.

The incidence of hypoxemia, its severity and occurrence during exercise in chronic lung disease, is unknown. Additionally, there is no current standard of care or state of the art for evaluation and management of SEIH. Based on a survey discussed later in this review, patients with this complex clinical disorder are routinely cared for in PR settings, and PR clinicians are faced with the need to evaluate, oxygenate, and, in most cases, provide safe, effective exercise programs. Evaluation and management should be based on a systematic approach to determining underlying cause(s) of SEIH, and developing and enlisting appropriate management strategies. If the patient is clinically stable, providing progressively incremented, monitored, supervised exercise in a PR program is reasonable as long as hypoxemia is controlled and the patient demonstrates both objective and subjective clinical stability and exercise tolerance.

## Etiology of Hypoxemia

Evaluation and treatment of SEIH begins with understanding the underlying cause(s) of hypoxemia and the impact of exercise on underlying lung disease(s). Hypoxemia may result from ventilation-perfusion mismatch, diffusion defect, right-to-left shunt, or alveolar hypoventilation. COPD associated with hypoxemia at rest and during low-level exertion is usually due to ventilation-perfusion mismatch.[2] At high exercise intensity a diffusion deficit may emerge as a contributing factor.[3] These patients usually become adequately oxygenated when administered supplemental oxygen. Patients with a right-to-left shunt have a more limited response to supplemental oxygen. As the shunt fraction increases, some patients will be refractory to up to 100% oxygen. This is because shunted blood bypasses alveoli required to transfer oxygen into the bloodstream.[4,5] Hypoxemia may also be triggered by depressed ventilatory drive. Hypoxemia related to oversedation is rare in the rehabilitation setting. It is typically accompanied by hypercarbia and low pH. Chronically low ventilatory drive (chronic respiratory acidosis) will be associated with hypercarbia and near normal pH. Hypoxemia, either at rest or with activity, may be triggered or worsened by residence at high altitude or during exacerbation of chronic lung disease.

## Evaluation of SEIH

Evaluation of hypoxemia begins with a comprehensive history and physical exam, including arterial blood gas (ABG) sampling to determine acid/base status, partial pressures of oxygen and carbon dioxide, and arterial oxygen saturation. Co-oximetry measurements may be considered to evaluate hemoglobin species and other indices that may contribute to or impact the clinical decision making process.[6] ABG testing during exercise is seldom performed in the rehabilitation setting. When performed, it normally includes a radial artery catheter inserted for serial collection of blood before, during, and following exercise. Additional assessments include electrocardiogram, blood pressure, and gas exchange measured at the mouth. In using this approach, many pathophysiologic processes can be evaluated and addressed. Evaluation of hypoxemia during exercise may be performed using either ABG sampling or pulse oximetry.[7] The decision regarding which technique to use is based on the underlying question being asked.

Noninvasive oximetry solely represents information of arterial oxygen saturation ($S_{aO_2}$). Pulse oximetry has advantages of being noninvasive, highly portable, accurate when used appropriately, and capable of monitoring oxygen saturation continuously under a variety of conditions, including exercise. In some situations, pulse oximetry monitoring may be preceded by ABG to ensure that $S_{pO_2}$ and $S_{aO_2}$ correlate. Once the quality of the $S_{pO_2}$ reading is established, it can provide point measurement or continuous trending of $S_{pO_2}$ with a small delay factor (typically $< 6$ s) inherent in the oximeter data processing algorithms. This information is used along with other patient feedback and physiologic measurements to address the patient's needs. Substantial reduction in diffusing capacity, obtained as part of resting pulmonary function testing, may also aid in predicting exercise-induced desaturation, though the correlation is modest.[8-9]

## Physiology of Oxygen Demand

During exercise, demand for oxygen by working muscle increases in proportion to the level of work performed.[10] This results in a higher cardiopulmonary demand to deliver necessary oxygen to active tissues. Numerous physiologic adjustments must occur in an organized manner for exercise to continue; hence, there is substantial potential for system failure or dysfunction during activity.[11] Peak oxygen uptake is a measure of exercise tolerance. Work rates above a level for a given individual are accompanied by relatively inefficient anaerobic processes; termination of exercise occurs when these processes are exhausted. For normal individuals the delivery of oxygen (cardiac output × arterial oxygen content) to tissues is regulated by changing cardiac output to meet the imposed metabolic demand of exercise; pulmonary ventilation is increased to prevent decreases in arterial oxygen content. In chronic lung disease the ability of the lungs to maintain arterial oxygen content is often impaired, oxygen delivery is compromised, and exercise ability is typically reduced.

## Management of SEIH

Supplemental oxygen can increase arterial oxygen content (thereby improving tissue oxygen delivery), decrease carotid body stimulation (thereby reducing pulmonary ventilation, respiratory muscle work and dyspnea), and relieve pulmonary vasoconstriction (thereby alleviating cardiac output restriction).[12] Oxygen improves the effectiveness of short- and long-term exercise training in PR by reducing dyspnea, hypoxic ventilatory drive, and hyperinflation, and by delaying acidosis. Ambulatory oxygen equipment has the potential to increase mobility, compliance, exercise tolerance, and autonomy in hypoxemic patients.

## Survey of PR Programs Practice for SEIH Patients

A nonscientific electronic and faxed survey was used to poll members of the American Association for Respiratory Care PR section, and state PR societies of California, Colorado, Connecticut, Michigan, Missouri, North Carolina, New York, and Texas. Sixty-eight responders reported a mean ± SD of 14 ± 25 patients with SEIH seen annually, or 18 ± 22% of annual program attendees. Interfaces used to treat SEIH in these programs included traditional nasal cannula (NC) (62%), high flow NC (50%), Oxymizer pendant (49%), non-rebreather (NRB) mask (41%), Oxymizer cannula (37%), and combination of NC and NRB (25%). Other interfaces used include Venturi mask (15%), OxyMask (10%), and transtracheal oxygen (3%). Single programs reported using CPAP, heliox, OxyArm, and humidity collar (Table). Mean maximum $F_{IO_2}$ delivered by mask reported used in SEIH was 0.85. Mean maximum oxygen flow utilized was 10 L/min. Twelve percent of programs reported that SEIH was a criterion for non-admission to PR, and 13% reported not permitting any SEIH patient to exercise. Adverse events experienced by SEIH patients during rehabilitation were reported by 7% of programs, and included epistaxis (3%), chest pain, dizziness, rhinorrhea, dry nose, and "burning" nose (all 1%). All programs taught breathing strategies, 99% taught pacing strategies, and 97% taught panic control techniques to SEIH patients. One percent of responders did not answer all queries.

Table. Types of Devices Used in Pulmonary Rehabilitation Programs for SEIH Patients

| Device | Programs Using the Device for SEIH (%) |
|---|---|
| Nasal cannula (NC) | 62 |
| Hi-flow nasal cannula | 50 |
| Oxymizer pendant | 49 |
| Non-rebreather mask (NRBM) | 41 |
| Oxymizer cannula | 37 |
| NC and NRBM combination | 25 |
| Venturi mask | 15 |
| OxyMask | 10 |
| Transtracheal oxygen | 3 |
| CPAP, bi-level, OxyMask, high-flow mask, OxyArm | 1 |

SEIH = severe exercise-induced hypoxemia

## Developing an Oxygen Prescription for SEIH

There are currently no clinical guidelines or recommendations for management of SEIH. Oxygen prescription in patients with SEIH should be based on a comprehensive assessment, including desaturation and oxygen requirements during exercise testing, such as 6 min walk test. Based on the survey described above, community practice suggests using 7–15 L/min by NC and/or delivering up to 100% oxygen by mask. Multiple interfaces are suggested, including NC, Oxymizer cannula and pendant, NRB mask, OxyMask, Venturi mask, transtracheal oxygen, and other interfaces in an attempt to meet the needs of this population during exercise.

In-patient practitioners have decades of experience with various high flow oxygen systems, including NRB masks and heated, humidified high flow oxygen. These modalities have historically had limited use in the out-patient setting, due to comfort concerns and/or lack of portability during exercise. Use, safety, and effectiveness of these systems during exercise are poorly understood.

## Oxygen Monitoring, Titration, and Exercise Training

In hypoxemic COPD patients, long-term oxygen therapy has been found to improve survival, exercise, sleep, and cognitive performance with a therapeutic goal of oxygen saturation level over 90% during rest, sleep, and exertion.[13] Patients with SEIH require monitoring while using ambulatory systems during physical activity, to assure adequate oxygenation. Patients with ongoing desaturation despite use of high flow oxygen require medical evaluation and management prior to resuming exercise.

Optimal strategies for exercise training for SEIH patients have not been established. SEIH patients require monitoring of oxygen saturation, dyspnea, heart rate, and blood pressure at rest and during exercise. Options for measuring dyspnea include the Borg scale and visual analog scale.[14] If available, PR programs should consider telemetry monitoring during the patient's first exercise session, and ongoing telemetry monitoring in patients with substantial pulmonary hypertension (PH) or cardiac abnormalities, including important arrhythmias. Progressive exercise routines should be predicated on physiologic findings such as adequate oxygenation based on accurate $S_{pO_2}$, symptom level, including dyspnea and fatigue, stable heart rate and blood pressure, and results of cardiopulmonary exercise testing if available. Interval training should be avoided in those with substantial PH, due to rapid changes in pulmonary hemodynamics and risk of syncope. Exercise should be stopped if the patient develops desaturation refractory to supplemental oxygen, substantial tachycardia or arrhythmias, severe dyspnea, hypotension or severe hypertension, dizziness, or chest pain. Patients should have ongoing evaluation and management of their chronic lung disease and comorbidities by a pulmonologist as well as a primary care provider and other appropriate consultants.

According to the American College of Chest Physicians/American Association of Cardiovascular and Pulmonary Rehabilitation evidence-based guidelines, exercise should include training of muscles of ambulation and strength-training to increase muscle strength and muscle mass.[15] Low intensity exercise is recommended in the initial states of exercise, until clinical findings such as dyspnea levels, oxygen saturation, and heart rate support the safety of incremental increase in intensity, based on clinical stability. Exercise prescription and a home exercise program should be established and communicated to the patient, as well as indications for stopping exercise and symptoms to report to their physician. Interval training exercise routines require investigation in SEIH to determine safety and effectiveness.

## Oxygen Delivery Devices

Patients requiring high flow oxygen may be provided oxygen via a variety of devices, including NC, simple and NRB masks, and various interfaces. Devices should be selected based on clinical effectiveness and patient comfort.

The standard NC employing continuous oxygen flow delivers an inspiratory oxygen fraction roughly equivalent to an $F_{IO_2}$ of 0.24–0.44 at supply flows ranging from 1–6 L/min, respectively. A rough estimate of the $F_{IO_2}$ may be derived from the equation[16]:

$$F_{IO_2} = 0.2 + (\text{liter flow} \times 0.04)$$

The actual $F_{IO_2}$ is strongly influenced by the breathing pattern with slower inspiration, yielding a higher $F_{IO_2}$ resulting from comparatively less dilution with room air. Conversely, a patient breathing rapidly will experience a lower $F_{IO_2}$ from comparatively more dilution with room air. Generally, the standard NC flow range is limited to the lower supply flows.

The standard face mask delivers an inspiratory oxygen fraction of 0.24–0.6 via supply oxygen flows of 5–10 L/min.[10] The dead space volume of the face mask is 100–300 mL. The $F_{IO_2}$ delivered by a face mask is also influenced by the patient's breathing pattern. The main indication is either for patients who require high $F_{IO_2}$ or do not tolerate NC because of epistaxis or nasal irritation. It is sometimes indicated if patients are strictly mouth breathers. On the down side, the face mask is uncomfortable, confining, and obtrusive. It impedes communication, obstructs coughing, and interferes with eating.

The Venturi mask is an air entrainment device operating at high flows, designed to mix oxygen with room air to accurately deliver a specific $F_{IO_2}$. Typical $F_{IO_2}$ settings are 0.24, 0.28, 0.31, 0.35, 0.4, and 0.5. It is prescribed for patients who require precise and constant $F_{IO_2}$. The Venturi mask is often employed when the clinician has a concern about $CO_2$ retention. On the down side, the Venturi mask is uncomfortable, confining, obtrusive, and impedes talking and eating.

The NRB mask is indicated for patients requiring an $F_{IO_2} > 0.5$. It may deliver an $F_{IO_2}$ up to 0.9 at the highest flow settings. Oxygen flows into the reservoir at a valved inlet between the mask and the reservoir at high flow rates of about 10 L/min. The patient inhales nearly pure oxygen from the reservoir. Exhaled gas escapes through valves in the mask housing. It is basically a one-way flow system in which oxygen is inhaled from the reservoir and exhaled gas is exhausted through valve ports in the side of the mask. The major drawback of the NRB mask is that it must be tightly sealed on the face, which can be uncomfortable. There is also a risk of appreciable $CO_2$ retention for some COPD patients (generally those with incipient respiratory failure) breathing high concentrations of oxygen.

High flow heated and humidified nasal oxygen mixtures are increasingly utilized instead of high flow mask oxygen. Typical delivery flows range from 10 to 40 L/min, with oxygen fractions of up to 100% oxygen. It appears that such high nasal flows are tolerated partly because the delivery gas is warm and humidified. At flows greater than 20 L/min, the resultant $P_{aO_2}$ from nasal oxygen is potentially greater than that achieved using mask oxygen.[17,18] Ultrasonic flow studies have demonstrated that mask oxygen remains outside the nose and mouth until the subject inhales, whereas nasal oxygen is stored in the reservoir of the upper airways during exhalation for additional delivery during the next inhalation.[17] This nasal presentation of high flows, when heated and humidified, is generally better tolerated than the NRB mask. It is therefore being increasingly utilized in in-patient settings.

Reservoir cannulae improve the efficiency of oxygen delivery by storing oxygen during exhalation in a reservoir situated under the nose or in a pendant reservoir. Upon the next inhalation, the patient inhales the oxygen in the reservoir in addition to the supply flow. In addition, at flows $> 8$ L/min there is an added storage effect in the nasopharynx and oropharynx. Reservoir cannulae deliver a higher $F_{IO_2}$ than NRB mask at high flow, by use of the nasopharyngeal storage reservoir.[19-21] These cannulae tend to be preferred by patients over the NRB mask.[19]

Transtracheal catheters deliver oxygen directly into the trachea. Oxygen is stored in the trachea and upper airways during exhalation for delivery upon the next inhalation. In addition, high-flow transtracheal catheters may reduce the work of breathing and augment $CO_2$ removal. Patients who have been extubated but still have a tracheostomy in place may benefit from interim high-flow transtracheal oxygen. Also, continuous high flow transtracheal delivery may confer an augmented ventilation effect while enabling the patient to remain active.

## Other Treatment Strategies

### Pharmacotherapy

Perhaps the strongest evidence of effectiveness of pharmacotherapy in chronic lung disease is in COPD, where bronchodilators increase airway diameter and reduce hyperinflation, thereby reducing both resistive and elastic work of breathing. Bronchodilators increase exercise capacity in COPD. PH-specific agents have not been adequately studied in exercise-induced hypoxemia, but may be considered when PH severity is disproportionate to the underlying lung disease.[22] Oxygen is first line therapy for hypoxemia associated with PH. The role of pharmacotherapy in SEIH associated with chronic lung diseases is poorly understood.

### Breathing Retraining

Patients undergoing PR are often taught pursed lips breathing and diaphragmatic breathing. Patients derive several benefits from pursed lips breathing, including improvement in gas exchange, dyspnea, hyperinflation, and exercise endurance.[23] Diaphragmatic breathing is not thought to produce these same benefits.[23] Pulse oximetry can also be utilized as a biofeedback device to guide the patient performing pursed lips breathing to raise their oxygen saturation.[24,25] Combining oxygen delivery devices with pursed lips breathing may further increase oxygen saturation.[25,26]

## Clinical Consequences of SEIH

When weighing possible safety issues related to supplemental oxygen, the risks of failure to correct hypoxemia must be considered. Negative consequences of chronic hypoxemia include PH, cardiac dysfunction, erythrocytosis, cognitive abnormalities, decline in self care, and increased mortality. Untreated hypoxemia may result in pulmonary arterial bed vasoconstriction with elevated right heart pressures, often worsening with exercise. Over time these abnormalities may lead to progressive right ventricular dysfunction. These mechanisms, along with inflammation, loss of capillaries, and remodeling, may lead to cor pulmonale. Cor pulmonale is manifested by right ventricular hypertrophy and dilation from PH often associated with chronic respiratory disorders. More research is needed to understand the impact of cor pulmonale on exercise capacity in chronic lung disease. Management of cor pulmonale in COPD focuses on supplemental oxygen and management of airway obstruction.[27] Chronic untreated hypoxemia may increase the risk of right heart strain. Arrhythmias in the presence of hypoxemia may be triggered from irritable foci that give rise to aberrant excitation of cardiac conduction pathways. Patients may experience occasional ventricular and/or atrial ectopy. Cardiac ectopy may be due to ischemia in cardiac tissue. Cardiac ectopy that is prolonged and/or life threatening, such as frequent ventricular ectopy or severe tachyarrythmias or bradyarrythmias, require immediate attention and management. Ongoing monitoring is required until the ectopy resolves, especially when changes in behavior are noted. Hypoxemia may be addressed through supplemental oxygen therapy. While this does not correct the underlying pathophysiology, it does improve oxygenation.

Patients should be educated on proper use and safety of oxygen systems, and be given humidification when appropriate. Practical safety considerations include keeping oxygen delivery devices away from potential fire hazards. Tubing should be kept clean and replaced regularly; fall risk related to tripping over tubing and oxygen canisters should be addressed.

A potential concern in COPD patients receiving oxygen is suppression of hypoxic ventilatory drive with consequent hypoventilation and $CO_2$ retention. Most cases of $CO_2$ retention result from ventilation-perfusion mismatch rather than respiratory drive suppression.[28,29] While with COPD patients in a stable state of their disease this concern is generally overestimated, particularly with low-flow oxygen, there is reason to believe that some COPD patients might experience clinically important respiratory drive suppression if high flow oxygen is administered.[30]

Other concerns about high flow oxygen therapy include absorptive atelectasis, oxygen toxicity due to the creation of reactive oxygen species, and the possible association of high flow oxygen and risk of pulmonary fibrosis in patients receiving bleomycin.[31] Non-medical hazards include the fact that oxygen in high concentrations can support combustion, and freezer burns may occur consequent to mishandling liquid oxygen.[32]

## Summary

Although there are no guidelines available for assessment and management of SEIH, a non-scientific survey suggests patients with SEIH commonly participate in PR. For patients with high flow oxygen requirements there are a number of options to increase $F_{IO_2}$, including standard NC, masks, Venturi masks, NRB masks, high flow nasal oxygen, transtracheal catheters, and reservoir cannulae. There are specific indications for each device, as well as practical considerations such as comfort, cost, and availability. Patients with pulmonary pathology who require high flow oxygen often have additional needs. Based on individual evaluation, these patients may benefit from bronchial hygiene, bronchodilators, corticosteroids, antibiotics, diuretics, and, sometimes, positive-pressure ventilation to treat the underlying illness. Clinicians should be aware of potential complications of high flow oxygen and monitor arterial blood gases appropriately. PR offers potential for improved function and symptom control in patients with SEIH in a monitored, supervised setting. A collaborative self-management approach provided by a multidisciplinary team is recommended. There is a need for larger trials of the impact of PR on patients with SEIH, to define effective treatment strategies, including exercise interventions, and to determine PR's influence on healthcare utilization and survival.

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