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Acute Respiratory Failure and Chronic Obstructive Lung Disease

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The approach to acute respiratory failure in patients with chronic obstructive lung disease (COPD) requires a special understanding of factors regarding diagnosis, patient evaluation, interpretation of laboratory data, and management that is inherent to this group of patients. Although the term COPD as commonly used encompasses a wide variety of patients with the underlying common denominator of limitation of airflow, most of these patients fall into the major categories of chronic bronchitis, asthma, and emphysema. Many of these patients manifest an overlap syndrome made up of several or all of the components. The term chronic bronchitis denotes a clinical syndrome characterized by chronic or recurrent bronchial hypersecretion clinically diagnosed by the presence of chronic productive cough with no other cause such as infection, neoplasm, or cardiac disease. The sputum may be mucous, purulent, or eosinophilic in character.[2, 22] The mechanisms of airflow limitation are related to generalized hypertrophy and hyperplasia of the mucus-secreting bronchial glands, diffuse inflammation with thickening of the tracheobronchial submucosa, and secretions in the airways. Asthma is characterized by an increased responsiveness of the tracheobronchial tree to various stimuli and is manifested by diffuse narrowing of the airways, which is reversible either spontaneously or as a result of therapy. The airflow limitation results from a combination of mucous plugging of the airways, smooth muscle hypertrophy and constriction, goblet cell hyperplasia, and diffuse mucosal edema.[2] Pulmonary emphysema is defined pathologically as an abnormal enlargement of the airspaces distal to the terminal bronchioles associated with destruction of the alveolar walls.[2] Airflow limitation results from the collapse of small airways due to loss of the elastic recoil of the lung parenchyma, which aids in maintaining the patency of the small bronchioles.

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DIAGNOSIS

The diagnosis of acute respiratory failure in patients with COPD requires a modification of the criteria usually applied to other patients with acute respiratory failure. Commonly used criteria are an arterial P_{O_2} less than 50 to 60 Torr and/or an arterial P_{CO_2} of greater than 50 Torr.[45, 52] The qualification that an elevated Pa_{CO_2} must be associated with a pH less than 7.35 is important to distinguish patients who chronically have elevated Pa_{CO_2} levels that have been compensated for metabolically.[40] In patients with COPD who chronically function with compensated hypoxemia and/or hypercarbia, it is important to add to the standard blood gas criteria the qualifier that the clinical status of the patient be rapidly deteriorating.[11] Bone and coworkers[7] defined acute respiratory failure in this group of patients solely on the basis of clinical deterioration of steady state symptoms for hours to days prior to presentation. The indication for endotracheal intubation and mechanical ventilation used in their study was purely clinical and was based on when the patient became stuporous and was unable to cooperate with therapy. Arbitrary blood gas criteria were not used as a criterion.

PROGNOSIS

The prognosis for patients with COPD who develop acute respiratory failure appears to have changed over the last decade. In a recent study of 36 patients who developed acute respiratory failure as a consequence of an exacerbation of chronic bronchitis, 94% survived the initial hospitalization with only one patient requiring intubation and ventilator support.[40] This compares with past experience, where hospital survival of the acute episode was about 70%[44, 63] and the need for intubation ranged from 22% to 80%.[7, 63] This improving picture is evidence that, with a better understanding of the pathophysiology and management, these patients have a good prognosis for surviving an episode of acute decompensation.

PATHOPHYSIOLOGY

Patients with COPD develop certain physiologic adaptations to compensate for their respiratory compromise. An understanding of these chronic compensations is necessary in order to evaluate and manage these patients when they develop an episode of acute respiratory failure.

Hypoxemia

COPD patients with severely decreasing vital capacities, decreasing timed forced expiratory volumes, increasing airway resistance, and increasing thoracic gas volumes show declining arterial P_{O_2} values. Although these patients have an increased workload of breathing due to their increased airflow resistance, they have normal oxygen consumption at rest. Initially, they are able to maintain these levels of oxygen consumption despite

reduced oxyhemoglobin saturation by increasing oxygen extraction at the tissue level. They appear able to extract more oxygen, thus decreasing their mixed-venous oxygen saturation below normal levels. The difference between arterial and mixed-venous oxygen content therefore remains normal. Eventually, however, a critical level of mixed-venous oxygen is reached, reduction below which is not tolerated because of the risk of tissue damage. At this point, the body compensates by increasing the hemoglobin concentration.[17]

Erythrocytosis is a common finding in patients with long-standing hypoxemia.[5, 17, 60, 68] The average increase in hematocrit and hemoglobin in hypoxemic patients with COPD is generally moderate, being 57% and 17 g/100 ml, respectively. Hemoglobin levels greater than 20 g/100 ml are uncommon. The increased red cell mass that these patients develop actually correlates better with the degree of arterial oxygen desaturation than do either the hematocrit or hemoglobin.[5] Another cause of erythrocytosis is smoking, which is almost universal in this group of patients. Increased levels of carboxyhemoglobin lead to decreased levels of oxyhemoglobin saturation, despite normal P_{O_2}. The tissue hypoxia may thus contribute to the stimulus for erythrocytosis.[56] The erythrocytosis maintains an adequate blood oxygen content despite severe hypoxemia and oxyhemoglobin desaturation.

Another compensatory mechanism at work in COPD patients with severe hypoxemia to ensure tissue oxygenation is a shift of the oxyhemoglobin desaturation curve to the right. This is explained by an increased red cell 2,3-diphosphoglycerate level, as well as by a reduced pH.[17]

An increased cardiac output does not appear to be a compensating mechanism for the hypoxemia.[17] In the normal individual, an increased cardiac output is the usual response to increased tissue oxygen needs. High pulmonary vascular resistance, however, counteracts the attempts at increasing cardiac output, resulting in normal or low cardiac output.[17, 41]

Acid Base Status

Arterial P_{CO_2} and pH provide major clues as to the acuteness or chronicity of the respiratory decompensation. Pure respiratory failure leads to an elevated Pa_{CO_2} and a reduced pH. In patients with chronic respiratory failure, renal mechanisms come into play to return the pH toward normal. COPD patients with chronic CO_2 retention present with elevated serum bicarbonate levels that are evidence of compensatory renal mechanisms. In addition, they have evidence of renal dysfunction related to chronic hypercapnia and/or hypoxemia. Fluid retention manifested as peripheral edema can accompany hypercapneic and hypoxic respiratory failure.

In chronic hypercapnia, the increment in plasma bicarbonate concentration is more than double that observed during comparable degrees of acute hypercapnia. Hydrogen ion concentration increases by only 0.32 nmol/L/mm Hg of P_{CO_2}. The control mechanisms in chronic hypercapnia, however, react with a bicarbonate concentration, which falls short of returning extracellular pH to normal levels.[8, 59]

Complicating the interpretation of the acid/base status is the fact that many of these patients are on diuretics as therapy for their cor pulmonale.

Diuretics in these patients induce a chloride diuresis. The chloride loss seems to facilitate the generation of bicarbonate in the kidneys by increased hydrogen ion excretion. Bicarbonate excess is probably maintained by a continued exchange of sodium for hydrogen ion, sustaining an elevated renal bicarbonate threshold. The metabolic alkalosis that results is associated with a rising pH, as well as a rising $PaCO_2$ due to a secondary respiratory hypoventilation. The elevated $PaCO_2$ can lead to a reduction in PaO_2.[23] KCl corrects bicarbonate excess. It facilitates renal bicarbonate loss by providing chloride, which lowers an inappropriately elevated bicarbonate threshold. By providing potassium, it also favors the exchange of sodium for potassium rather than hydrogen ion by the renal tubules.

COPD patients with moderate hypoxemia but not hypercapnea have normal glomerular filtration rates, normal effective renal plasma flow, normal sodium excretion, and the ability to excrete a water load normally.[20] Hypercapnea with levels of $PaCO_2$ greater than 65 Torr, however, is related to a reduced ability of the kidney to excrete a water load and reduced ability to excrete sodium. Hypercapneic patients have a normal glomerular filtration rate but a decreased effective renal plasma flow. The defect in water excretion does not appear to be related to abnormal vasopressin secretion or metabolism. The alteration in sodium excretion may be due to a hypercapneic-induced increase in renal bicarbonate reabsorption and/or abnormal renal blood flow.[20, 33]

Arterial P_{O_2} levels at physiologic extremes affect renal function. When arterial P_{O_2} is >125 Torr, renal plasma flow and glomerular filtration rates are reduced. As the arterial P_{O_2} is reduced, the glomerular filtration rate progressively increases until arterial P_{O_2} is reduced below 40 Torr. At this point, urine output and sodium excretion fall.[33]

Cardiovascular System

Alterations occur commonly in the cardiovascular system. Cor pulmonale is a consequence of pulmonary hypertension brought on in these patients by hypoxia,[21] hypoxemia, and destruction of vascular bed, as occurs in emphysema. Electrocardiographic (ECG) abnormalities are common. Two thirds of patients show ECG evidence of right ventricular hypertrophy or signs compatible with COPD, such as right atrial hypertrophy, right axis deviation, or low voltage. Twenty per cent have arrhythmias detected on routine ECG, while up to 84% show arrhythmias, both atrial and ventricular, on Holter monitoring.[35] The mechanism is probably multifactorial with hypoxemia, acidosis, and electrolyte imbalance all contributing. Bronchodilator therapy also may contribute, but whether one drug class is more arrhythmogenic than another is unclear.[29]

PRECIPITATING FACTORS

Acute bronchoconstriction in patients with an asthmatic component to their disease is a major cause of acute respiratory failure. Inhalation of allergens or nonspecific irritants, viral respiratory infection, or emotional stress can all trigger bronchoconstriction. Acute CO_2 retention can occur

because of reduced alveolar ventilation secondary to a shallow, rapid breathing pattern that these patients assume.[49]

Respiratory tract infections can lead to acute decompensation. The primary infections usually are viral or *Mycoplasma pneumoniae* in etiology.[64, 65] Smith and coworkers[64] found viral or mycoplasma infections associated with 18% of the episodes of decompensation in patients with COPD. Rhinoviruses, influenza, parainfluenza, and coronaviruses were each significantly associated with acute respiratory illnesses. These lead to a hyperproduction of secretions with a worsening of the bronchitic as well as asthmatic components of obstruction. Viral infections of the respiratory tract in patients with COPD are associated with increased colonization and potentially infection by pathogenic bacteria, with *Streptococcus pneumoniae* and *Hemophilus influenzae* being the most common.[47, 65, 67]

Thromboembolic disease can complicate an already-compromised pulmonary vascular bed. At postmortem examination, pulmonary emboli can be found in about a quarter of cases.[46] Premortem diagnosis, however, is difficult because the clinical picture is similar to the symptoms of COPD, and ventilation–perfusion lung scans correlate poorly with the diagnosis due to the severe pulmonary vascular distortion resulting from the underlying lung disease.[39] The significance of emboli as a cause of decompensation in COPD patients remains unclear. The incidence of venous thrombosis, which would predispose to pulmonary emboli, varies from uncommon to 45%[54, 72] in COPD patients.

Spontaneous pneumothorax is an uncommon cause of respiratory failure in these patients. A review of 22,000 patients revealed 57 who experienced 95 episodes.[14]

Many drugs have the potential to exacerbate COPD. Beta-adrenergic receptor blockers commonly are used today in the treatment of a wide variety of diseases. The use of propranolol in COPD has the potential to cause marked deterioration. More $beta_1$-selective agents, such as metoprolol, cause fewer problems than propranolol but still can lead to bronchoconstriction at higher doses. Predictive factors are unknown, so careful observation during treatment is necessary.[73] It is important to recognize that beta blockers applied topically can have significant pulmonary effects. Timolol, a potent beta-adrenergic blocker used in the treatment of glaucoma, can result in significant bronchoconstriction in some patients.[12]

Administration of excessive levels of supplemental oxygen may lead to a depression of ventilatory drive by removing the hypoxic stimulus to patients who have respiratory centers with blunted sensivities to CO_2.[7, 55] Morphine and barbiturates also have the potential to depress minute volume and effective alveolar ventilation leading to respiratory acidosis.[71]

Parenteral nutrition with high carbohydrate loads can result in acute respiratory failure. Total peripheral nutrition leads to increased CO_2 production. In patients with COPD and a relatively fixed ventilatory response, hypercapnia may result with a subsequent respiratory acidosis.[13]

EVALUATION

The initial evaluation of the patient should include a history focusing on the patient's baseline cardiopulmonary status as well as potential causes

for a respiratory decompensation. The physical examination should focus on the pulmonary abnormalities and the cardiac response to these. Laboratory evaluation should include a chest radiograph and arterial blood gases. A complete blood count provides information as to the presence of infection and the level of the hemoglobin can give an indication as to the chronicity of hypoxemia. Serum electrolytes, in conjunction with the arterial pH and P_{CO_2}, provide an assessment of the patient's acid/base status and whether metabolic abnormalities are complicating the respiratory decompensation. Examination of the sputum should be carried out by the clinician. A sputum-wet preparation examination looking for eosinophils and Charcot-Leyden crystals can give an impression of the asthmatic component active in the patient's disease. A Gram's stain looking for a predominating organism can aid in the evaluation and treatment.

MANAGEMENT

Bronchodilator therapy is the mainstay in the treatment of these patients. Theophylline preparations are of value in patients with known asthmatic components and, in addition, they have been shown to improve airflow obstruction in patients without the classic findings of asthma or allergy. Eaton was able to improve the FEV_1 21.3% in this latter group of patients using theophylline.[16] In addition to the bronchodilating effect, theophyllines benefit the patient by augmenting the ventilatory response to hypoxia (although it does not appear to affect hypercarbic drive).[37] Aminophylline also increases respiratory muscle contractility[4, 61] and increases right and left ventricular ejection fractions.[42]

Aminophylline should be used in maintenance infusions at a rate of 0.5 mg/kg/h. It has been shown that smokers have higher drug clearances and require 0.8 mg/kg/h, while patients with pneumonia or congestive heart failure have lower clearances and require doses as low as 0.2 mg/kg/h.[53] Aminophylline clearances vary markedly in critically ill patients, however, and serum levels should be monitored every 24 hours until stable and every 48 hours thereafter, with appropriate dosage changes made.[70] Maintaining serum concentrations between 15 and 20 mg/L are more effective than lower levels and are associated with greater improvement in pulmonary function and a shorter duration of the need for intravenous (IV) medication.[69] It should be kept in mind that IV aminophylline may not make any difference in patients who have only a minor asthmatic component to their disease or have already been on oral preparations.[59] Additionally, since these patients often have been on oral preparations, the usual loading dose of 6 mg/kg aminophylline may not be necessary and, in fact, can lead to toxicity.

Beta-adrenergic drugs are useful in combination with theophyllines since their modes of action may complement each other. Beta agonists directly stimulate the production of bronchial smooth muscle cyclic AMP, while theophyllines inhibit phosphodiesterases and block the breakdown of cyclic AMP. This leads to smooth muscle relaxation and bronchodilation. Beta agonists can be given orally, parenterally, or by inhalation. Terbutaline, isoetharine, metaproterenol, and albuterol preparations are all available for administration by one or more routes. The choice of route depends

on the clinical situation. Oral or parenteral administration theoretically will have an effect on both the large and small airways, but have the drawback of potential systemic side effects. Inhaled medication works primarily at the larger airway level, but has the disadvantage that in some patients, bronchospasm may actually be induced by a deep inspiration with a metered dose inhaler. In critically ill patients, a nebulizer should be used to reduce the potential for paradoxic bronchospasm. In addition to the pulmonary effects, beta$_2$-adrenergic drugs, such as terbutaline, also have positive cardiovascular effects by improving right and left ventricular performance.[9, 25]

In recent years, there has been a resurgence of interest in the use of anticholinergic drugs, such as atropine methonitrate and ipratropium bromide, in the management of obstructive lung disease.[24, 28, 38, 51] The mechanism of action of these drugs appears to be a blocking of the normal baseline cholinergic tone to the bronchial smooth muscle, thus resulting in bronchodilation.[24] Responsiveness to anticholinergic drugs appears greatest in chronic bronchitis and emphysema, as opposed to classic atopic asthma;[28] in the former group of patients, the bronchodilating response is greater than it is to beta-agonist drugs.[24, 51] The appropriate dosage of atropine methonitrate is 0.025 to 0.05 mg/kg by nebulization.[50]

Corticosteroids play a role in the management of the compromised COPD patient. The mechanism of action is unclear; however, a beneficial effect in the asthmatic component of the disease is well known. Patients with an atopic history, reversibility of obstruction following bronchodilators, or having blood or sputum eosinophilia are those most likely to respond.[57] Data are conflicting as to the efficacy in patients who have primarily emphysema or bronchitis. In patients without definite asthma, steroids should be tried; however, a definite endpoint must be set to determine a response. Oral doses in the range of 30 to 40 mg/d are appropriate initially during an acute flare. IV dosage should be in the range of 0.5 m/kg every 6 hours of methylprednisolone or the equivalent dose of hydrocortisone.[1, 19] There is no evidence that therapy with higher doses of corticosteroids has any benefit in this group of patients.[66]

Hypoxemia should be treated with supplemental oxygen to improve tissue oxygenation as well as to relieve hypoxic-induced pulmonary hypertension. Because of the potential for suppression of ventilation discussed above, it is important to administer oxygen in a controlled fashion, using a venturi-type mask delivering an inspired fraction of oxygen of 0.24 or 0.28. Delivering oxygen by nasal cannula does not provide a flow that is adequately quantifiable. The breathing pattern of a critically ill patient is such that, with rapid shallow respirations, the fraction of oxygen delivered to the patient at 1 to 2 L/min by nasal cannula may actually be equivalent to greater than 0.30, which might prove to be excessive. It is unknown which patients will have ventilatory drive suppressed by supplemental oxygen; close clinical observation is required. Using an oxygen tension/carbon dioxide tension diagram, Bone and coworkers suggested that severe hypoxemia and acidosis initially are more discriminatory for CO_2 retention than baseline hypercarbia.[7]

Increased secretions should be treated aggressively. Eosinophilic sputum responds well to corticosteroids. Purulent secretions should be man-

aged with bronchial hygiene techniques and chest physical therapy. The use of antibiotics in this setting is controversial. Since the usual infectious etiology of acute bronchitis is viral, it theoretically would not matter if antibiotics directed against bacteria were used. Studies have found both a benefit[67] and no benefit.[47] Despite this data, most clinicians would treat a purulent bronchitis without evidence of an obvious pneumonia with a broad spectrum antibiotic, such as ampicillin or a cephalosporin.

If the patient has a hypochloremic alkalosis secondary to diuretic therapy, this should be corrected to reduce any component of hypoventilation in response to the metabolic abnormality. The treatment of choice is KCl supplementation. It is important to realize that, in this group of patients, one is treating the hypochloremia and is not as concerned about the patient's potassium levels. If the patient is normokalemic, the kidney should spill any excess potassium given to the patient. Potassium preparations that do not include chloride are obviously of no value in treating this problem. Acetazolamide, a carbonic anhydrase inhibitor, has been advocated as a way of correcting a metabolic alkalosis.[36, 62] In these patients, the primary problem, however, is a hypochloremic alkalosis; these drugs should therefore be used only as a temporizing adjunct while chloride is replaced.

Respiratory stimulants are not very effective in this group of patients. Acetazolamide has been advocated in the past, but does not really cause a sustained improvement in COPD patients.[62] Medroxyprogesterone acetate in a dose of 20 mg tid has been shown to be a mild respiratory stimulant in the awake COPD patient;[15] however, there is no evidence that it is beneficial during an acute decompensation. Aminophylline will augment the ventilatory response to hypoxia,[37] but is used in these patients for their bronchodilating effects. Doxapram HCl is an effective central stimulant of ventilation and has been used in the management of COPD patients.[48] Unless the patient has ventilatory failure due to sedatives or excessive oxygen, the use of doxapram in this type of patient is not recommended. If the patient's respiratory rate is less than 10, doxapram may temporarily aid management. In most COPD patients with acute decompensation, the drive to breathe is maintained, but the patient is physically unable to maintain adequate alveolar ventilation. Adding doxapram to this situation may only increase the patient's sense of dyspnea and psychologic discomfort without improving ventilation.

Drug manipulation of pulmonary hypertension, which complicates the clinical picture of these patients, recently has been undergoing a great deal of research.[26] Oxygen remains the drug of choice. Drugs such as nitroprusside, nitroglycerin, hydralazine, and nifedipine all have been used with conflicting results.[9, 31, 32, 43] The rationale for the use of these drugs in the decompensated COPD patient would be to reverse the cor pulmonale that they develop. Vasodilators might directly relieve pulmonary hypertension or improve cardiac function by causing afterload reduction. Although these drugs have the potential to reduce pulmonary hypertension and improve right ventricular function, they also can reduce preload and worsen right ventricular function. In addition, they have the potential to worsen ventilation-perfusion relationships in the lung and cause a worsening of gas exchange. At the present time, these drugs should not be considered as

standard modes of therapy for the COPD patient with acute decompensation.

In the patient with a hematocrit of greater than 55%, phlebotomy may occasionally be of benefit. Central nervous system findings, accompanied by evidence of sludging in the retinal blood vessels, would be indications for phlebotomy. Right ventricular function also can be improved.[18] The decision to phlebotomize, however, should be weighed against the reduction in oxygen-carrying capacity.

If the patient develops further ventilatory failure with a falling pH and rising P_{CO_2}, despite aggressive medical management, then management with a ventilator should be considered. If the respiratory failure is the result of an obviously reversible process, the decision is easy and the patient should be intubated. If the cause of the failure is a gradual deterioration of the patient's underlying lung disease, the decision to intubate or not is more difficult and should take into account ethical as well as medical issues. Basic ventilatory management is well described elsewhere.[6]

There are several features of ventilator management that are unique to this group of patients. The minute volume that these patients receive should be adjusted to maintain a pH between 7.35 and 7.40. One should not strive to normalize the Pa_{CO_2} because this will tend to reduce the metabolic compensation by the kidney. If the acid/base status of the patient re-equilibrates at a Pa_{CO_2} lower than the patient can maintain on his own, then weaning will be much more difficult. The supplemental oxygen should be titrated to maintain an adequate Pa_{O_2} level of at least 60 Torr, but not so much that the ventilatory drive is suppressed. Flow rates on the machine should be adjusted to assure an adequate expiratory phase. If expiration of a breath is incomplete, a phenomenon known as dynamic hyperinflation occurs. The gas remaining in the chest at the end of a tidal volume breath gradually increases, leading to an increased functional residual volume. This is a disadvantage to the patient because ventilation takes place at a less-than-optimal point on the normal compliance curve, and the work of breathing is increased.[34] This group of patients, however, may actually require a small amount of resistance to expiration to maintain patency to their airways.[30] The time spent on the ventilator should be kept as short as possible. The ventilator should be used to help the patient over the acute episode. Prolonged time on the ventilator leads to problems with muscular dyscoordination, risks of barotrauma, infection, alteration in normal acid/base equilibrium, and a general decline in overall status. When the patient is ready, aggressive efforts should be made to wean the patient. Slow weaning only prolongs the time on the ventilator and leads to complications.

SUMMARY

Patients with COPD who develop acute respiratory failure require special attention in their management. Patients with severe COPD often have cor pulmonale, complex acid/base compensations, and altered respi-

ratory control mechanisms. These need to be considered when approaching the patient with an acute decompensation. Because of the improving prognosis in this group of patients, aggressive management should be undertaken using combinations of bronchodilator medications, oxygen, bronchial hygiene, and antibiotics.

REFERENCES

1. Albert, R. K., Martin, T. R., and Lewis, S. W.: Controlled clinical trial of methylprednisolone in patients with chronic bronchitis and acute respiratory failure. Ann. Intern. Med., 92:753–758, 1980.
2. American Thoracic Society: Definitions and classification of chronic bronchitis, asthma and pulmonary emphysema. Am. Rev. Respir. Dis., 85:762–769, 1962.
3. Ashutoch, K.: Comparison between long-term treatment of chronic bronchitic airway obstruction with piatropium bromide and metaproterenol. Ann. Allergy, 53:401–406, 1984.
4. Aubier, M., Troyer, A. D., Sampson, M., et al.: Aminophylline improves diaphragenic contractility. N. Engl. J. Med., 305:249–252, 1981.
5. Balcerzak, S. P., and Bromberg, P. A.: Secondary polycythemia. Semin. Hematol., 12:353–382, 1975.
6. Bone, R. C.: Treatment of respiratory failure due to advanced chronic obstructive lung disease. Arch. Intern. Med., 140:1018–1021, 1980.
7. Bone, R. C., Pierce, A. K., and Johnson, R. L.: Controlled oxygen administration in acute respiratory failure in chronic obstructive pulmonary disease. Am. J. Med., 65:896–902, 1978.
8. Brackett, N. C., Cohen, J. J., and Schwartz, W. B.: The carbon dioxide titration curve of normal man; the effect of increasing degrees of acute hypercapnia on acid base equilibrium. N. Engl. J. Med., 272:6–12, 1965.
9. Brent, B. N., Berger, H. J., Matthay, R. A., et al.: Contrasting acute effects of vasodilators (nitroglycerin, nitroprusside, and hydralazine) on right ventricular performance in patients with chronic obstructive pulmonary disease and pulmonary hypertension: A combined radionuclide-hemodynamic study. Am. J. Cardiol., 51:1682–1689, 1983.
10. Brent, B. N., Mahler, D., Berger, H. J., et al.: Augmentation of right ventricular performance in chronic obstructive pulmonary disease by terbulatine: A combined radionuclide and hemodynamic study. Am. J. Cardiol., 50:313–319, 1982.
11. Burk, R. H., and George, R. B.: Acute respiratory failure in chronic obstructive pulmonary disease. Arch. Intern. Med., 132:865, 1973.
12. Charan, N. B., and Lakshminarayan, S.: Pulmonary effects of topical tinolol. Arch. Intern. Med., 140:843–844, 1980.
13. Covelli, H. D., Black, J. W., Olsen, M. S., et al.: Respiratory failure precipitated by high carbohydrate leads. Ann. Intern. Med., 95:579–581, 1981.
14. Dines, D. E., Clagett, O. T., and Payne, W. S.: Spontaneous pneumothorax in emphysema. Mayo Clin. Proc., 45:481, 1970.
15. Dolly, F. R., and Block, A. J.: Medroxyprogesterone acetate and COPD—effect on breathing and oxygenation in sleeping and awake patients. Chest, 84:394–398, 1983.
16. Eaton, M. L., Green, B. A., Church, M. S., et al.: Efficacy of theophylline in "irreversible" airflow obstruction. Ann. Intern. Med., 92:758–761, 1980.
17. Elst, A. M. C. vd, and Kreukniet, J.: Some aspects of the oxygen transport in patients with chronic obstructive lung diseases and respiratory insufficiency. Respiration, 43:336–343, 1982.
18. Erickson, A. D., Golde, W. A., Claunch, B. C., et al.: Acute effects of phlebotomy on right ventricular size and performance in polycythemic patients with chronic obstructive pulmonary disease. Am. J. Cardiol., 52:163–156, 1983.
19. Fanta, C. H., Rossing, T. H., and McFadden, E. F.: Glucocorticoids in acute asthma: A critical controlled trial. Am. J. Med., 74:845–851, 1983.

20. Farber, M. O., Bright, T. P., Strawbridge, R. A., et al.: Impaired water handling in chronic obstructive lung disease. J. Lab. Clin. Med., *85*:41–49, 1975.
21. Fishman, A. P.: Hypoxia and the pulmonary circulation: How and where it acts. Circ. Res., *38*:221–231, 1976.
22. Fletcher, C. M.: Definitions of emphysema, chronic bronchitis, asthma, and airflow obstruction: 25 years on from the CIBA symposium. Thorax, *39*:81–85, 1984.
23. Goldring, R. M., Turino, G. M., and Heinemann, H. O.: Respiratory-renal adjustments in chronic hypercapnia in man. Am. J. Med., *51*:772–784, 1971.
24. Gross, N. J., and Skorodin, M. S.: Role of the parasympathetic system in airway obstruction due to emphysema. N. Engl. J. Med., *311*:421–425, 1984.
25. Hooper, W. W., Slutsky, R. A., Kocienski, D. E., et al.: Right and left ventricular response to subcutaneous terbutaline in patients with chronic obstructive pulmonary disease: Radionuclide angiographic assessment of cardiac size and function. Am. Heart J., *104*:1027–1032, 1982.
26. Hyman, A. L., and Kadowitz, P. J.: Vasodilator therapy for pulmonary hypertensive disorders. Chest, *85*:145–147, 1984.
27. Jenne, J. W.: Beta blockers and COPD. Chest, *78*:675–676, 1980.
28. Jolobe, O. M.: Reversible airflow obstruction: Clinical spectrum and responsiveness to anticholinergic drugs. Respiration, *45*:232–236, 1984.
29. Josephson, G. W.: Dysrhythmogenesis associated with the treatment of acute reversible airway obstruction. Ann. Emerg. Med., *11*:425–428, 1982.
30. Khan, F. A., Mukjerji, R., Chikara, R., et al.: Positive airway pressure in patients receiving intermittent mandatory ventilation at zero rate: The role in weaning in chronic obstructive pulmonary disease. Chest, *84*:436–438, 1983.
31. Keller, C. A., Shepard, J. W., Chun, D. S., et al.: Effects of hydralazine on hemodynamics, ventilations, and gas exchange in patients with chronic obstructive pulmonary disease and pulmonary hypertension. Am. Rev. Respir. Dis., *130*:606–611, 1984.
32. Kennedy, T. P., Michael, J. R., Huang, C. K., et al.: Mifedipine inhibits hypoxic pulmonary vasoconstriction during rest and exercise in patients with chronic obstructive pulmonary disease: A controlled double-blind study. Am. Rev. Respir. Dis., *129*:544–551, 1984.
33. Kilburn, K. H., and Dowell, A. R.: Renal function in respiratory failure. Arch. Intern. Med., *127*:754–762, 1971.
34. Kimball, W. R., Leith, D. E., and Robins, A. G.: Dynamic hyperinflation and ventilator dependence in chronic obstructive pulmonary disease. Am. Rev. Respir. Dis., *126*:991–995, 1982.
35. Kleiger, R. E., and Senior, R. M.: Long term electrocardiographic monitoring of ambulatory patients with chronic airway obstruction. Chest, *65*:483–487, 1974.
36. Krintel, J. S., Haxholdt, O. S., Berthelsen, P., et al.: Carbon dioxide elimination after acetazolamide in patients with chronic obstructive pulmonary disease and metabolic alkalosis. Acta Anaesthesiol. Scand., *27*:252–254, 1983.
37. Lakshminarayan, S., Sahn, S. A., and Weil, J. V.: Effect of aminophylline on ventilatory responses in normal man. Am. Rev. Respir. Dis., *117*:33, 1978.
38. Lefcoe, N. M., Toogood, J. H., and Blennerhassett, G.: The addition of an aerosol anticholinergic to an oral beta agonist plus theophylline in asthma and bronchitis. Chest, *82*:300–309, 1982.
39. Lippmann, M., and Fein, A.: Pulmonary embolism in the patient with chronic obstructive pulmonary disease: A diagnostic dilemma. Chest, *79*:39–42, 1979.
40. Martin, T. R., Lewis, S. W., and Albert, R. K.: The prognosis of patients with chronic obstructive pulmonary disease after hospitalization for acute respiratory failure. Chest, *82*:310–314, 1982.
41. Matheu, P. N., Pugsley, S. O., Powles, A. C. P., et al.: Effect of diuretics on cardiopulmonary performance in severe chronic airflow obstruction. Arch. Intern. Med., *144*:2154–2157, 1984.
42. Matthay, R. A., Berger, H. J., Loke, J., et al.: Effects of aminophylline upon right and left ventricular performance in chronic obstructive pulmonary disease. Am. J. Med., *65*:903–910, 1978.
43. Melot, C., Hallemans, R., Naeije, R., et al.: Deleterious effect of nifedipine on pulmonary gas exchange in chronic obstructive pulmonary disease. Am. Rev. Respir. Dis., *130*:612–616, 1984.

44. Moser, K. M., Shibel, E. M., and Beaman, A. J.: Acute respiratory failure in obstructive lung disease: Long term survival after treatment in an intensive care unit. J.A.M.A., *225*:705, 1973.
45. Murray, J. F.: Mechanisms of acute respiratory failure. Am. Rev. Respir. Dis., *115*:1071–1078, 1979.
46. Neuhaus, A., Bentz, R. R., and Weg, J. G.: Pulmonary embolism in respiratory failure. Chest, *73*:460, 1978.
47. Nicotra, M. B., Livera, M., and Awe, R. J.: Antibiotic therapy of acute exacerbations of chronic bronchitis: A controlled trial using tretracycline. Ann. Intern. Med., *97*:18–21, 1982.
48. Ohi, M., Heki, S., Kato, M., et al.: Doxapram HCl in treatment of acute exacerbation of chronic respiratory failure. Chest, *74*:453, 1978.
49. Oliver, A., Cherniack, N. S., Deal, E. C., et al.: The effects of acute bronchoconstriction on respiratory activity in patients with chronic obstructive pulmonary disease. Am. Rev. Respir. Dis., *131*:236–241, 1985.
50. Pak, C. C. F., Kradjan, W. A., Lakshminarayan, S., et al.: Inhaled atropine sulfate: Dose-response characteristics in adult patients with chronic airflow obstruction. Am. Rev. Respir. Dis., *125*:331, 1982.
51. Passamonte, P. M., and Martinez, A. J.: Effect of inhaled atropine or metaproterenol in patients with chronic airway obstruction and therapeutic serum theophylline levels. Chest, *85*:610–615, 1984.
52. Petty, T. L., Harris, T. M., and Whitehouse, A. C.: Management of acute respiratory failure (a systematic approach). Ann. Allergy, *26*:405–413, 1968.
53. Powell, J. R., Vozeh, S., Hopewell, P., et al.: Theophylline disposition in acutely ill hospitalized patients. Am. Rev. Respir. Dis., *118*:229, 1978.
54. Prescott, S. M., Richards, K. L., Tikoff, G., et al.: Venous thromboembolism in decompensated chronic obstructive pulmonary disease: A prospective study. Am. Rev. Respir. Dis., *123*:32–36, 1981.
55. Rudolf, M., Banks, R. A., and Semple, S. J. G.: Hypercapnia during oxygen therapy in acute exacerbations of chronic respiratory failure. Lancet, *2*:483, 1977.
56. Sagone, A. L., Jr., and Balcerzak, S. P.: Smoking as a cause of erythrocytosis. Ann. Intern. Med., *82*:512–515, 1975.
57. Sahn, S. A.: Corticosteroids in chronic bronchitis and pulmonary emphysema. Chest, *73*:389–396, 1978.
58. Schwartz, W. B., Brackett, N. C., Jr., and Cohen, J. J.: The response of extracellular hydrogen ion concentration to graded degrees of chronic hypercapnia: The physiologic limits of the defense of pH. J. Clin. Invest., *44*:291–301, 1965.
59. Seidenfeld, J. J., Jones, W. N., Moss, R. E., et al.: Intravenous aminophylline in the treatment of acute bronchospastic exacerbations of chronic obstructive pulmonary disease. Ann. Emerg. Med., *13*:248–252, 1984.
60. Shaw, D. B., and Simpson, T.: Polycythaemia in emphysema. Q. J. Med., *30*:135–152, 1961.
61. Sigrist, S., Howell, T. S., and Rousso, C.: The effect of aminophylline on inspiratory muscle contractility. Am. Rev. Respir. Dis., *126*:46–50, 1982.
62. Skatrud, J. B., and Dempsey, J. A.: Relative effectiveness of acetazolamide vs. medroxyprogesterone acetate in correction of chronic carbon dioxide retention. Am. Rev. Respir. Dis., *127*:405–412, 1983.
63. Sluiter, H. J., Blokqijl, E. J., vanDijl, W., et al.: Conservative and respirator treatment of acute respiratory insufficiency in patients with chronic obstructive lung disease. Am. Rev. Respir. Dis., *105*:932–943, 1972.
64. Smith, C. B., Golden, C. A., Kanner, R. E., et al.: Association of viral and mycoplasma pneumonia infections with acute respiratory illness in patients with chronic obstructive pulmonary disease. Am. Rev. Respir. Dis., *121*:225, 1980.
65. Smith, C. B., Golden, G., Klauber, M. R., et al.: Interactions between viruses and bacteria in patients with chronic bronchitis. J. Infect. Dis., *134*:552, 1976.
66. Tanaka, R. M., Santiago, S. M., Kuhn, G. J., et al.: Intravenous methylprednisolone in adults in status asthmaticus. Chest, *82*:438–440, 1982.
67. Turco, P., Pomari, C., Zoccatelli, O., et al.: Therapy for intercurrent respiratory infections in cold patients: Report on 200 patients. Int. J. Clin. Pharmacol. Ther. Toxicol., *21*:260–261, 1983.

68. Vanier, T., Dulfano, M. J., Wu, C., et al.: Emphysema, hypoxia and the polycythemic response. N. Engl. J. Med., *269*:169–178, 1963.
69. Vozeh, S., Kewitz, G., Perruchoud, A., et al.: Theophylline serum concentration and therapeutic effect in severe acute bronchial obstruction: The optimal use of intravenously administered aminophylline. Am. Rev. Respir. Dis., *125*:181–184, 1982.
70. Westerfield, B. T., Carder, A. J., and Light, R. W.: The relationship between arterial blood gases and serum theophylline clearance in critically ill patients. Am. Rev. Respir. Dis., *124*:17–20, 1981.
71. Wilson, R. H., Hoseth, W., and Pempsey, M. E.: Respiratory acidosis: Effects of decreasing respiratory minute volume in patients with severe chronic pulmonary emphysema with specific reference to oxygen, morphine, and barbituates. Am. J. Med., *17*:464–470, 1954.
72. Winter, J. H., Buckler, P. W., Bautista, A. P., et al.: Frequency of venous thrombosis in patients with an exacerbation of chronic obstructive lung disease. Thorax, *38*:605–608, 1983.
73. Wunderlich, J., Mocha, H. N., Wudicke, H., et al.: Beta adrenoceptor blockers and terbutaline in patients with COPD. Chest, *78*:714–720, 1980.

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