ACUTE RESPIRATORY FAILURE

IN

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

INTERNAL MEDICINE GRAND ROUNDS

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MARCH 4, 1993

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INTRODUCTION

The American Thoracic Society has recommended that the diagnosis of chronic obstructive pulmonary disease (C.O.P.D.) be used for patients with emphysema and/or chronic bronchitis who have significant airflow limitation which does not change markedly over periods of several months of observation, thus distinguishing these patients from those with asthma (1). The clinical characteristics and modes of therapy may overlap with asthma, but there are important differences which warrant the separate consideration of C.O.P.D. Furthermore, there are important differences in C.O.P.D. patients with respect to therapeutic strategies when comparing stable patients and those who have acutely decompensated. This presentation will focus on the management of patients with C.O.P.D. who present with acute respiratory failure.

Definitions:

Respiratory failure represents an impairment in the overall respiratory system which leads to significant gas exchange abnormalities. By convention this is usually defined in terms of blood gas criteria: $P_aO_2 < 50$ mmHg breathing room air and/or $P_aCO_2 > 50$ mmHg (2). Acute respiratory failure is present when a patient with C.O.P.D. has these gas exchange abnormalities along with an abrupt exacerbation of their dyspnea and other symptoms. In addition to the patient's subjective deterioration, objective evidence of acute decompensation may be present such as impaired or deteriorating mental status, acidosis, documented decline in P_aO_2 or rise in P_aCO_2 from baseline, or deterioration of blood gas values during evaluation and therapy, including a rise in P_aCO_2 of more than 10 mmHg in response to supplemental oxygen (see below). As thus defined, patients with acute exacerbations of C.O.P.D. and acute respiratory failure represent a group who are critically ill, unstable, and in need of hospitalization. All will require careful observation and intensive treatment, whether this is provided in a formal intensive care unit, a "step-down" unit, or on a general ward. Some of these patients may require mechanical ventilation. Clinical experience would also suggest that some patients who present with acute symptoms who appear to be in significant distress may be considered in this context and managed accordingly prior to the onset of overt gas exchange abnormalities.

Background:

Although some cigarette smokers never develop clinically significant airways disease (3,4), C.O.P.D. is a common disorder with significant mortality and morbidity, of which 82% is attributable to cigarette smoking (5). Symptomatic improvement (6) and retardation of the rate of decline in lung function (3,6) can be accomplished with smoking cessation. Unfortunately, however, there are no reliable early predictors which would identify susceptible individuals (7) and smoking cessation rates remain disappointing (8-11). Clinically significant C.O.P.D. may affect as many as 10 million people in the United States (12). In 1986 there were over 400,000 hospital

admissions for C.O.P.D. (13); the length of hospital stay averages 9 days (14). As approximately 30% of emergency room visits for C.O.P.D. result in hospitalization (15), it is likely that there are in excess of one million E.R. visits for C.O.P.D. annually and many of these represent recurrent episodes (16).

The total mortality due to C.O.P.D. in 1986 was over 70,000 dead in the United States (5), representing the third most common cause of death (13). The most recent available comparative data showed that in 1989 the death rate from C.O.P.D. was four times that of H.I.V. infection in the United States (17). Death rates appear to be increasing (13,18), especially in women (13,19). Although the overall case fatality rate for patients admitted because of C.O.P.D. is about 7% (18), the mortality for those admitted with C.O.P.D. and acute respiratory failure is 28% (20,21). Furthermore, many of those with acute respiratory failure require I.C.U. care and approximately 36% require mechanical ventilation (20,21). Mechanical ventilation may be prolonged (22) and some patients remain ventilator-dependent indefinitely (23-25). Thus, acute respiratory failure due to C.O.P.D. is an all too common problem with significant mortality, morbidity, and cost which will continue to challenge the critical care physician for some time to come.

PATHOPHYSIOLOGY

Airway obstruction

The principal physiologic alteration in C.O.P.D. is expiratory flow limitation (1). This is generally well tolerated during periods of compensated stability such that significant abnormalities are evident only during maximal expiratory efforts or exercise (26-28). While the expiratory limitation is relatively constant over time ("fixed obstruction"), acute changes in expiratory resistance may occur and lead to inspiratory dysfunction, deterioration in gas exchange, respiratory muscle fatigue, and cardiovascular alterations which we recognize as acute respiratory failure.

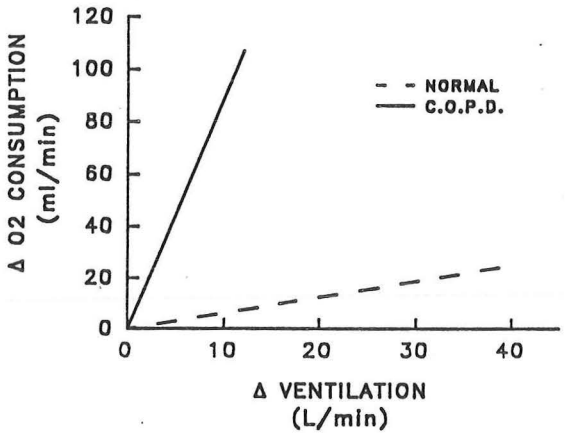
Expiratory obstruction results from narrowing of the peripheral airways (29) from mucous hypersecretion (30), impaired ciliary clearance (31) and mucous plugging (29,30). Bronchial mucosal hyperplasia and edema also contribute to anatomic obstruction (29,30). Infection (32-34) and inflammation (35-39) may compound the airway narrowing through recruitment of neutrophils and local mediator-released bronchoconstriction (40,41). Emphysematous lungs lose elastic recoil, which decreases the driving pressure during exhalation (42-44) and minimizes the stromal support of the airways, both of which contribute to functional airway narrowing (45-48) and even collapse (a form of Starling resistor or "flutter valve"). Although bronchial smooth muscle contraction is typically associated with asthma, patients with C.O.P.D. may also experience some degree of bronchospastic airways obstruction, as evidenced by acute responses to inhaled adrenergic or cholinergic stimulants or

methacholine challenge (49-51). Upper airway obstruction may also contribute to expiratory flow limitation due to functional narrowing of central airways during marked expiratory effort (52), glottic narrowing (53), tracheal stenosis from prior intubation (54), or narrow bore endotracheal tubes during mechanical ventilation (55,56).

Gas exchange and ventilation

These airways alterations are distributed heterogeneously and consequently ventilation is very inhomogeneous so that some regions are relatively underventilated (low ventilation/perfusion, V/Q) resulting in alveolar hypoxia and hypoxemia (57,58). Other areas are relatively overventilated relative to perfusion (57) and breathing pattern alterations may occur (59,60), both of which contribute to increasing physiologic dead space (61). These changes in gas exchange predispose to hypoxemia and hypercapnia; to compensate, the patient must significantly increase minute ventilation. Increasing minute ventilation is difficult in such patients and comes at the expense of a marked and disproportionate increase in the oxygen cost of breathing (62,63).

OXYGEN COST OF INCREASING MINUTE VENTILATION
IN NORMAL SUBJECTS AND COPD PATIENTS



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Airtrapping, hyperinflation, and auto-P.E.E.P

The inhomogeneous distribution of airflow obstruction (64) may create regions with such high resistances (and thus prolonged expiratory time constants) that alveolar emptying is incomplete at the beginning of the next inspiration (65). The result is that the preceding tidal volume is not completely exhaled, leading to air-trapping and hyperinflation (66). Because these alveoli are incompletely emptied, they are distended above the resting volume. Thus, at the end of the expiratory phase there is still a tendency for the alveoli to recoil inward and thus a positive end-expiratory alveolar pressure (P.E.E.P.) exists in those areas where air-trapping is occurring. This

is referred to as intrinsic P.E.E.P. (67) or auto-P.E.E.P. (68). Air-trapping, hyperinflation, and the development of auto-P.E.E.P. will be most likely to occur with increasing severity and inhomogeneity of airways obstruction (69,70), during dynamic airways compression (65,71), and with any change which minimizes expiratory time, such as during hyperventilation (72-74). Increasing respiratory frequency decreases the time available for exhalation (T_E) by decreasing total cycle time (T_{TOT}). For obstructed patients receiving mechanical ventilation, prolonging the inspiratory phase (T_I) using slow inspiratory flow rates or large tidal volumes will encroach upon T_E and predispose to air-trapping.

Consequences of Hyperinflation and Auto-PEEP

Respiratory Mechanics
- Increased elastic load
- Inspiratory threshold load

Barotrauma
- Reduced cardiac preload
- Risk of pneumothorax

Respiratory Muscle Inefficiency
- Shortened operating length
- Flattened diaphragm contour

The consequences of hyperinflation may be significant. The end-expiratory lung volume becomes higher than the true resting lung volume; this is recognized as hyperexpansion on the chest X-ray and as an increase in residual volume (RV) and functional residual capacity (FRC). This means that tidal breathing is occurring higher on the pressure-volume curve of the respiratory system; thus, greater inspiratory pressures are required to generate the same inspiratory volume. This increase in elastic load contributes to the increase in inspiratory work (75,76). Furthermore, the presence of auto-P.E.E.P. requires that inspiratory airway pressure must first be lowered below this threshold load before airflow can begin (67). Thus, air-trapping significantly adds to inspiratory work. Hyperinflation also causes the inspiratory muscles to be shorter at the beginning of inspiration (77). The diaphragm can accommodate to this shorter length and thus readjust its length-tension relationship (78) so that maximal force generation is relatively well preserved during chronic hyperinflation (79). However, during acute hyperinflation the inspiratory muscles are shorter (80) and must contract at less-than optimal length leading to a loss of force generating capacity (81). Further, hyperinflation may flatten the diaphragmatic contour, causing the diaphragm to become less efficient (82) and increasing elastic load (83). These effects on inspiratory muscles render them less efficient both mechanically and energetically, predisposing to fatigue (84,85). Further, the increased inspiratory load may contribute to the onset of a more shallow, rapid breathing pattern (59-61); this in turn, worsens the dead-space/tidal volume ratio and further potentiates hypercapnia.

Cardiovascular function

Alveolar hypoxia is a potent stimulant to local pulmonary vasoconstriction (86). This is adaptive to the extent that this redistributes blood flow to areas where ventilation is better maintained. However, if the pulmonary capillary bed has been truncated through emphysematous destruction or if the redistribution to other regions exceeds the capacity to recruit additional capillary area, then pulmonary vascular resistance will increase. This in turn places a strain on the relatively pressure-intolerant right ventricle. Ultimately this may lead to pulmonary hypertension or overt right heart failure. In this condition, the heart becomes more pre-load dependent (87). Auto-P.E.E.P. may impair right ventricular preload (67-69,88). This may be particularly evident in the setting of volume depletion, which is especially common when patients have been ill for several days with decreased nutrient and fluid intake prior to seeking medical attention. Tachycardia is also common in these patients due to endogenous and pharmacologic adrenergic stimulation; this contributes to reduced diastolic filling and hence diminished preload (89). These circumstances may lead to significant reductions in cardiac output and even hypotension, especially with the institution of mechanical ventilation (68).

Hemodynamic Compromise Due to Auto-P.E.E.P.
Demonstration by Brief Interruption of Mechanical Ventilation

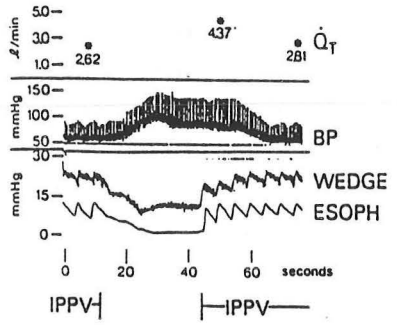


Fig. 1. Effect of temporary discontinuation of intermittent positive pressure ventilation (IPPV) on cardiac output ($\dot{Q}T$), systemic blood pressure (BP), wedge and esophageal (ESOPH) pressures in a patient with severe airflow obstruction (Patient 1).

Pepe and Marini, Am Rev Resp Dis 126:166,1982

Other effects of hypoxia

Alveolar hypoxia also causes regional bronchoconstriction, further contributing to airflow obstruction (90,91). Hypoxemia may interfere with respiratory muscle performance and contribute to respiratory muscle fatigue (92). Arterial desaturation and hypercapnia both may anesthetize the patient, producing somnolence and inability of the patient to cooperate with therapy (93). With profound hypoxia, lactic acidosis may ensue.

Respiratory drive

Patients with C.O.P.D. have increased neural drive (59,94) even though these patients may be less responsive to changes in arterial pH or CO_2 relative to normal individuals (95,96). Although it has commonly been observed that some C.O.P.D. patients with acute respiratory failure exhibit increases in PCO_2 during oxygen administration (97-99), it is not entirely clear that this occurs due to suppression of hypoxic drive (99,100). Hypoxic drive suppression has been reported during prolonged mechanical ventilation (100). However, in spontaneously breathing C.O.P.D. patients with acute decompensations, it is less clear whether this is due to loss of hypoxic drive as such patients exhibit a rise in PCO_2 without a decrease in minute ventilation (99). The change is more often ascribed to alterations in ventilation/perfusion matching induced by relief of hypoxic vasoconstriction (99,101-103). Furthermore, it should be noted that stable C.O.P.D. patients rarely exhibit significant CO_2 retention during oxygen administration (104) and when they do, it is usually on the order of only 3-5 mmHg (98,99). During acute episodes of respiratory failure on the other hand, changes in CO_2 due to ventilation/perfusion alterations with oxygen therapy are more pronounced, averaging 10-13 mmHg (98,99,105). Increases in arterial PCO_2 in excess of this would have to be taken as evidence of clinical deterioration.

Increases in $PaCO_2$ During Oxygen Breathing

Stable COPD	< 5 mmHg
Acute COPD	10-13 mmHg
Decompensating patient	> 15 mmHg

Respiratory muscle dysfunction

During an acute exacerbation, the respiratory muscles must work against substantially increased loads to accomplish greater levels of ventilatory work. As noted, the muscles must do so while operating at a mechanical disadvantage as the diaphragm is shorter and flattened. Other inspiratory muscles must be

recruited and the breathing pattern shifts towards greater rib cage and less abdominal displacement. Further, expiratory muscles are recruited and contribute significantly to the total work of breathing. To compound matters, hypoxia (92), acidosis (106), hypercapnia (107), low cardiac output (108,109), malnutrition (110-112), and electrolyte abnormalities such as hypophosphatemia (113,114), hypomagnesemia (115), hypocalcemia (116) or hypokalemia (117) may contribute to respiratory muscle dysfunction and fatigue.

The decompensating patient thus experiences increasing resistive and elastic work, marked increases in ventilatory requirements and the work of breathing (both inspiratory and expiratory), greater oxygen consumption and carbon dioxide elimination requirements, respiratory muscle inefficiency and fatigue, worsening gas exchange, and significant cardiovascular changes. The net effect of such changes is often a overwhelming cascade which culminates in overt respiratory failure.

PRECIPITATING CAUSES OF ACUTE EXACERBATIONS

Infection

The presence of a change in cough or sputum, fever, or leukocytosis (though not specific) should suggest acute infection. Infection of the lower airways is particularly common in these patients and may account for as many as half of all episodes of acute respiratory failure (118). C.O.P.D. patients appear to become infected with common respiratory pathogens (such as mycoplasmal and chlamydial agents, influenza and parainfluenza viruses, rhinoviruses, and coronaviruses) with a frequency which is similar to otherwise normal subjects in the same population (119,120). However, viral or mycoplasmal infection may be less well tolerated by C.O.P.D. patients (34), or perhaps more importantly, may predispose to bacterial colonization of the lower airways and acute bacterial bronchitis (121). When this occurs, the most common potentially pathogenic bacteria isolated are *S. pneumoniae, H. influenza, N. catarrhalis* (121,122). Despite the frequent occurrence of these agents in the sputum of patients with acute exacerbations of C.O.P.D., it remains difficult, if not impossible, to determine if an isolate is truly causing disease in a given patient (33). When present, bacterial bronchitis is thought to worsen airways function both through direct effects of purulent material blocking the airways, but also through local release of histamine by the infecting micro-organisms and/or recruited inflammatory cells (41,123,124). Invasive parenchymal infection may be present in a minority of patients with acute worsening of symptoms, however, the presence of pneumonia may portend a worse prognosis, a more prolonged course, and a greater need for intensive antibiotic therapy. Opportunistic infection can occur and should be considered in patients who have been on prolonged corticosteroid therapy, especially if they fail to respond to empiric antibiotic therapy (125-127).

Heart failure

Left-ventricular heart failure can cause or mimic an acute exacerbation of C.O.P.D. (12,118). The diagnosis may be difficult as C.O.P.D. patients with acute respiratory failure may experience orthopnea and have edema or central venous congestion due solely to their lung disease. Further, the radiographic pattern may not be characteristic due to the presence of bullous disease, vascular pruning, and hyperinflation with the resulting more vertical alignment of the heart shadow. The presence of diffuse infiltrates or pleural effusions should heighten the index of suspicion for the presence of heart failure. We have found that comparison of current films with older chest films is particularly valuable in this regard.

Pulmonary embolism

Patients with C.O.P.D. are prone to pulmonary embolism and this in turn may precipitate acute respiratory failure. Unfortunately for the clinician, pulmonary embolism may be particularly difficult to diagnose (128,129). The use of ventilation/perfusion lung scanning in patients with severe C.O.P.D. is particularly problematic. The diffuse yet inhomogeneous ventilation/perfusion abnormalities induced by the underlying disease diminishes the overall clinical utility of lung scanning since relatively few patients will have scans of sufficient specificity to be clinically useful, that is, either "high probability" or "normal" (130-133). The presence of deep venous thrombosis should be sought when the diagnosis is suspected since non-invasive methods may be used and anticoagulation would be indicated if studies were positive. However, nearly 30% of patients with pulmonary emboli have no detectable evidence of deep vein thrombosis (134,135). Thus, pulmonary angiography remains the primary diagnostic tool in many cases. This procedure, though invasive, is safe when properly performed; the mortality rate is 0.5% using modern techniques, even in the presence of significant pulmonary hypertension (136). Thrombolytic therapy should be considered only in those patients with an established diagnosis and hemodynamic compromise (137,138).

Other causes

Pneumothorax will be found in less than 1% of C.O.P.D. patients who present acutely (139,140) and is easily missed on the chest film when severe bullous disease is present (141). It should be considered nonetheless as correction of even a small pneumothorax may lead to profound clinical improvement in the tenuous patient (142). Inability or unwillingness of patients to use their medications may contribute to worsening of their status. Drug interactions or unwanted side-effects such as sedation should also be considered. Smoking may increase and drugs such as cimetidine or erythromycin may lower serum theophylline concentrations. Co-incident use of β-agonists and steroids may lead to

significant hypokalemia, which may interfere with respiratory muscle function (117). The over-use of diuretics may also cause problems due to potassium loss and hypokalemic effects on muscle function as well as volume-contraction metabolic alkalosis and subsequent suppression of respiratory drive (140).Non-specific airway irritants such as air pollutants or cigarette smoke may also contribute to or cause acute decompensations (143-145).

APPROACH TO MANAGEMENT

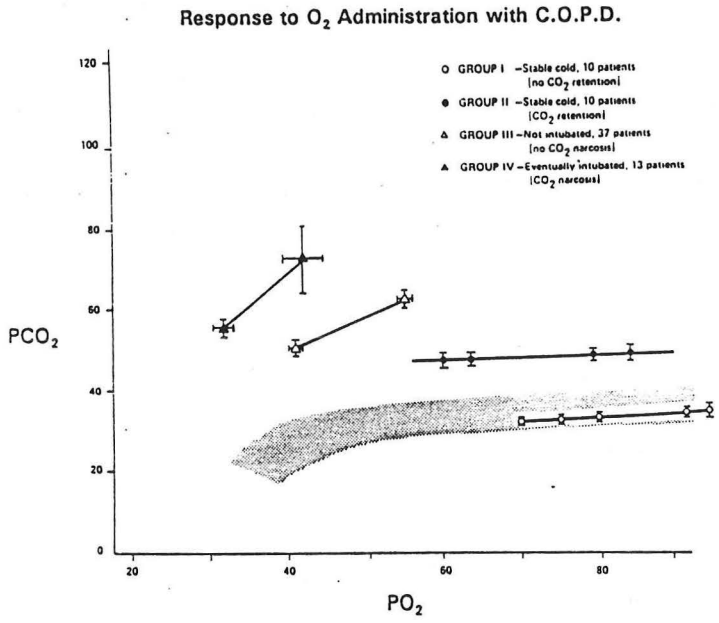
Oxygen therapy

The single most important therapeutic intervention in C.O.P.D. patients with acute respiratory failure is the correction of hypoxemia (12,97). Given the adverse consequences of hypoxia (see above), the beneficial effects oxygen administration include: reversal of global hypoxia, especially to critical organs such as brain and heart, elimination of lactic acid production, cardiac afterload reduction through relief of reactive pulmonary vasoconstriction, improved cardiac output, diuresis, correction of cardiac dysrhythmias, reduction in minute ventilation requirements, diminished work of breathing, decreased oxygen consumption, lower carbon dioxide production, relief of dyspnea, improved respiratory muscle endurance, and bronchodilation (86,89-93,101,146,147).

The goal of oxygen therapy should be to achieve an acceptable level of arterial oxygen content, which will occur at O_2 saturation levels of about 90% (12). Because the principal mechanism for hypoxemia in this setting is ventilation/perfusion mismatching (57), correction of hypoxemia can usually be accomplished through the administration of low levels of supplemental oxygen, for example 2-4 L/min of oxygen via nasal cannula (98). Oxygen is begun at 1-2 L/min and is incrementally advanced until an arterial saturation of about 90% is achieved. Controlled oxygen can also be administered using low-F_IO_2 Venturi masks using the same approach of starting at low levels and advancing as needed. We prefer the use of nasal canula as this does not interfere with administration of inhaled medications, suctioning, expectoration, talking, eating, or drinking. Further, most patients in this condition find any type of mask to be confining and claustrophobic. There need not be concern about the patients pattern of breathing ("mouth" vs "nose") as long as the patient does not have complete nasal obstruction; oxygen instilled into the nasopharynx will be entrained with the inspiratory airstream in any event. Simple face masks with low flow oxygen are unacceptable due to the excessive dead space ventilation.

It has long been recognized that the PCO_2 level may increase following the administration of oxygen (97-99). As discussed above, contrary to earlier teachings, the mechanism by which this occurs is primarily through alterations in

ventilation/perfusion relationships rather than via suppression of the so-called hypoxic respiratory drive (12,99-103). Thus, it is reasonable to expect a modest increment in the PCO_2 in some patients following the administration of oxygen and it is reasonable to give only as much supplemental oxygen as is necessary to raise the oxygen saturation to about 90%. The practice of removing oxygen from a hypoxic patient has no justification based upon our current understanding (12). Further, even the brief or intermittent removal of oxygen can lead to levels of hypoxia significantly in excess of pre-treatment levels and re-establishment of adequate oxygenation may not occur immediately upon restoring supplemental oxygen.



Bone et al, Am J Med 65:896,1978

This is not to say that PCO_2 levels should not be monitored. Blood gases should be obtained over the course of management to both insure that adequate oxygen is being administered and to gauge the patient's response to overall therapy. Oximetry is unreliable in this regard as excessive oxygenation may be missed and no information about PCO_2 is available (148). End-tidal CO_2 monitoring has not reached a level of technical reliability to be useful in this circumstance (149) .In this regard it should be remembered that patients who are truly at their baseline rarely exhibit increases in PCO_2 in response to oxygen therapy (104,150), and when they do it is only on the order of 3-5 mmHg (98,99,150). During an acute illness, changes in PCO_2 ascribable solely to oxygen administration are usually only about 10-13 mmHg (98,99,105). Any increase in PCO_2 at all should be taken as evidence that the patient is in fact not at baseline (150) and increases in excess of 10-13 mmHg should be interpreted as representing overall deterioration.

Adrenergic bronchodilators

The use of inhaled adrenergic stimulants in C.O.P.D. patients with acute respiratory failure is well established (12,118,140). Despite the fact that stable patients have little or no demonstrated pulmonary function response to adrenergic challenge, most will demonstrate both objective and symptomatic response to these agents during acute exacerbations (151-153). In general it is preferable to use agents which are β-selective in order to attempt to minimize side-effects; however, it is likely that greater advantage is achieved in this regard by using proper administration technique rather than through the choice of a particular drug (see below). Inhaled β-agonists are often required in higher doses and more frequently during acute exacerbations (see below). Initial treatments can be given every hour for 3-4 doses as long as the patient is carefully monitored; as the patient improves, the dosing interval is prolonged to every 4 or 6 hours (118). Shorter acting agents may be considered during the initial phases of management. In general, patients with C.O.P.D. tend to be older and to have a higher incidence of underlying cardiovascular disease than asthmatics; as such we avoid non-β-selective agents such as isoproterenol or epinephrine as well as avoiding parenteral or oral routes of administration in patients with C.O.P.D.

Cholinergic bronchodilators

The respiratory airways contain both adrenergic and cholinergic receptors. Atropine and its related congeners causes bronchodilation through competitive inhibition of the parasympathetic innervation of bronchial smooth muscle (154). Further, the muscarinic receptors to which atropinergic agents bind are distributed predominantly in the larger, proximal airways, unlike the adrenergic receptors which are found predominantly in the peripheral airways. This differential mode of action and anatomic distribution serves as the principal rationale for the use of atropine and its related compounds alone or in combination with other agents (50,154). These differences might be particularly salient during an acute exacerbation when aerosol deposition to the lower airways is least achievable.

Atropine causes bronchodilation but because it is a tertiary amine (and thus lipid soluble) it is rapidly absorbed from the respiratory tract and causes significant side-effects. It also tends to dry the airways. For these reasons, atropine is no longer recommended as a bronchodilator. Ipratropium bromide is an atropine-like compound which is a quaternary amine (and thus lipid insoluble) which has similar bronchodilating properties, but which is not systemically absorbed. Systemic side-effects are thus practically non-existent (154). Though not available in the United States in solution form for jet nebulization, the drug can be given to mechanically ventilated patients using an adapter in the inspiratory circuit (155).

Ipratropium has similar bronchodilating activity compared to β-agonist agents in C.O.P.D. patients who are stable (156,157) and during acute exacerbations (151,153,156). The dose of ipratropium must be doubled in the acute setting to achieve maximal effect (153). There is conflicting evidence with regard to presence of any additive benefit to using both ipratropium and a β-agonist in combination for patients with acute exacerbations of C.O.P.D. (152,158). It may be that any additive effect may occur only in the early stages of treatment (158). β-agonists may cause transient hypoxemia through their effects on the distribution of pulmonary blood flow and ventilation; ipratropium does not appear to cause hypoxemia in this setting (151,159,160). Ipratropium also appears to have a longer duration of action than some β-agonists (157). For these reasons it would seem reasonable to consider using ipratropium as a first line agent, as alternative therapy in those with tenuous oxygenation, or in combination with β-agonists during the first few hours of treatment.

Aerosol delivery

The use of aerosolized medications, especially β-agonist agents is well established as a means of promoting both objective and symptomatic improvement in patients with C.O.P.D. (see above). However, there are several important aspects to be considered for hospitalized C.O.P.D. patients with acute respiratory failure including the method of aerosolization and dose administered.

Aerosol medications can be delivered using metered-dose inhaler (M.D.I.), metered-dose inhaler with a spacing adaptor (M.D.I.-spacer), or using pressure-driven jet nebulization (nebulizer). Although intermittent positive pressure breathing devices (I.P.P.B.) have previously been used for this purpose, there is little, if any, role for I.P.P.B. as a method of delivering medications in current practice (161).

Lower airway deposition is responsible for clinical efficacy (162). Oropharyngeal deposition, on the other hand, leads to systemic absorption which produces little bronchodilation at these doses while producing significant unwanted side-effects (163,164). Even though each of these methods is inherently inefficient in terms of lower airway deposition, each is capable of delivering adequate drug to the lower airway to promote clinically significant bronchodilation (163-167). In achieving this goal, however, the method chosen, technique employed, administered dose, and relative degree of airways obstruction may all be important (163,164). Methodologic short-comings may be overcome by increasing the administered dose. However, if a large fraction of this is wasted (e.g. vented to the room) or results in oropharyngeal deposition, then the net result will be no additional clinical improvement and/or an unacceptable level of side-effects (164).

Metered-dose inhaler delivery is convenient and relatively inexpensive; however, a significant number of patients cannot learn to use the device properly,

even with instruction (168,169). The addition of a spacing device can largely overcome user-dependent methodologic problems, as well as enhancing lower airway deposition (168) while minimizing oropharyngeal deposition and side-effects (170). Compressor driven nebulization has traditionally been used in acutely ill patients, but because it is inherently less efficient much larger doses must be administered as compared to M.D.I. (163). There is no demonstrable clinical advantage to nebulization over M.D.I. (particularly with a spacing device) in stable outpatients with either asthma (171,172) or C.O.P.D. (173,174). Similarly, in the acute management of patients in the emergency room there is no significant difference between the two methods of aerosol delivery (175,176). Indeed, the use of M.D.I. can lead to significant cost savings relative to nebulization (177).

Several studies have shown similar results in patients hospitalized with acute exacerbations of C.O.P.D. (178-180). However, standard maintenance doses delivered using M.D.I. to hospitalized patients produces less bronchodilation than nebulization (181). Because extremely impaired airways function reduces the fraction of administered aerosol delivered to the lower airway (170,182), higher doses can be required during an acute illness to produce equivalent bronchodilation (163,165,183). When higher doses of drug are administered via M.D.I. with a spacer during an acute exacerbation of C.O.P.D., then similar results can be obtained as compared to nebulization (180) at less cost (177). To achieve these results, the dosage of drug administered via M.D.I. may need to be increased by two to four fold (163,165,180). Thus, it would seem reasonable to use metered-dose inhaler delivery with a spacer and with an appropriate dosage adjustment in many hospitalized patients. However, it should be noted that most studies comparing these techniques have excluded patients with severe illness and there are no reliable data which compare these two delivery systems in C.O.P.D. patients with acute respiratory failure. As nebulization may be superior to M.D.I. in patients with very severe obstruction (167,184) or when patients cannot fully co-operate with proper M.D.I. use (163,165), it would seem prudent to continue to use nebulization in at least some patients who present with acute respiratory failure.

Aminophylline

Controversy continues to surround the use of theophylline and aminophylline (185). The methylxanthines are mild to moderate bronchodilating agents (186-190). Theophylline has other activities which affect the respiratory system including enhanced diaphragmatic contractility and endurance (191-196), better right ventricular performance (197), and improved mucociliary clearance (198). However, the drug has the potential for serious toxicity, a narrow therapeutic window, and its clearance and bioavailability may be altered considerably during an episode of acute respiratory failure (199-202). For these reasons it has generally been recommended that the drug be given as an

intravenous infusion for seriously ill patients such as those with acute respiratory failure (185) and that drug levels be used to adjust dosing (199,200). It has been suggested that one potential advantage to the use of intravenous aminophylline is that more steady concentrations are achieved and that this might serve to provide more even bronchodilation between aerosol treatments (203). Nonetheless, one placebo-controlled trial of intravenous aminophylline failed to demonstrate benefit in C.O.P.D. patients with acute exacerbations; however, it is important to recall that the study by Rice, et al, excluded patients requiring mechanical ventilation (204).

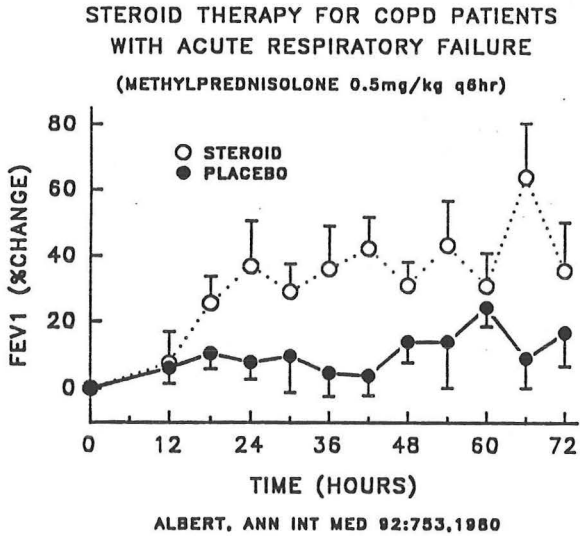
Given the overall risk/benefit profile of this drug, it would seem prudent to always err on the side of more conservative drug levels. It is our current practice use intravenous aminophylline as a continuous infusion (.05-.10 mg/kg/hr) while monitoring drug levels and attempting to establish steady concentrations between 10 and 15 mg/L (note that this is lower than previous convention which was to use a range of 10-20 mg/L). Loading doses should probably not be given unless the pre-infusion drug level has been measured.

Antibiotics

Antibiotics have long been in used in general practice to treat acute exacerbations of C.O.P.D. and most general reviews of the subject continue to recommend their use (12,118,140). However, the evidence favoring their use in patients who do not have proven, invasive infection (i.e. pneumonia) is lacking; several carefully performed, placebo controlled trials have shown no benefit in patients with acute exacerbations of C.O.P.D. (205,206). This is not surprising since bacterial isolates are not invariably identified and may or may not be truly pathogenic when present, and since other infectious agents such as viruses or non-specific irritants may cause precipitations in many cases (see above). Several authors have expressed concern about withholding antibiotics in severely ill patients, arguing that the patient's respiratory reserve may be so tenuous that even marginal benefits might be important (207). When bacterial pathogens are isolated they are usually found to be *S. pneumoniae, H. influenza, or M. catarrhalis* (124). Antibiotics which would be useful in this setting are generally well-tolerated (205,206). Given these considerations it would seem prudent to use simple, broad-spectrum antibiotics in those C.O.P.D. patients with acute respiratory failure, especially if signs suggesting infection are present (such as fever, leukocytosis, purulent sputum). Agents such as trimethoprim-sulfamethoxazole, ampicillin, amoxicillin, a tetracycline, or erythromycin are generally effective and well-tolerated. More expensive agents such as oral cephalosporins and quinolones are probably as effective. Oral agents can be used in most cases. Parenteral antibiotics should be used in those who cannot tolerate oral therapy, in those who are immunocompromised, or for suspected pneumonia.

Corticosteroids

Only a small percentage of patients with stable C.O.P.D. benefit from the long-term use of corticosteroids (208,209) and it is difficult to identify such patients without an empiric trial (210). In the setting of acute respiratory failure requiring hospitalization, however, one important study has shown that, on average, patients benefit from the administration of systemic corticosteroids (211). Albert, et al, studied 44 patients with C.O.P.D. who were admitted with acute respiratory failure. All patients received standardized therapy and were prospectively randomized to receive either placebo or intravenous methylprednisolone, 0.5 mg/kg (approximately 40 mg) every 6 hours for 72 hours. Patients receiving steroids showed significantly greater improvement in $F.E.V._1$. No convincing effect was apparent in the first 12 hours and the study was not extended beyond 72 hours. No other reliable studies are available in patients with C.O.P.D. who are hospitalized with acute respiratory failure. Studies in hospitalized asthmatics would suggest that there is no benefit to doses of methylprednisolone in excess of the dose used in the study by Albert et al. (212). There is no data which addresses the issue of how long to continue steroid therapy beyond 72 hours in patients with C.O.P.D. Common practice would suggest that patients who were not previously receiving maintenance doses of oral steroid can either receive no further steroid or an abbreviated tapering course of prednisone beyond the initial period of intravenous therapy. The use of steroids for a patient with C.O.P.D. who requires hospitalization should never be taken as evidence that the patient should receive long-term steroid therapy. There is no indication for the use of inhaled steroids in the acute setting; indeed, patients do not tolerate many of these agents well, if at all, during acute exacerbations.



Physiotherapy

Chest physiotherapy includes assisted cough, suctioning, chest percussion, postural drainage, and fiberoptic bronchoscopy. Generally, the patient who has an effective spontaneous cough will be able to successfully clear their airways of secretions. However, some patients who have ineffective spontaneous cough or whose secretions are particularly copious or thick may derive modest benefit from some form of chest physiotherapy (213,214). However, while these techniques may increase the volume of sputum produced in some patients (214), there is little data which suggests that this improves gas exchange, shortens the duration of symptoms or hospitalization, or improves survival (215-217). Further, these techniques may actually cause decrements in PO_2 during and after treatment (215,216,218) and significant cardiac arrhythmias can occur in as many as 11% (218). Thus, these techniques should be used sparingly and only in patients who cannot spontaneously cough and who have significantly thick or copious secretions, who can co-operate with the treatment, who can tolerate the treatment, and who demonstrate some objective and subjective benefit after an initial trial. Assessment of benefit should be made based upon secretion clearance, lung mechanics, and blood gas data. If no improvement occurs after initial trials of physiotherapy, then it should be stopped.

Bronchoscopy has been used as an adjunct to removal of secretions in patients receiving mechanical ventilation. However, the literature suggests that bronchoscopy is no different than standard measures in managing airway secretions or resolving atelectasis (219). It may be reasonable to employ bronchoscopy as a diagnostic tool to exclude or remove an obstructing lesion such as a tumor or aspirated foreign body in selected patients. However, beyond an initial evaluation in patients with significant radiographic volume loss or atelectasis which does not clear with standard therapy, bronchoscopy is serving only as an expensive suctioning catheter.

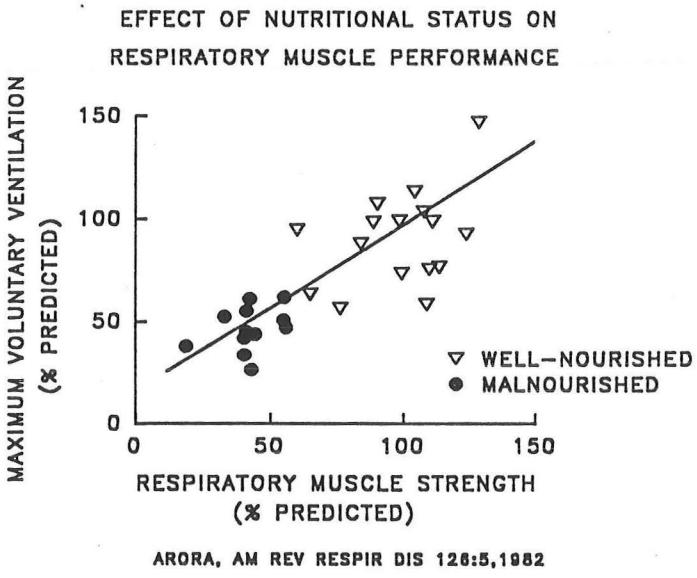
Mucolytics

Oral mucolytics have been reported to shorten the duration of expectoration in episodes of acute bronchitis (220,221); however, they have no proven benefit in the setting of acute respiratory failure. Although conventional teaching suggests that sputum expectoration can be improved through the administration of fluids, this has not be shown to occur when it has been tested (222). Fluid management should be directed at correcting volume and/or electrolyte deficits. Aerosolized mucolytics such as acetylcysteine produce intense bronchial irritation, cough and bronchospasm in most patients. This agent cannot be recommended in the majority of cases and probably should be avoided in patients who are breathing spontaneously. Dilute acetylcysteine may be used in a small number of selected

patients who are receiving mechanical ventilation and who have significant, bronchoscopically proven mucous inspissation which has not responded to standard measures. The patient is first given a bronchodilator treatment and then 10% acetylcysteine diluted 1:10 in 10 ml of normal saline is injected into the airway. This is followed by saline lavages and further suctioning.

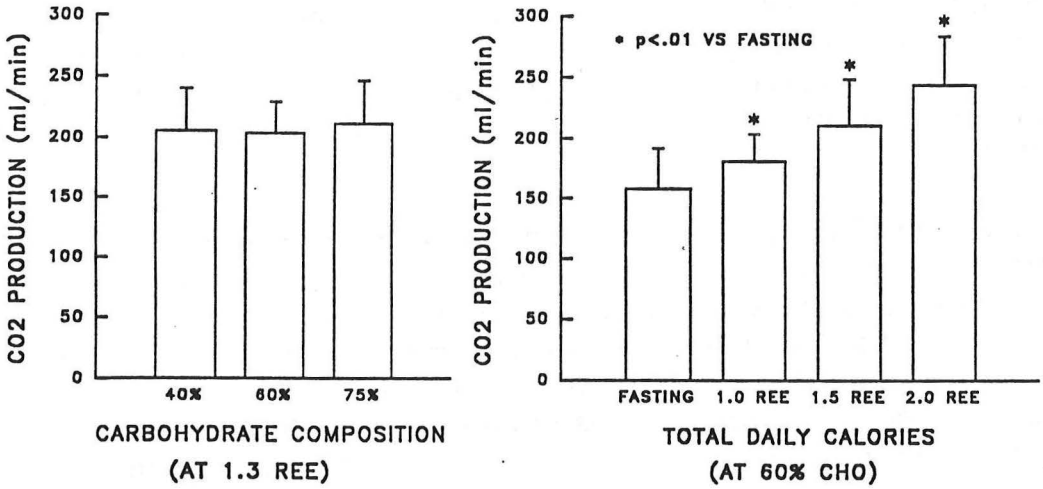
Nutritional support

The topic of nutritional support in the critical care setting was fully explored by Dr. Claibe Yarbrough in his recent Internal Medicine Grand Rounds (223). This section will be confined to observations pertinent to those patients with C.O.P.D. Malnutrition is common in patients with C.O.P.D. (110,224-228) and tends to be particularly prevalent in those with emphysema (226) and those with the most severe lung function (227,228). Nutritional status tends to decline markedly during acute illness in C.O.P.D. patients (224,225,228) and patients may not recover to their previous nutritional state during convalescence, leading to a step-wise decline over time (229). Malnutrition is associated with impaired respiratory muscle function (110,111) and immune status (224,225). Improvement in the patient's nutritional state has been associated with improvement in indices of respiratory muscle function in both stable (112) and acutely-ill patients (110,230). One study (though retrospective and non-randomized) has suggested that nutritional support may be an important determinant of weaning success (231). Thus, there are data which support the theory that nutritional intervention would be of benefit to C.O.P.D. patients with acute respiratory failure.



Nonetheless, there are a paucity of data which demonstrate conclusively that nutritional intervention effects outcome in these patients. Indeed, it could be said that, "there is no such thing as a free lunch." Caloric administration in any amount or type will lead to an increase in total oxygen consumption and carbon dioxide production, both of which will increase ventilation requirements (232). In susceptible patients, the administration of nutritional support may lead to worsening hypercapnia (233) or overt respiratory failure (234). The respiratory quotient (RQ) is the ratio of carbon dioxide produced relative to oxygen consumed during metabolism (VCO_2/VO_2). Because the RQ associated with carbohydrate oxidation (RQ = 1.0) is higher compared to other substrates such as protein (RQ = 0.8) or lipid (RQ = 0.7), some have raised concerns about providing nutritional support in high carbohydrate concentrations to patients with severely impaired lung function (234,235). The practical significance of recommendations to provide a greater fraction of caloric intake in the form of lipid has been questioned (229,236). In those cases where nutritional support has been reported to cause worsening hypercapnia (233,234), the total caloric supplementation being provided was very high (usually 2000-2500 kcal/day or more). Talpers, et al has shown that when mechanically ventilated patients are provided isocaloric diets of varying carbohydrate composition (40-75% of calories as carbohydrate), there is no significant difference in carbon dioxide production. However, these investigators did observe significant increases in carbon dioxide elimination with progressive increases in total calories provided with constant carbohydrate composition (236). This suggests that total calories rather than carbohydrate composition is of greater relevance.

EFFECT OF CARBOHYDRATE COMPOSITION VS
TOTAL CALORIC INTAKE ON CO2 PRODUCTION
TALPERS, CHEST 102:551(1992)



Based upon these observations it would seem reasonable to provide nutritional support to C.O.P.D. patients as soon as possible during an episode of acute respiratory failure. The goal of therapy should be to provide adequate, but not excessive, nutrition. In general, this can best be accomplished using enteral alimentation where possible to provide total calories of from 1.25 to 1.3 times the resting energy expenditure (R.E.E.) of the patient (236). The R.E.E. can be derived in one of several ways: (1) calculated using the Harris-Benedict equations (237), (2) determined by indirect calorimetry, where oxygen consumption, VO_2, and RQ are measured using a metabolic cart (238,239), or (3) estimated using the Fick relationship from pulmonary artery catheter measurements of cardiac output, hemoglobin, and arterial and mixed venous O_2 saturations to determine VO_2, where R.E.E. (kcal/day) = VO_2 (ml/min) X 7.0 = Q X [Hb] X (SaO_2 -SvO_2) X 95.18 (240).

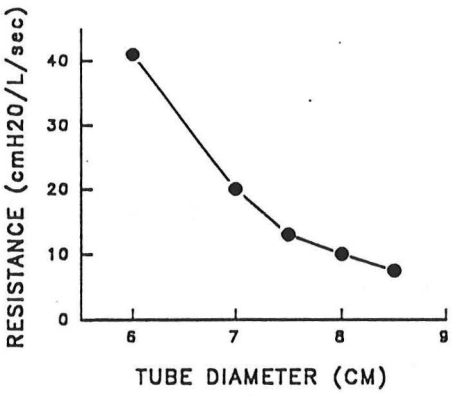
MECHANICAL VENTILATION

Supportive mechanical ventilation

Mechanical ventilation may be required in many, but not all, C.O.P.D. patients with acute respiratory failure. The indications for intubation are largely based upon clinical judgement. Blood gas values, especially the combination of pH and PO_2, are of some use in predicting which patients will ultimately require intubation (98). However, it is not possible to establish blood gas criteria which alone would determine the need for intubation. Important in this regard are such considerations as the patient's mental status, hemodynamic function, response to initial treatment, and appearance of fatigue or distress. The direction and rate of change in blood gas values are probably of greater value than absolute values. The patient's wishes regarding the use of life-support interventions should be considered if known. Clearly, where ambiguity exists with regard to the latter, it is generally wiser to institute mechanical ventilation if it is felt to be medically indicated.

Mechanical ventilation is initiated after endotracheal intubation. This should be performed expeditiously, but without undue haste; ventilation and oxygenation can almost always be maintained in the short-term with properly applied bag-assisted ventilation using 100% oxygen. Intubation should be performed with the largest size endotracheal tube possible to facilitate the later weaning process (56). The goal of mechanical ventilation is to provide ventilatory support for a period sufficient to allow reversal of the acute process and respiratory muscle rest and recovery. For these reasons, it is desirable to provide support using a mode in

EFFECT OF ENDOTRACHEAL TUBE DIAMETER
ON AIRWAY RESISTANCE AT 120 L/min



WRIGHT Am Rev Respir Dis 140:10(1989)

which the ventilator performs the bulk of the work of breathing. This can be accomplished using controlled ventilation (C.M.V.). Although other modes of ventilation such as assist/control or intermittent mandatory ventilation (I.M.V.) may not ablate the patient's respiratory work altogether (241), when used in the proper fashion they serve as effective means of supportive ventilation. Indeed, if the patient's respiratory drive is ablated through physiologic (respiratory alkalosis) or pharmacologic (sedation/paralysis) means, then each of these modes become functionally equivalent.

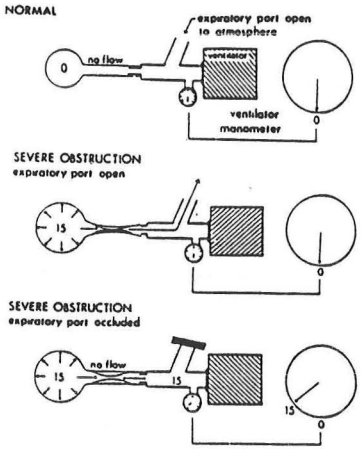
Initial Ventilator Settings for COPD

Tidal volume	10-12 ml/kg
Breathing frequency	8-10 breaths/min
Inspiratory flow rate	100 L/min
Oxygen concentration	100%

The management and manipulation of the volume ventilator during an episode of acute respiratory failure were discussed by Dr. Alan Pierce in his excellent Grand Rounds (242); the reader is referred there for a more comprehensive discussion of this subject. The initial tidal volume should be approximately 10-12 ml/kg as these patients are already significantly hyperinflated and breathing near TLC where the risk of barotrauma is greatest (243). The respiratory frequency should be held to 8-10 breaths/min to avoid excessive alkalosis and reduced cerebral blood flow (244). A high inspiratory flow rate of around 100 L/min should be used as this tends to maximize gas exchange and respiratory mechanics (245). All three of these strategies will also have the salutary effect of maximizing the time available for exhalation, thus reducing air-

trapping, hyperinflation, and auto-P.E.E.P. (see above). Reducing tidal volume and increasing inspiratory flow rate reduce inspiratory time; reducing respiratory rate prolongs the total cycle time. These parameters may need to be individualized as needed based upon patient tolerance and comfort as well as subsequent blood gas values. While the higher inspiratory flow rate may require fairly high peak proximal airway pressures in this setting, in general the beneficial effects with regard to improved gas exchange and minimization of auto-P.E.E.P. outweigh this problem.

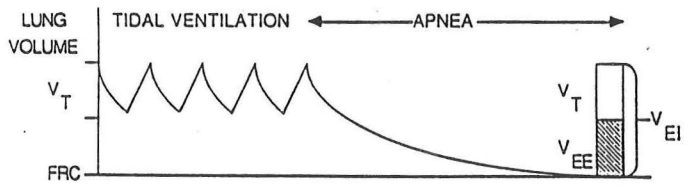
Measurement of Auto-P.E.E.P. During Mechanical Ventilation
The End-Expiratory Hold Maneuver



Normal alveoli have returned to their resting volume by the end of exhalation and pressures are atmospheric. In the presence of severe obstruction, alveoli may not have completely emptied at the end of the expiratory phase and thus are inflated above resting lung volume and still have a positive recoil pressure. This is not detected in the proximal airway during normal exhalation because of the upstream resistance and as the expiratory port is open to atmoshpere. The presence of this occult positive end-expiratory alveolar pressure (auto-PEEP) can be demonstrated by observing the proximal airway pressure during an occlusion of expiratory port at the very end of the expiratory phase (i.e. immediately prior to the next inspiratory cycle).

Pepe and Marini, Am Rev Resp Dis 126:166,1982

Estimation of Hyperinflation During Mechanical Ventilation



The total volume exhaled from the end-inspiratory volume (V_{EI}) during a period of apnea includes the tidal volume (V_T) and the volume trapped at end-exhalation (V_{EE}) due to dynamic hyperinflation (from Tuxen and Lane, Am Rev Resp Dis 136:872,1987).

The patient is usually begun at a high F_IO_2 in order to insure adequate oxygenation; however, this can generally be reduced promptly based upon blood gas and/or oximetric data. Frequently only modest levels of oxygen supplementation are needed since the primary mechanism of hypoxemia is ventilation/perfusion mismatching. The F_IO_2 should be reduced to the lowest level needed to maintain oxygen saturation around 90%.

Mechanical Ventilation for COPD:
Indicators of Improvement

Peak airway pressure
Minute ventilation
Dead space
Auto-PEEP
Airtrapping
A-aO_2 gradient

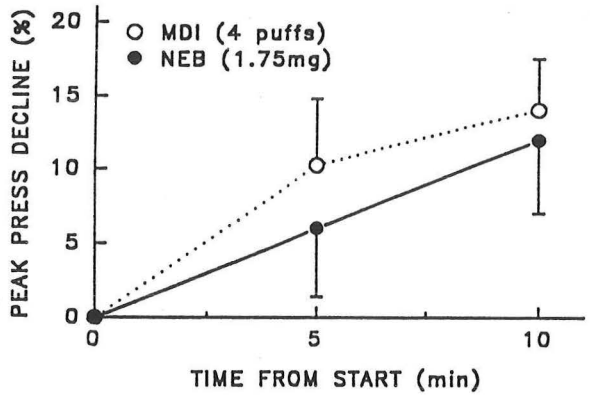
Improvement will be accompanied by a reduction in peak airway pressure, decline in minute ventilation requirements relative to PCO_2 (dead-space ventilation), improvement in A-aO_2 gradient, decline in auto-P.E.E.P., and reduction in airtrapping. Auto-P.E.E.P. is assessed by performing an end-expiratory hold maneuver (68). One should recall that most patients with severe C.O.P.D. will have some degree of auto-P.E.E.P. (5-10 cm H_2O) even when stable (70). Although determination of absolute intrathoracic gas volumes is not practical in the I.C.U., the degree of hyperinflation above the patient's true end-expiratory lung volume (FRC) can be estimated by briefly turning the respiratory frequency down so that expiratory time is greatly extended; the difference between the delivered tidal volume and the total volume exhaled during this prolonged expiratory phase is an indication of the volume trapped during ongoing ventilation (88,246,247). Neither of these methods may be possible if the patient is agitated or making significant respiratory effort. Paralytic agents should not be used solely for the purpose of making such assessments.

Aerosol delivery during mechanical ventilation

Aerosolized medication delivery is possible for patients receiving mechanical ventilation using either nebulization or metered-dose inhalers. The nebulizing device is placed in-line with the inspiratory circuit limb leading to the patient rather than in the connecting piece or Y-adapter (248-251). The medication solution is then nebulized by a gas source driven either by the ventilator or by an external pressurized gas source (compressed air or 100% oxygen). External nebulizing techniques produce continuous nebulization and thus are much quicker to administer, reducing therapist time and delivering the drug more rapidly to the patient. However, as the gas source is usually not of the same O_2 fraction as the ventilator, the patient's actual F_IO_2 during the nebulization will likely be quite different from the ventilator's setting. Further, the externally supplied gas will likely lead to differences in delivered inspiratory flow rate and volume than would be expected from the ventilators settings. Thus, extreme caution must be exercised when interpreting physiologic or blood gas data collected during nebulization. Many modern ventilators have a nebulization circuit which can be used to drive the in-line nebulization. This usually obviates the variations in F_IO_2 encountered when externally-driven nebulization is used. However, it is important to realize that some

ventilators use continuous nebulization while others use intermittent nebulization which cycles only with each inspiration. Continuous nebulization generally results in more rapid deposition of aerosol (248,251) and more complete deposition to the patient (251) as compared to intermittent nebulization. Use of a higher flow rate to drive the nebulizer (e.g. 8 L/min) results in more rapid drug delivery and better deposition (252).

METERED–DOSE INHALER (MDI) vs JET NEBULIZATION (NEB)
ADMINISTRATION OF FENOTEROL DURING MECHANICAL VENTILATION



FULLER, AM REV RESPIR DIS 141:440,1990

Medication can also be delivered to mechanically ventilated patients using metered-dose inhalers to achieve significant bronchodilation (155,249,253,254). An adapter with a reservoir (249) is placed in-line with the inspiratory circuit limb; the M.D.I. is attached and activated at the very end of the expiratory cycle or just at the beginning of inspiration. The machine is allowed to cycle through several breaths between each actuation. The use of in-line M.D.I. produces similar levels of bronchodilation and is as well tolerated as compressor-driven nebulization (253,254). Further, the use of the M.D.I. requires less time to deliver and may result in cost savings (254). As noted above, the dose administered using M.D.I. in mechanically ventilated patients likely must be increased above standard maintenance doses (183,253,254); however, the ideal number of activations has yet to be determined for any of the medications available in M.D.I. form.

Weaning from mechanical ventilation

Patients with C.O.P.D. who require mechanical ventilation will need ventilatory assistance until the precipitating factors and physiologic consequences of the acute episode are corrected so that respiratory work requirements are minimized (12,55). Concomitantly, the respiratory muscles will need a period of

relative rest to overcome muscular fatigue so that function of the ventilatory pump is restored (255). In general, restoration of respiratory muscle function requires approximately 24-48 hours of mechanical ventilation (255-257). By this point, consideration should be given to removing the patient from the ventilator. Indeed, 3 out 4 patients will be successfully weaned within the first 72 hours (258). The first step in this process is to evaluate the overall balance between the patient's ventilatory needs and ventilatory reserve. This is generally accomplished by combining the physician's clinical assessment of the patient with simple bed-side physiologic measures. A variety of such measures, referred to as "weaning parameters," have been described. All such schemes attempt to incorporate simple measurements which give information about the mechanics of breathing, ventilation requirements, gas exchange, and respiratory drive. In general, these measures are predictive of weaning success. However, it should be remembered that the majority of patients will be readily extubated without complication in the first 72 hours and as many as 29% of patients who do not fulfill these criteria can still be readily extubated (55). Indeed, in patients with C.O.P.D. who require prolonged mechanical ventilation, initial measures of standard weaning criteria have a poor correlation with ultimate weaning success (259-263) and clinical improvement and successful progression to weaning occur without necessarily being accompanied by improvement in these weaning parameters (264).

Commonly Used Weaning Parameters

Resting minute ventilation (V_E)	< 10-15 L
Vital capacity (VC)	> 10 ml/kg
Max. inspiratory pressure (MIP)	< -20 cmH_2O
F_IO_2 for O_2 90% saturation	< 0.60
Max. voluntary ventilation (MVV)	> 2 X V_E
Ratio of f/V_T (breaths/min/L)	< 100

Once the initial support phase of mechanical ventilation has passed, then simple weaning parameters can be measured. At the same time, the patient should be placed on a brief period (15-30 minutes) of spontaneous T-piece breathing for purposes of assessment (258). The proper conduction of such a trial requires that the patient be adequately prepared. The patient should be seated comfortably in a chair or in Fowler's position if he must be kept in bed. The trial should ideally take place early in the day when the patient is well rested. The patient should be well rid of the effects of sedation or paralytic agents. The process and intent of the trial should be carefully explained to the patient. The airway should be cleared by having the patient attempt to cough and by suctioning. Once the patient is fully prepared, then the ventilator is discontinued and the patient is attached to 40-50% oxygen which is warmed, humidified and attached to the patient's endotracheal tube via a T-piece connector. The flow rate of adjusted so that there is still evidence of the humidified gas escaping from the end of the tube during inspiration; this ensures that the patient is not entraining room-air. The patient is then coached to breath comfortably with slow,

deep inspiratory efforts and a slow breathing frequency (265). The trial is continued as long as the patient appears comfortable, maintains an acceptable cardiac rhythm and rate, maintains a respiratory rate which is acceptable (e.g. less than 25-30 breaths/minute), and continues to have adequate oxygenation (e.g. saturation >90%). At the end of the trial a blood gas sample is obtained and the patient is returned to the ventilator (258,264). The trial is considered successful if the patient remains comfortable, has stable pulse and respiratory rate, maintains adequate oxygenation (e.g. PO_2 >60 mmHg, and saturation >90%), and there is no significant CO_2 retention (e.g. < 5 mmHg PCO_2 increase or fall in pH).

Those who demonstrate the ability to sustain unassisted ventilation during such a trial and who have met the standard bedside weaning criteria can be immediately extubated and expected to do well 90% of the time (258). Those who did not meet the standard weaning criteria but who nonetheless were able to sustain T-piece breathing without problem should be considered for extubation at that point. Those who appear to do poorly during the initial trial should undergo a repeat T-piece trial several hours later as patients may demonstrate changes early after first discontinuing mechanical ventilation which are not necessarily reflective of their more sustained performance (259-262,266). Ultimately, the decision to extubate the patient is a clinical judgement which tempers the patient's ability to sustain spontaneous breathing and the resources immediately available to handle clinical deterioration. Extubation may relieve the patient of a significant source of airways resistance, especially if the endotracheal tube if of narrow bore (55,56). If adequately trained personnel are readily available, then the risk of re-intubation under controlled circumstances should be minimal (267,268). The potential risks and morbidity of unnecessary continued mechanical ventilation cannot be accurately determined, but clearly mechanical ventilation is not without risk or discomfort.

A more prolonged and concerted effort may be required to achieve successful weaning in the small group of patients who fail early attempts to extubate. In these patients it is not likely that the choice of a specific mode of weaning is of particular relevance (12). T-piece trials (264,269), intermittent mandatory ventilation (I.M.V.) (269-272), and pressure support ventilation (P.S.V.) (273) have all been used with success. However, no outcome-based study has demonstrated the superiority of one mode over another (269). The choice should be based upon such factors as the experience and familiarity of staff with a particular mode as well as patient comfort and tolerance.

T-piece allows the patient to breath spontaneously and completely free from the ventilator while simultaneously requiring that a member of the patient care team be present to coach, encourage, and monitor the patient. Using this technique, the patient is started on short periods of T-piece breathing (e.g. 5-10 minutes) interspersed with two-hour periods of rest on a support mode of mechanical ventilation (258,264). The duration of T-piece trials is then progressively increased as

tolerated until the patient is able support continuous spontaneous breathing. If the patient is not carefully attended during the T-piece run, there is no back-up mode of ventilatory assistance and there are no operative ventilator alarms.

It has been fashionable to attempt to obviate the later problem by leaving the patient connected to the ventilator and using the C.P.A.P. mode but with a low level of actual C.P.A.P. This practice should not be used in attempt to obviate the need for careful direct monitoring of the patient and should be used with caution since it is not equivalent to T-piece breathing because of the internal resistance of the ventilator circuits, which can be considerable, especially with demand-flow systems (274,275). The application of C.P.A.P. at low levels (5-15 cm H_2O) has been suggested to overcome this problem and to reduce the inspiratory work of breathing (276). However, it is not clear if this approach offers any advantage over T-piece (277).

Pressure support ventilation allows the patient to breath spontaneously; the patient determines the overall respiratory pattern, including both the initiation and termination of inspiration (278). As the patient is still connected to the ventilator, the monitoring, alarm, and back-up ventilation functions can be left intact. The work of breathing is partially offset by the ventilator through the administration of additional inspiratory flow adjusted to maintain a pre-set inspiratory airway pressure. As such, the work of each breath is performed partially by the patient and partially by the ventilator (278,279). This allows the patient to develop a larger tidal volume (and thus lower breathing frequency) for the same spontaneous effort (280). Pressure support is usually started at a level which results in an adequate tidal volume and breathing frequency. This will usually require about 15-25 cm H_2O pressure support (281) to achieve a tidal volume of approximately 10-12 ml/kg. The level of pressure support is then gradually decreased as long as the generated tidal volume is adequate and the respiratory rate is not too rapid. At low levels (5-10 cm H_2O) the pressure support is likely serving principally to overcome the internal resistances of the ventilator (282) and the patient should be considered for extubation.

Intermittent mandatory ventilation (I.M.V.) has been used to wean such patients and the method has been well described elsewhere (270-272). We have not found this method to be particularly useful in difficult to wean patients. During I.M.V. there are no prolonged periods of rest as the mandatory breaths are interspersed with spontaneous breaths. As the I.M.V. rate is lowered significantly, the patient may begin to tire and experience significant respiratory muscle fatigue. If this is allowed to occur or goes unrecognized, then the training effect may be lost and a significant period (24-48 hours) may be required to return the patient to his previous status (256). Further, the internal resistance of the ventilator circuit through which the patient must breath can be considerable and may result in a unacceptable superimposed load and work of breathing (283).

Of greater importance than the mode of weaning employed are all of the other factors which determine the patients overall condition. Morganroth et al reported that successful weaning accompanied improvement in what they called an "adverse factor score" which attempted to quantify the patient's overall status. In difficult to wean patients this was more predictive than standard measures of ventilatory performance (264). Regardless of which mode of weaning is chosen, we prefer to conduct all weaning activities during the daytime. At night the patient is allowed to sleep and the respiratory muscles are rested using a support mode of ventilation. Unnecessary nocturnal interruptions such as phlebotomy, X-rays, weighing or dressing changes should be avoided. During the day, a program is planned which incorporates the weaning trials as well as the patient's normal daily activities. As much as possible, patients should be encouraged to perform the majority of these tasks for themselves (e.g. bathing, shaving, eating, dressing). Sedatives and paralytic agents should be avoided or at least minimized (284). Mobility should be encouraged so that the patient is out of bed as much as possible and even ambulating with ventilatory assistance when possible. In this context, invasive monitoring should be minimized. The patient should be kept fully informed of plans, progress, and goals. Communication should be facilitated as much as possible, including the use of writing pads, communication boards, and even assisted speaking devices or fenestrations in those with tracheostomy. Tracheostomy should be considered if the process is anticipated to be lengthy, primarily to enhance patient comfort and mobility (285). Tracheostomy also may allow the patient to eat.

Nutritional support has been discussed elsewhere, but should be designed to provide adequate protein and caloric intake to meet needs while avoiding excesses which serve only to increase the ventilatory burden through increased oxygen consumption and carbon dioxide production (225,234,236). The patient's cardiovascular and volume status should be optimized. Contraction alkalosis must be avoided as this will suppress respiration. Electrolyte abnormalities which may affect muscle function such as hypophosphatemia (113,114), hypokalemia (117), hypomagnesemia (115), and hypocalcemia (116) must be corrected. Underlying endocrinopathies such as hypothyroidism (286) or adrenal insufficiency should be suspected when appropriate (258). Adequate pharmacologic therapy must be maintained, including bronchodilators, steroids, and antibiotics as needed. Prophylactic measures against thromboembolism and gastric bleeding should also be considered (139,287). With a concerted effort the vast majority of patients should be successfully weaned; only about 2% of all patients should be expected to remain truly ventilator dependent (23-25).

Non-invasive ventilatory assistance

In recent years there have been a number of reports of largely uncontrolled empiric trials in which mechanical ventilatory assistance has been used to intermittently provide respiratory support for stable patients in an effort to prevent

nocturnal decompensation or improve overall status (288-293). These reports have included patients with restrictive neuromuscular disorders for whom nocturnal support was required or patients with obstructive lung disease in whom the intent was to provide rest for the respiratory muscles. The forms of mechanical assistance used with these techniques are variations of modes available with standard mechanical ventilators. These forms of therapy have been touted largely because they are "non-invasive". This is to say that what all of these modalities have in common is that the interface between the mechanical assist device and the patient is achieved with some form of mask rather than a tube.

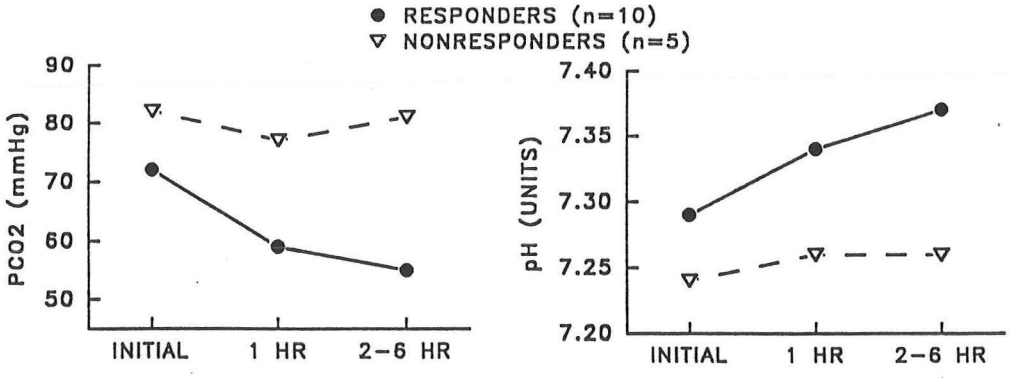
There are now reports of using these techniques in the setting of acute respiratory failure (288,294-298). These reports include myriad permutations involving the following variables: patient population; type of mask (full-face vs nasal); method of ventilatory assistance (including full support such as C.M.V. or assist/control volume-cycled modes and pressure-cycled modes such as I.P.P.V., inspiratory pressure assistance such as pressure support ventilation or I.P.A.P., expiratory positive pressure, or E.P.A.P., and continuous positive pressure such as C.P.A.P. or P.E.E.P.); level or intensity of positive pressure; duration of use (continuous or intermittent); and total duration of application.

The rationale for using standard support modes of ventilatory assistance is the same whether a mask or tube is used; the patient's ventilation is supported allowing the respiratory system time to recover and regain respiratory muscle function. The two most consistently reported techniques for providing supportive ventilation in C.O.P.D. patients with acute respiratory failure are the use of controlled ventilation via a nasal mask (295,297,298) or the use of inspiratory pressure support via a tightly sealed full-face mask (296,299,300). When a nasal mask is used, it is usually of the type used with nasal C.P.A.P. for patients with obstructive sleep apnea (297). Some of these patients require chin supports to keep the mouth closed. When a full-face mask is used it is of the type used to deliver C.P.A.P. to non-intubated patients or a full-face anesthesia mask (296,299,300). A nasogastric tube is usually placed when a full-face mask is used to minimize gastric distention and the risk of aspiration (299,300). In all cases, the mask is tight fitting. Controlled ventilation is applied using standard mechanical ventilators and standard settings are used (295,297). Alternatively, inspiratory pressure support can be supplied using the pressure support mode on newer ventilators or using the I.P.A.P. component of the Bi-PAP devices. Pressure support levels are adjusted to achieve adequate minute ventilation, respiratory rate, and tidal volume; this usually requires 20-30 cm H_2O of pressure support (296,299). Ventilatory assistance is usually provided intermittently; treatment periods of 1-6 hours are interspersed with periods with the mask removed (296,297,299).

In addition to these techniques, the use of externally applied continuous positive pressure (C.P.A.P., P.E.E.P., or Bi-P.A.P.) has been advocated by some. The rationale for continuous positive pressure in patients with C.O.P.D. is that external positive pressure may offset the threshold elastic load caused by intrinsic P.E.E.P. which the patient must overcome during inspiration (69,75,301). In addition, positive pressure applied during expiration may minimize dynamic airway compression and reduce air-trapping and hyperinflation in much the same way as occurs during pursed-lips breathing (302,303). However, this approach should be considered cautiously as application of P.E.E.P. in any form may lead to further increases in FRC, pushing the patient closer to TLC and the consequent risks of barotrauma (69).

Up to 30-50% of patients reported in the literature were not able to tolerate the mask-delivered ventilation (295,296,299). Approximately two thirds those who were able to tolerate the technique showed improvement in breathing pattern and gas exchange parameters and were successfully managed with this technique without resorting to mechanical ventilation (296-300). It is important to note however, that those who were successfully managed with non-invasive techniques tended to have better initial respiratory status. In studies in which an attempt was made to compare the therapy to standard methods, there has been no difference with respect to overall outcome (295,296). Also, patients who avoided intubation showed objective improvement within the first hour or two of therapy (300).

CLINICAL RESPONSE OF COPD PATIENTS
TO MASK VENTILATION DURING ARF



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These methods are not without their problems. Complications include gastric distention, aspiration, conjunctivitis, skin lesions, and sinus and nasal drying and congestion (295,300). Use of masks interferes with the patients ability to expectorate, eat, drink, speak, and receive aerosol medications. The technique is

generally not indicated for patients who are agitated, unable to co-operate with therapy, or who have significant difficulties with managing their airway secretions (298).

Given our present state of knowledge, it would seem that mask-delivered ventilatory support cannot be recommended as initial management for the majority of patients who are in need of mechanical assistance. It should probably be restricted to co-operative patients for whom intubation is felt to be contraindicated based upon the patient's overall prognosis and expressed wishes. When it is employed, it should be done only in settings where the patient can be adequately monitored. If the patient does not show early objective improvement (i.e. within the first 1-2 hours), then intubation and use of conventional ventilation should be considered in those for whom this is not otherwise precluded. The technique has also been used emperically in some patients felt to need ventilatory assistance in the immediate post-extubation period. If used as palliation for patients in end-of-life circumstances, these methods should only be used to the extent that they make the patient more comfortable.

PROGNOSIS

The clinical paradox of applying group statistics in an effort to make prognostic decisions for individuals is nowhere better demonstrated than in patients with severe C.O.P.D. As a group they tend to do well in the short-term (though a significant minority die or experience important morbidity) while the long-term outcome for the group is quite poor (though a significant minority may do quite well).

Acute mortality

The acute mortality for C.O.P.D. patients admitted with acute respiratory failure reported in the literature ranges from as low as 6% (304) to as high as 61% (22). However, when studies including comparable and representative groups of patients are considered, the mortality is remarkably consistent, ranging from 22 to 36% (20,21,23,25,257,305-308) with an overall average of 28% (20,21).

Several factors influence the likelihood of surviving an acute episode of respiratory failure. Some of these factors would be known prior to the onset of such an episode and thus would be useful in making anticipatory decisions (e.g. Living Will preparation) while other factors which relate to the severity of the acute illness and which clearly influence survival would only become known after the patient presents and treatment has been initiated. Severity of underlying lung function (20,21,23), pre-morbid functional status (20,21,23,305,309), and co-existing illnesses are the most useful anticipatory predictors of outcome. The expected mortality of C.O.P.D. patients with an acute episode of respiratory failure is 72% if the baseline $F.E.V._1$ is less than 25% of predicted or 74 % if the baseline functional status is such that the patient is

confined to home or bed (23). Conversely, if the patient has neither of these baseline characteristics, the expected mortality is 29%; if the patient has an $F.E.V._1$ over 40% of predicted and is working or living independently the mortality is only 10% (23). The presence of baseline hypercarbia or cor pulmonale may also predict higher mortality (310). The patient's age does not appear to affect the outcome of an episode of acute respiratory failure independent of these other factors (311). The advent of acute respiratory failure in patients with concomitant illnesses such as malignancy or class III or IV cardiomyopathy is generally associated with mortality rates in excess of 90% (312,313).

EFFECT OF FUNCTIONAL STATUS AND BASELINE LUNG FUNCTION ON MORTALITY FROM ACUTE RESPIRATORY THERAPY WITH COPD

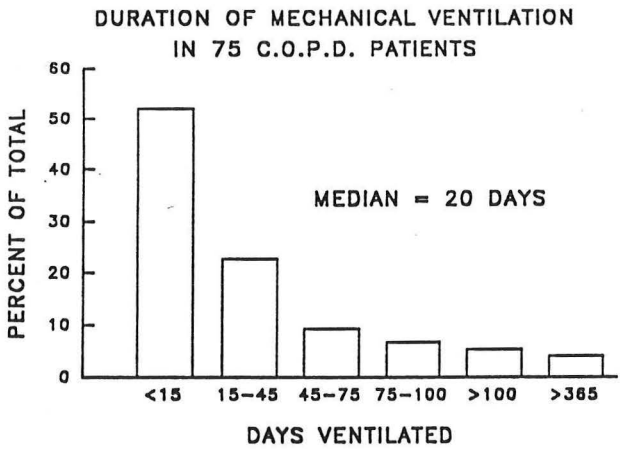
	FEV_1 < 25%	FEV_1 25-40%	FEV_1 >40%
Housebound	74%	73%	75%
Some restriction	75%	37%	43%
Independent	50%	33%	10%

Menzies, et al, Chest 95:398(1989)

Features of the acute episode which reflect severity of illness may also have prognostic importance. Patients who present with severe acidosis (pH less than 7.25) have greater mortality (314-317). The presence of parenchymal or systemic infection (pneumonia and/or sepsis) in this setting, while often considered "reversible" actually is associated with a significantly worse prognosis (257,318). Patients whose illness is precipitated by an acute exacerbation of chronic bronchitis can be expected to do exceptionally well, with 94% being discharged alive (304). Conversely, those patients who do not appear to have any definable acute decompensation, who are manifesting the inexorable progression of end-stage illness, can be expected to do quite poorly (21,306). Patients who require prolonged mechanical ventilation have a significantly worse prognosis (22); however, it is not clear whether this can be attributed to the mechanical ventilation or if, as is more likely, this does not simply reflect the selection of sicker, less functional patients (21). Furthermore, it does not appear that the use of mechanical ventilation per se independently affects survival (21).

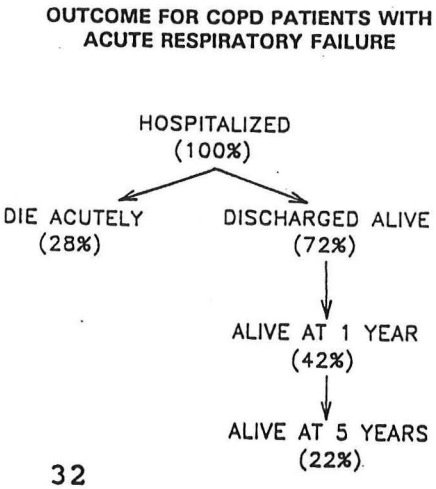
Duration of mechanical ventilation

Fortunately, the majority of C.O.P.D. patients with acute respiratory failure can be managed with "conservative therapy," a term which belies the intensity of such management and which usually is used to denote the absence of mechanical ventilation. However, approximately 35% of patients will require (or receive) mechanical ventilation (20). The duration of mechanical ventilation is extremely variable and difficult to predict. The majority of patients require only a few days of ventilatory support (258), but the average duration is from 10 to 20 days for those requiring more than 48-72 hours of ventilaiton (23,257). Very prolonged mechanical ventilation can be required and about 2% become ventilator dependent indefinitely (23,25).



Long-term survival

Patients discharged alive after an episode of respiratory failure tend to have long-term survival which mirrors the natural progression of C.O.P.D. with similar lung function impairment (21,304,319). The long-term survival of those discharged alive is approximately 58% (range 54-75%) at one year (23,25,305,308) and 30% at five years (305,320). Thus, of all patients admitted with acute respiratory failure due to C.O.P.D. 72% will be discharged alive, 42% will be alive one year later, and 22% will be alive at five years.



Terminal care of the end-stage patient

Given appropriate information regarding prognosis and therapeutic options, patients who are considered to have end-stage disease may elect to forgo certain interventions, including mechanical ventilation, during the final stages of their disease or with the onset of acute respiratory failure. In such circumstances, the therapy the patient receives may nonetheless be quite intense and may legitimately be conducted in an intensive care unit. All reasonable efforts to correct or reverse acute problems should be made. The patient should be reassured that the decision to withhold mechanical ventilation does not equate with the withholding of other indicated therapy. Further, relief of the sensation of air hunger may be accomplished through the administration of modest doses of opiates without necessarily causing significant worsening of ventilatory function or unwarranted sedation (321,322). Anxiolytics such as diazepam do not appear to improve dyspnea, but may cause unwanted sedation (323).

APPENDIX: DRUG DOSAGE GUIDELINES FOR C.O.P.D. PATIENTS WITH ACUTE RESPIRATORY FAILURE

Aerosolized bronchodilators:

	Metered-Dose Inhaler (with spacer)		Nebulizer Solution (unit dose equivalent)	
Drug	mg/puff	dose* (puffs)	dose (mg)	final volume (ml)
Albuterol	.09	2-6	2.5	3 ml
Metaproterenol	.65	2-6	15	2.5 ml
Isoetharine	.34	2-4	5	2.5 ml
Terbutaline	.20	2-6	N/A	N/A
Ipratropium	.02	2-6	N/A	N/A

* upper dose limit not formally approved or established

Corticosteroids:

Methylprednisolone 40 mg I.V. every 6 hours for 72 hours.

Then either D/C or taper rapidly with oral prednisone starting at 40-60 mg/day

Aminophylline:

Aminophylline continuous infusion at .05-.10 mg/kg/hr.

Monitor drug levels and adjust to 10-15 mg/L.

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